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**Manuscript Submission**
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Mission Statement: The Archives of Dermatology publishes information concerning the skin, its diseases, and their treatment. Its mission is to exponentially expand the structure and function of the skin and its diseases and the art of using this information to deliver optimal medical and surgical care to the patient. We attempt to enhance the understanding of cutaneous pathophysiology and improve the clinician’s ability to diagnose and treat skin disorders. This journal has a particular interest in publishing clinical and laboratory studies that reveal new information pertinent to the interests and needs of the medical dermatologist, dermatologic surgeon, and all those concerned with state-of-the-art care of cutaneous disease. We believe that knowledge derived from well-designed clinical trials and studies of cost-effectiveness are especially important for improving the practice of dermatology. Studies that increase the understanding of the outcomes of dermatologic disease can be measured and reduced to promote the health of patients with skin disease will receive special priority. The Archives regularly publishes reports on clinical investigations, editorials, and reviews. It also features reports and discussions on clinicopathologic correlations; clinical disorders of unique didactic value; pharmacologic, medical and surgical therapies; and ethical, moral, socioeconomic, and political issues.

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Injection Drug Use: An Understudied Cause of Venous Disease

Injection drug use (IDU) accounts for 12% of all illicit drug use in the United States. Intravenous routes are often preferred because of the rapid drug response. Intravenous injecting typically begins in the veins of the arms and upper body, but as these sites become more difficult to find, the veins of the groin, leg, and feet are used. Complications of IDU include venous scarring and collapse, abscess formation, nerve and muscle damage, and lymphatic blockage. In addition, IDU augments or intensifies the typical chronic venous disease (CVD) risk factors affecting the general population. In this review, Pieper et al point out the importance of obtaining a substance-abuse history when evaluating for risk of CVD.

Physical Activity and Adherence to Compression Therapy in Patients With Venous Leg Ulcers

Venous insufficiency causes 70% of all leg ulcers. Physical activity and adequate compression therapy are essential noninvasive treatments for venous leg ulcers. Leg exercises (particularly walking) stimulate the calf muscle pump, supporting venous circulation. Compression therapy improves calf muscle pump effectiveness, reduces venous volume, lowers venous pressure, and improves the microcirculation, thus preventing edema and reducing the development of venous skin changes. In this descriptive cross-sectional study, Heinen et al demonstrate that moderate strenuous activity levels in patients with venous leg ulcers are quite low and that less than half of patients report full compliance with compression therapy. Strict compliance with these noninvasive treatments provide demonstrable benefit with respect to wound healing, suggesting that patients should be more fully educated and urged to follow these recommendations.

Association Between the Use of β-Adrenergic Receptor Agents and the Development of Venous Leg Ulcers

It has been more than 25 years since β-adrenergic receptors were first noted to be expressed in the skin, but their functional importance remains unclear. β-Adrenergic receptors may play a role in cutaneous wound repair. Receptor agonists decrease the rate of keratinocyte migration in vitro and impede wound healing in vivo. Receptor antagonists increase cultured keratinocyte migratory speed and improve wound epithelialization in vivo. In this retrospective cohort study, Margolis et al demonstrate a strong protective association between β-adrenergic receptor agonists and venous leg ulcers. These epidemiologic data are supported by strong laboratory evidence, suggesting the need for a randomized clinical trial of these agents.

Staphylococcus aureus Virulence Factors Associated With Infected Skin Lesions: Influence on the Local Immune Response

Staphylococcus aureus is a major cause of local skin infections. Virulence factors include over 40 secreted proteins, enzymes, and toxins that establish and maintain infections, sometimes through an effect on the local immune response. In this study, Mertz et al demonstrate a direct association between the number of white blood cells (WBCs) in a local skin infection and the toxin genes that S aureus carries. Although the physical appearance did not differ, lesions with the fewest WBCs were more likely to be infected with S aureus strains capable of producing exfoliative toxins A and B, while the lesions with the most WBCs were more likely to be infected with a Panton-Valentine leukocidin–producing organism. These data suggest that the local immune response may not always offer an accurate estimate of the seriousness of an infection.

Hydroxyurea-Induced Leg Ulcers Treated With a Protease-Modulating Matrix

Hydroxyurea is a chemotherapeutic agent that inhibits DNA synthesis and promotes cell death in the S phase of the cell cycle. Hydroxyurea is generally well tolerated and has a low toxicity profile, but painful leg ulcers may rarely complicate long-term, high-dose use for myeloproliferative disease. In this case series, Romanelli et al describe a pronounced association between hydroxyurea therapy and the development of painful leg ulcers unresponsive to standard therapy. These patients were successfully treated with local Promogran dressing therapy (Johnson & Johnson Wound Management, Piscataway, New Jersey) every other day and then twice weekly. Promogran is a freeze-dried sponge containing oxidized regenerated cellulose and bovine purified collagen that may inhibit the degradation of growth factors and tissue destruction, thus limiting the damage to collagen synthesis due to hydroxyurea.
NOTICE.

By the initiative of Professor Gaucher, the pupils and friends of Dr. Hallopeau have opened a subscription with the object of offering a medal commemorating Dr. Hallopeau’s twenty-five years’ service at L’Hôpital Saint Louis, of his promotion to the grade of officer of the Legion of Honor and of his numerous scientific publications. The medal is to be designed by Chaplin, with allegorical reverse and will be presented before the end of the year. The amount of each subscription is not limited. Each subscriber of five dollars (25 francs) becomes entitled to a copy of the medal. Subscription open until November 15, 1907. Send postal orders to J. B. Balliere, 19 Rue Hautefeuille, Paris.

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COMMEMORATIVE MEDALS.

Honor a physician with the honor due unto him. . . .

Ecclesiasticus 38:1
Negative Pressure Dressing in the Management of Pyoderma Gangrenosum Ulcer

Marcelo M. Ghersi, MD; Carlos Ricotti, MD; Carlos H. Nousari, MD; Martin I. Newman, MD; Department of Surgery, Mount Sinai Medical Center, Miami Beach, Florida (Dr Ghersi); Department of Dermatology, University of Miami, Miami, Florida (Drs Ricotti and Nousari); and Department of Plastic Surgery, Cleveland Clinic Florida, Weston (Dr Newman)

The medical management of pyoderma gangrenosum (PG) ulcers has been a challenging practice since the description of these chronic wounds. Advances in biotechnology in the past 2 decades have given us a better understanding of the histopathologic nature of this disease, and as a result, better therapeutic modalities have evolved. However, on occasion PG ulcers will present in a refractory manner that will mandate additional strategies to attain wound closure. We present herein the novel use of negative pressure dressings to effectively treat such a complex wound.

REPORT OF A CASE

A 57-year-old woman with a history of a very slowly healing PG ulcer on the lower part of her left leg for 2 years presented with increasing pain and ulcer size after more recent physical trauma. On physical examination, she had a rounded ulcer (diameter, 10 cm) with central granulation tissue, scant purulent drainage, and erythematous-violaceous undermining borders (Figure, A). No lymphadenopathy, fever, or other constitutional symptoms were observed. Partial response and intolerance to previous therapies including intravenous pulses of methylprednisolone, intralesional triamcinolone acetonide, intravenous immunoglobulin, mycophenolate mofetil, and cyclophosphamide was noted.

Routine histological examination of a skin biopsy specimen taken from the erythematous-violaceous border showed a diffuse interstitial dermal neutrophilic-rich infiltrate, without evidence of vasculitis. The results of special stains for pathogenic mycobacteria or fungi were negative. Tissue cultures obtained for wide spectrum microorganisms revealed only methicillin-resistant Staphylococcus aureus (MRSA) sensitive to vancomycin. Findings from venous and arterial Doppler studies excluded underlying vascular disease. Results from extensive serological, coagulation, and hematological studies failed to demonstrate evidence of underlying connective tissue disease, antiphospholipid syndrome, myelodysplastic syndrome, paraproteinemia, or any other hematologic disease.

At the 3-week follow-up examination, after having received intravenous vancomycin and continued local wound care, the erythematous-violaceous undermining borders of the ulcer had significantly improved. However, the lesion was still tender and no reduction in ulcer size was appreciated.

SOLUTION

Negative pressure dressing with the vacuum-assisted closure (VAC) system was concurrently used with intravenous antibiotic therapy to accelerate healing of the ulcer (KCI International, San Antonio, Texas). At the time of application of the VAC, the ulcer was completely filled with granulation tissue, there was no evidence of purulent drainage, and there was complete resolution of the erythematous-violaceous undermining borders. A polyurethane foam dressing was placed on the wound, followed by draping as per the manufacturer’s instructions to create an airtight seal. Suction tubing was applied and connected to the therapy unit. Intermittent therapy (5 minutes active and 2 minutes inactive) with 125 mm Hg of negative pressure was administered, with scheduled wound dressing changes every 48 hours.

At the time of the first VAC system dressing change, the wound borders had reepithelialized further into the wound bed, there was no evidence of erythematous-violaceous undermining borders, and the associated pain
had significantly subsided (Figure, B). The VAC system was well tolerated and was used until complete wound closure, approximately 6 weeks after initiating therapy (Figure, C). At the 6-month follow-up examination, the PG ulcer remained completely healed.

**COMMENT**

The mainstay of therapy for PG is immunomodulatory and immunosuppressive medical therapy as well as management of possible underlying associated disease. Surgical and other invasive modalities are contraindicated as the primary or sole treatment of active PG ulcers. However, some authors have described a role for adjunctive surgical management including skin grafts, muscle flaps, and cultured keratinocyte autografts concomitant with or preceding primary effective immunopharmacologic therapy in noninfected and controlled PG ulcers.

In 1997, Argenta and Morykwas reported the successful use of the VAC system as a primary treatment of nonhealing skin ulcers (KCI International). Over recent years, the VAC system has become an important tool for the management of large, complex, acute, and chronic skin ulcers from a wide variety of causes. The mechanism of action of subatmospheric pressure therapy includes increased tissue perfusion, increased granulation tissue formation, reduced bacterial load, and removal of excess interstitial edema. In addition to its role in treating ulcers, the VAC system has also been used to bolster skin grafts and to reepithelialize donor sites.

The optimal subatmospheric pressure with the VAC system for wound healing appears to be approximately 125 mm Hg, using an alternating pressure cycle of 5 minutes of suction, followed by 2 minutes off suction. Dressing changes should be made every 48 to 72 hours to prevent growth of granulation tissue into the foam dressing. The VAC device can be applied over any type of tissue. Prior to application, the wound should be free of necrotic tissue and well vascularized. Complications with the VAC system are infrequent and usually yield low morbidity. These complications are typically associated with inadequate wound bed preparation, infrequent dressing changes, or inadequate pressures applied. Therapy with the VAC system has also been associated with local skin irritation, pain, maceration, tissue necrosis, bleeding, and infection. Owing to its mechanism of action, ie, through the application of subatmospheric pressure, the VAC system could be considered a minimally invasive interventional therapy and thus a potential eliciting factor for pathergy in PG ulcers. However, as shown in this report, the VAC system appears to exert its beneficial effect on long-term wound healing without the theoretical detrimental effects in a stable PG ulcer.

Negative pressure dressing in the management of PG was first described by Niezgoda and colleagues in 2006.
Contrary to our single modality approach, these authors used wide surgical debridement, hyperbaric oxygen, and VAC, followed by skin grafting, to successfully treat a similar patient with a medically stable lower extremity PG ulcer.14 Although optimal outcomes were achieved in both cases, more studies are necessary to accurately determine the role each of these modalities have on the healing of this complex wound. For now, the VAC system has proven to be a safe tool that should be included in the adjudvant therapeutic armamentarium for the management of controlled and slow-healing PG ulcers.

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Financial Disclosure: None reported.

REFERENCES


Clinicians, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Manuscripts should be prepared double-spaced with right margins unjustified. Pages should be numbered consecutively with the title page separated from the text (see Instructions for Authors [http://archderm.ama-assn.org/misc/tifora.dll] for information about preparation of the title page). Clinical photographs, photomicrographs, and illustrations must be sharply focused and submitted as separate JPG files with each file numbered with the figure number. Material must be accompanied by the required copyright transfer statement (see authorship form [http://archderm.ama-assn.org/misc/auinst_crit.pdf]). Preliminary inquiries regarding submissions for this feature may be submitted to George J. Hruza, MD (ghruza@aol.com). Manuscripts should be submitted via our online manuscript submission and review system (http://manuscripts.archdermatol.com).
Objective: To investigate the use of a topical oxygen emulsion (TOE), consisting of a supersaturated oxygen suspension using perfluorocarbon components, on second-degree burns and partial-thickness wounds.

Design: Oxygen is a required substance for various aspects of wound repair, and increased oxygen tension in a wound has been shown to stimulate phagocytosis and to reduce the incidence of wound infection. Second-degree burns and partial-thickness wounds were created on the backs of specific pathogen-free pigs. Wounds were then randomly assigned to 1 of the following treatment groups: TOE, TOE vehicle, or air-exposed control.

Main Outcome Measure: Wounds were assessed for complete epithelialization using a salt-split technique.

Results: The TOE was able to significantly (P = .001) enhance the rate of epithelialization compared with both vehicle and untreated control. These data suggest that topical oxygen may be beneficial for acute and burn wounds.

Conclusions: The results obtained from this double-blind, control, in vivo study demonstrate that TOE can significantly enhance the rate of epithelialization of partial-thickness excisional wounds and second-degree burns. These findings could have considerable clinical implications for patients with surgical and burn wounds by providing functional skin at an earlier date to act as a barrier against environmental factors, such as bacteria invasion. Other types of wounds may also benefit from this therapy (eg, chronic wounds and surgical incisions). Additional studies, including clinical studies, are warranted.

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A CONSTANT AND ADEQUATE oxygen supply is important for cell and tissue homeostasis. It is well documented that oxygen can play a key role in energy production, cell membrane maintenance, mitochondrial function, and cellular repair. Physical injury to skin can compromise the arterial, venous, or capillary systems of tissue, which in turn may cause hypoxia and ischemia.

CME available online at www.archdermatol.com

The tissue repair process requires an increased metabolic activity of a variety of cells, resulting in a high oxygen demand. Recent research has demonstrated that increased oxygen tension in a wound promotes wound healing by stimulating several processes, including phagocytosis (engulfing of microorganisms, cells, or debris by macrophages or neutrophils), degradation of necrotic wound tissue, collagen production, neovascularization, and neutrophil-mediated oxidative microbial killing.

Many different treatment modalities have been attempted to increase local oxygen supply to wounds to accelerate repair. One potentially successful method is hyperbaric oxygen (HBO) therapy, which is somewhat controversial because studies have shown positive and neutral effects. Clinical research has demonstrated that HBO therapy accelerates reepithelialization of chronic leg ulcers. Although HBO therapy can be effectively applied to treat wounds, especially in hypoxic tissues, HBO is not always practical or readily available, and can be relatively costly.

After treatment with HBO therapy, fibroblasts, an essential component of skin repair, show a dose-dependent increase in cellular proliferation. Fibroblasts cannot synthesize collagen in the absence of molecular oxygen, which is required for the hydroxylation of proline and lysine residues in the nascent procollagen molecule. Hyperbaric oxygen therapy depends on the lungs to increase the oxygen tension in the blood, which is then transported systemically throughout the body and finally to the wound.

Topical application of gaseous oxygen, at normal or elevated partial pressures, to skin wounds and ischemic lesions has been attempted; however, as a gas, oxygen has
limited ability to penetrate the skin. On exposure to atmospheric pressures, oxygen microbubbles nucleate, coalesce, and effervesce from the topical preparation, thereby reducing the oxygen content to ambient levels. Peroxide-containing formulations have been developed, some of which are available commercially. These formulations can provide small quantities of oxygen to tissues by either spontaneous breakdown or enzymatic breakdown following tissue contact. Peroxide formulations are mildly bactericidal and are used primarily to remove dirt and debris from acute traumatic lesions. Unfortunately, peroxides are irritating to raw tissue, have limited capacity to support metabolic oxygen requirements, and are believed to delay wound healing, thus limiting their use as wound-promoting agents.

The ideal topical oxygen agent would provide sufficient quantities of oxygen to a wound several hours after application and be nontoxic to the skin to accelerate local tissue repair. TherOx Inc has developed a technique by which an emulsion-containing supersaturated oxygen can be delivered topically to a wound, where it can slowly release additional oxygen over time. This technology is based on perfluorocarbon droplets being encapsulated within an aqueous continuous phase. The oxygen solubility of the perfluorocarbon is relatively high (approximately 20 times greater than water); therefore, it has a high oxygen-carrying capacity. Oxygen is dissolved into the perfluorocarbon emulsion and stored under pressure in a small dispensing bottle. By maintaining pressure on the emulsion, dissolution and outgassing are prevented during storage and the maximum oxygen concentration is delivered on dispensation. The topical cream is formulated with biocompatible emulsifying agents to ensure adequate stability of the dispersed perfluorocarbon droplets. Before dispensation, the dissolved oxygen concentration contained in the topical emulsion is approximately 2.0 mL of oxygen (standard temperature and pressure) per milliliter of emulsion.

Herein, we report the use of a novel topical oxygen emulsion (TOE) that promoted wound healing of second-degree burns and partial-thickness wounds.

METHODS

EXPERIMENTAL ANIMALS

Pigs were used as our experimental animal because they have skin that is anatomically and physiologically similar to humans and are considered an excellent tool for the evaluation of therapeutic agents. There is a strong correlation between pigs and human wound-healing studies. Sixteen pigs were used for these studies (8 for partial-thickness wounds and 8 for second-degree burns) using well-defined porcine models. The animal protocol used for this study was approved by the University of Miami Institutional Animal Care and Use Committee. Animals were monitored daily, and to help minimize possible discomfort, an analgesic, buprenorphine, 0.03 mg/kg, was given to each animal the first day while under anesthesia and a transdermal agent (fentanyl [Duragesic]), 25 µg/h, was used during the entire experiment.

WOUNDING TECHNIQUE

Three grids were outlined on the dorsum and flanks of each pig. For the partial-thickness wounds, the injuries (0.7 × 10.0 × 0.3 mm) were made with an electrosurgical knife. A total of 120 partial-thickness wounds were created on each pig.

The burn wounds were made using the following method. Five specially designed cylindrical brass rods weighing 358 g each were heated in a boiling water bath to 100°C. A rod was removed from the water bath and wiped dry before it was applied to the skin surface to prevent water droplets from creating a steam burn on the skin. The brass rod was held at a vertical position on the skin (6 seconds), with all pressure supplied by gravity, to make a burn wound 8.5 mm in diameter by 0.8 mm deep. Again, 120 burn wounds were made on the anterior two-thirds of the animal. Burn wounds and partial-thickness wounds were randomly assigned to 1 of the following treatment groups according to the following experimental design.

TREATMENTS AND EXPERIMENTAL DESIGN

Treatments (active TOE containing oxygen, vehicle without oxygen, or untreated air exposed) were randomly assigned to the wounds. The treatments were given to the investigators in a blinded fashion (pressurized containers labeled A and B). Wounds were treated twice daily for the first 5 days and once thereafter until all wounds were 100% completely reepithelialized. Treatments were covered with a secondary dressing (Release nonadherent gauge) and secured in place with Coban self-wrapping bandages. The experimental design for both the partial-thickness study and the second-degree burn study included 8 animals, with 120 wounds per animal (for a total of 960 wounds), 40 wounds per treatment group.

EPIDERMAL MIGRATION ASSESSMENT

The partial-thickness wounds were assessed on days 3 to 9 after wounding (day 0), and the second-degree burns were assessed on days 7 to 14 after burning. Beginning on the first assessment day and on each day thereafter until all wounds were 100% reepithelialized, 5 wounds and surrounding normal skin from each treatment group were excised using a standard-width (22 mm) electrosurgical knife set at a depth of 0.5 mm. Specimens that were not excised intact were discarded. Excised skin containing the wound site was incubated in 0.5M sodium bromide at 37°C for 24 hours, allowing for a separation of the dermis from the epidermis. After the separation, the epidermal sheet was examined macroscopically for defects. Defects were defined as holes in the epidermal sheet in the area of the wound. Reepithelialization is considered complete if no defects were present; any defect in the wound area indicates that healing was incomplete, and if no defects were seen, the wound is considered...
pletely epithelialized or healed (Figure 2). The epidermis must be fairly mature (at least 5-7 cell layers) to withstand the separation technique. The number of completely healed (reepithelialized) wounds was then divided by the number of wounds assessed. This gives a percentage of wounds that are completely reepithelialized (eg, on day 8, [12/40] × 100% = 30% of wounds completely reepithelialized).

STATISTICAL ANALYSES

After the study is completed, the number of wounds healed (completely epithelialized) will be divided by the total number of wounds sampled per day and multiplied by 100. The percentage of wounds will be plotted against days after wounding. Analysis by χ² 4-fold tables was performed on the combined data to determine any treatment response.

RESULTS

For the partial-thickness wound study, the wound that received the TOE had a significantly enhanced rate of epithelialization compared with the vehicle and untreated air-exposed wounds (on days 4, 5, and 6). In the second-degree burn study, the TOE also had a significantly enhanced rate of epithelialization compared with vehicle and untreated burn control wounds (on days 7, 8, and 9 after the burn) (Table 1 and Table 2). The vehicle also showed a significant increase in epithelialization when compared with untreated control wounds (for partial-thickness wounds, on days 5, 6, and 7; and for second-degree burn wounds, on days 10, 11, and 12).

COMMENT

Following tissue injury, several wound repair mechanisms are sequentially activated. These activities are grouped into the 3 overlapping phases of wound healing: inflammation, proliferation, and remodeling. All physiologically active processes involved in these phases are in need of an adequate supply of oxygen.

After the initial trauma, there is vascular damage followed by hemostatic mechanisms to prevent blood loss. Coagulation and vasoconstriction are physiologic mechanisms of hemostasis in the wound. Oxygen delivery via the vasculature to the wound at this stage is compromised. The oxygen supply is limited, and delivery to the wound is dependent on diffusion from the surrounding tissue and atmosphere. In normal wound healing, the decrease in oxygen supply is transient. Schweiki et al demonstrated in vitro that hypoxia leads to an increase in translation of vascular endothelial growth factor. This increase in vascular endothelial growth factor stimulates angiogenesis, resulting in the reestablishment of the vascular network in the wound bed. Interestingly, for the endothelium to be maximally responsive to vascular endothelial growth factor, it must first sense hypoxia. Hypoxic environments also increase collagen production by fibroblasts and promote fibroblast proliferation. These cellular processes (angiogenesis, collagen production, and cell proliferation) are part of normal tissue and cellular adaptation when their normal environment changes. For normal wound healing, the initial hypoxic environment may promote the healing process; however, long-term hypoxia impedes wound healing, and oxygen delivery would be beneficial.

Over time, the result of an increase in oxygen demand by leukocytes and fibroblasts and a reduced oxygen supply in a wound leads to anaerobic metabolism. Extended anaerobic metabolism leads to an increase in metabolites and a lack of energy production. Inadequate cell energy levels impair protein production and cell homeostasis. At the same time, vascular compromise and loss of blood flow disable the tissue from eliminating metabolites, such as lactic acid, from the wound. Lactic acid, a byproduct of anaerobic metabolism, accumulates and acidifies the wound environment, which may lead to cell death. Long-term hypoxia and loss of the ability for cells to adapt to hypoxia lead to impaired and pathologic wound healing. Research has focused on increasing oxygen supply to hypoxic and ischemic tissues to promote wound healing.

The administration of external supplemental oxygen may help in the wound healing process by providing ischemic tissue cells with the required oxygen tension needed to survive and proliferate, especially in the situation of extended oxygen limitation. When the new vasculature is well established and oxygen molecules can reach the repairing cells by diffusing throughout the new blood vessels, therapies such as HBO may prove to be effective. In addition to the direct effects of oxygen in wound healing and cellular repair, the role of oxygen in controlling infections has been examined. The open wound bed is a fertile breeding ground for a broad variety of pathogenic microorganisms. Wounds that are well perfused and oxygenated have been shown to be less likely to become infected.

Systemic HBO therapies entail the inhalation of 100% oxygen under pressures between 2 and 3 atmospheric pressure. The high pressure, in addition to the high levels of oxygen, considerably increases the dissolved oxygen levels into blood plasma. This therapeutic approach is indicated to treat acute traumatic ischemias, necrotizing fasciitis, irradiated tissues, refractory osteomyelitis, and certain chronic wound conditions. However, as previously mentioned, HBO therapies are effective if the vascular network is functional in the wounded tissues. Hyperbaric oxygen may not be effective on ischemic chronic leg ulcers and superficial burns. In addition to the limited research of these therapies on various types...
of wounds, these hyperbaric therapies require the use of large and cumbersome machinery. This inconvenience limits their widespread use in the clinical setting and their potential use for the military on the battlefield.

Topical HBO therapy is oxygen delivered at slightly increased atmospheric pressures directly to the surface of the wound. The name HBO therapy implies that pressures used in treatment are greater than 1 atm. Because “topical” HBO therapy is applied at pressures barely over 1 atm, the use of the term topical hyperbaric therapy is not only misleading but a misnomer. One should be wary of any so-called topical hyperbaric therapies that make various healing and/or rejuvenation claims, especially when few or no data are available to support their use. Hyperbaric oxygen is becoming a more accepted treatment modality, especially as an adjunctive therapy, because of the increase in studies showing potential mechanisms of action. Heng et al35 compared topical HBO therapy with the standard of treatment for necrotic gangrenous wounds that lack blood supply. Forty patients were included in the study, and 90% of patient ulcers that received topical HBO healed compared with 25% of patient ulcers treated with standard wound management therapy. No oxygen reperfusion damage was noted. The group also demonstrated that the topical HBO-treated ulcers had an increase in angiogenesis in the wound bed.

One appealing method for oxygen treatment is topical delivery. Many different topical oxygen delivery systems have been attempted for wound healing, but unfortunately most of these therapies have yielded poor results. One of the major criticisms of topical oxygen therapies is the inadequate delivery of oxygen deep into skin to provide fibroblasts, keratinocytes, and inflammatory cells increased oxygen required for repair. Recent advancements have allowed the creation of a hyperoxygenated emulsion for topical delivery of oxygen to wounds. Unpublished ex vivo assays performed by our group determined that our hyperoxygenated emulsion consistently increased subcutaneous oxygen tension when compared with vehicle and phosphate-buffered solution. The treated viable tissue also demonstrated an initial peak in PO2 levels with a decrease over time. Treated nonviable tissue results show an increase in PO2 levels without the decrease over time. This suggests that the cells in the viable tissue may be using the supplied oxygen from the topical emulsion in metabolic pathways. Once we established that the vehicle was able to carry the oxygen deep into skin, we set out to study this TOE on wounds. The fact that the vehicle also enhanced the rate of epithelialization in the porcine wound models is not surprising because it has previously been shown that vehicles are not inert and can either adversely or beneficially affect the healing process.26 In both of these studies (burns and acute partial-thickness wounds), we found the TOE to have a significant effect over vehicle alone.

Interestingly, the use of a TOE not only stimulated epithelialization of ischemic second-degree burns but also of well-vascularized acute wounds. Using the same porcine models, we have also evaluated possible mechanisms of topical oxygen and found an up-regulation of vascular endothelial growth factor, collagens I and III, and matrix metalloproteinase levels after treatment with the TOE. These findings will be the subject of a subsequent article that will document possible mechanisms of this therapy. Although hypoxia and hypoxemia have been shown to influence either keratinocyte proliferation or differentiation and collagen synthesis in vitro,28,37,38 these studies simply suggest that an external factor, such as low oxygen levels, which may be present during tissue repair, can influence various specific cellular processes. Purposefully in-

### Table 1. Partial-Thickness Epithelialization Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active</td>
<td>0/40</td>
<td>18/40 (45)</td>
<td>34/40 (85)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0/40</td>
<td>4/40 (10)</td>
<td>15/40 (38)</td>
<td>29/40 (72)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
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<tr>
<td>Untreated</td>
<td>0/40</td>
<td>0/40</td>
<td>0/40</td>
<td>3/40 (8)</td>
<td>25/40 (62)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
</tr>
</tbody>
</table>

aData are given as number of wounds completely epithelialized/total number of wounds assessed (percentage). On days 4 and 5, \( P < .001 \) for the active group vs the vehicle and untreated groups; on day 5, \( P < .001 \) for the vehicle group vs the untreated group; on day 6, \( P < .001 \) for the active group vs the vehicle and untreated groups and for the vehicle group vs the untreated group; and on day 7, \( P < .001 \) for the active and vehicle groups vs the untreated group.

### Table 2. Second-degree Burn Epithelialization Results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
</tr>
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<td>Active</td>
<td>9/40 (22)</td>
<td>28/40 (70)</td>
<td>37/40 (92)</td>
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<td>40/40 (100)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>0/40</td>
<td>13/40 (32)</td>
<td>20/40 (70)</td>
<td>38/40 (95)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
<td>40/40 (100)</td>
</tr>
<tr>
<td>Untreated</td>
<td>0/40</td>
<td>0/40</td>
<td>3/40 (8)</td>
<td>10/40 (25)</td>
<td>22/40 (55)</td>
<td>31/40 (78)</td>
<td>35/40 (88)</td>
<td>40/40 (100)</td>
</tr>
</tbody>
</table>

aData are given as number of burns completely epithelialized/total number of wounds assessed (percentage). On days 7 and 8, \( P < .001 \) for the active group vs the vehicle and untreated groups; on day 9, \( P < .02 \) for the active group vs the vehicle group and \( P < .001 \) for the active group vs the untreated group; on days 10 and 11, \( P < .001 \) for the active and vehicle groups vs the untreated group; and on day 12, \( P < .01 \) for the active and vehicle groups vs the untreated group.
ducing hypoxic environments to wounds clinically would most likely lead to necrosis and impaired healing.

The results obtained from this double-blind, control, in vivo study demonstrate that the TOE can significantly enhance epithelialization of partial-thickness acute wounds and second-degree burns. We believe that the oxygen supplied by the emulsion to the wound environment directly promotes cellular repair and the local immune response to speed wound healing. Our findings may have important clinical implications for patients with wounds by providing functional skin at an earlier date to act as a barrier against environmental factors, such as water loss and bacteria invasion. Other types of wounds may also benefit from this therapy (eg, ischemic and chronic wounds), and more studies, including clinical studies, are warranted.

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Author Contributions: Mr Davis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Davis, Ricotti, Zalesky, Hsu, Creech, and Mertz. Acquisition of data: Davis, Cazzaniga, Ricotti, Hsu, and Mertz. Analysis and interpretation of data: Davis, Cazzaniga, Ricotti, Eaglestein, and Mertz. Drafting of the manuscript: Davis, Ricotti, and Creech. Critical revision of the manuscript for important intellectual content: Davis, Cazzaniga, Ricotti, Zalesky, Hsu, Eaglestein, and Mertz. Statistical analysis: Ricotti. Obtained funding: Davis, Ricotti, Hsu, and Mertz. Administrative, technical, and material support: Davis, Cazzaniga, Hsu, and Creech. Study supervision: Davis, Zalesky, Eaglestein, and Mertz.

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Additional Contributions: Kurt Henry, MD, LCDR (US Navy), and Matt Healy, PhD (Booze Allen Hamilton Inc), provided help and support with this project.

REFERENCES

Staphylococcus aureus Virulence Factors Associated With Infected Skin Lesions

Influence on the Local Immune Response

Patricia M. Mertz, BA; Tatiana C. P. Cardenas, BS; Richard V. Snyder, PhD; Megan A. Kinney, BS; Stephen C. Davis, BS; Lisa R. W. Plano, MD, PhD

Objectives: To evaluate Staphylococcus aureus isolates from infected skin lesions for their potential to produce immune system–modulating toxins and to correlate these with white blood cell (WBC) counts associated with these lesions.

Design: Specimens were obtained for bacterial culture and gram staining from 105 infected skin lesions, and the number of WBCs per low-power field (LPF) was determined. Chromosomal DNA was prepared from 84 bacterial isolates and subjected to real-time polymerase chain reaction analysis to determine the presence of genes encoding potential immunomodulating toxins. Bacterial populations were divided into 2 groups: those associated with low WBC counts (0-5 WBCs/LPF) and those with high WBC counts (>5 WBCs/LPF). We applied χ² statistical analyses to compare the toxin gene profiles associated with WBC counts on initial swab for culture.

Patients: Samples were obtained from patients at a single geographic location.

Results: A higher than expected percentage of bacteria capable of producing the exfoliative toxins A and/or B (ETA and/or ETB) and Panton-Valentine leukocidin (PVL) was seen in all skin lesions infected with S. aureus without regard to WBC count with initial cultures. Comparison of the toxins associated with the low WBC group vs the high WBC group showed that low WBC counts were associated with ETA and ETB, while high WBC counts were associated with PVL and toxic shock syndrome toxin. There were no differences in the clinical appearance of the lesions between groups.

Conclusions: Staphylococcus aureus virulence factors ETA, ETB, and PVL are associated with WBC counts from infected skin lesions. The exact role they play in affecting the WBC counts remains to be determined.

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STAPHYLOCOCCUS AUREUS IS A major cause of multiple types of infections both in and outside of the hospital setting. These infections range from superficial skin infections to deeper infections of hair follicles, abscesses, and deep tissue infections, and even to systemic infections including those of the heart, lungs, bones, and blood.1 Staphylococcus aureus carries a large repertoire of virulence factors, including over 40 secreted proteins and enzymes that it uses to establish and maintain infections.2,3 Some of these virulence factors are know to cause or be associated with specific diseases, for example, toxic shock syndrome toxin (TSST) and toxic shock syndrome; Panton-Valentine leukocidin (PVL) and necrotizing pneumonia and skin diseases4,5; the exfoliative toxins A and B (ETA and ETB) and scalded skin syndrome, impetigo, skin infections, and atopic dermatitis6,7; and the family of staphylococcal enterotoxins A and B (SEA and SEB) and food poisoning.3

Also among these virulence factors are several toxins that have the potential to manipulate components of the immune response. These include leukotoxins that specifically affect white blood cells (WBC) (PVL and leukocidin D-E [LukD-E]); toxins that function as superantigens that can manipulate the immune system by hyperstimulating the release of cytokines (SEA, SEB, and TSST); and hemolysins that are active to lyse red blood cells and WBCs as well as other cell types, as described by Foster.8

To our knowledge, an association of WBCs in infected skin lesions and the presence of bacteria capable of producing potentially immunomodulating toxins has not been reported. Our hypothesis is that the presence of immunomodulating or cytotoxic virulence factors produced by certain bacterial pathogens in infected skin lesions will have an effect on the number of WBCs associated with secondarily infected skin lesions. In the present study, S. aureus cultures isolated from second-
arily infected skin lesions were evaluated for their potential ability to produce immune system–modulating toxins by identification of the encoding genes using polymerase chain reaction (PCR). The association of these virulence factors with the level of localized WBC response was determined.

**METHODS**

**BACTERIAL COLLECTION**

Swab specimens of infected skin lesions were obtained for bacterial culture and gram staining, and photographs were taken from 105 patients at a single geographical location after institutional review board approval and appropriate informed patient consent were obtained. Specimens were processed by a centralized laboratory. Slides were prepared for light microscopy, and bacterial and WBC counts per low-power field (LPF) were determined. Bacterial isolates including *S aureus* and *Streptococcus* species were obtained from 85 of 105 lesions. Seventy-two isolates were determined to be *S aureus* by standard identification methods and PCR detection of *S aureus*–specific *gyrA* gene. These 72 isolates were considered in the analysis of virulence factors associated with *S aureus* from infected skin lesions. Sixty-one of the 72 bacteria were isolated without coinfecting streptococci and were divided into 2 groups according to corresponding WBC count in the lesions and considered in the analysis of the effect of *S aureus* infection on the presence of localized WBCs.

**DNA ISOLATION**

Chromosomal DNA samples were obtained from each of the 84 bacterial isolates collected. DNA was prepared using a DNeasy tissue kit (Qiagen, Valencia, California) according to the manufacturer’s recommendations and with the addition of lysozyme to aid in the lysis of *Staphylococcus* species. The DNA was collected in 10mM Tris–hydrochloric acid. Concentrations of DNA were determined using a Quant-iT dsDNA BR or Qubit Fluorometer (Invitrogen, Carlsbad, California). The quality of the chromosomal DNA was confirmed by agarose gel electrophoresis using 0.8% gels, with ethidium bromide staining. Samples of DNA were diluted for consistent concentrations to determine the presence or absence of selected virulence genes of interest, and the results for all toxin genes were reported in eTable 2 (available at http://www.archdermatol.com). Individual reaction conditions were optimized for each oligonucleotide primer pair with gradient control templates to establish best reaction conditions. Real-time PCR reactions were carried out in a 96-well plate format using iCycler iQ PCR plates with Microseal “B” Film optically clear adhesives (Bio-Rad Laboratories). Thermal cycling was done in an iCycler, and detection was performed by an iCycler IQ Optical Module. Each unknown sample reaction plate contained duplicate samples and appropriate positive and negative controls for each toxin gene. The PCR reactions were done in 25-µL volumes containing iQ SYBR Green Supermix (Bio-Rad Laboratories), appropriate forward and reverse primers at a final 0.2µM concentration each with 1 to 10 ng of DNA template and nuclease-free water. Cycling reaction conditions were those optimized for each individual toxin primer pair. The real-time cycle threshold (Ct) curves were monitored, and data were collected at the end of each run. Corresponding melting temperature curves were determined for each sample for PCR product confirmation. The test for the presence of toxin genes was considered positive for an isolate with a Ct within 6 cycles of control Ct and an appropriate melting curve. Selected samples were further confirmed by agarose gel electrophoresis on 4% agarose gels. Control chromosomal DNA samples were obtained from our standard laboratory controls (CLP001-eta, CLP007-eth, and CPM003-seb) or strains provided by the Network on Microbial Resistance in *S aureus* (NRS384-pvl, -mecA, and -cha [CHIP]; NRS385-hla; NRS383-sea and -gyrA; and NRS178-luk-D-E).

**REAL-TIME PCR REACTIONS FOR IDENTIFICATION OF *S AUREUS*–SPECIFIC GENES**

Real-time PCR analyses were preformed on all bacterial isolates to determine the presence or absence of selected virulence or control genes. Seventy-two isolates were determined to be *S aureus* by standard identification methods and PCR detection of the *S aureus*–specific *gyrA* gene. The selected genes encoding α-hemolysin (*hla*), *PVL* (pvl), LukD-E (lukD-E), *SEA* (sea), *SEB* (seb), *TSST* (tst), *ETA* (eta), ETB (etb), and methicillin resistance (*mecA*) and chemotoxins-inhibiting protein (CHIP) (*chs*) were determined using real-time PCR with confirming melt curves and agarose gel visualization of selected DNA products for confirmation. The gene encoding *S aureus* DNA gyrase A (*gyrA*) was included as a positive control for PCR reactions. Oligonucleotide primer pairs used were either those used currently in our laboratory or were designed for this study using the Beacon Designer for Real-Time PCR Assay Design (Bio-Rad Laboratories, Hercules, California) (eTable 1; available at http://www.archdermatol.com). All 72 isolates were analyzed for the presence of *S aureus* virulence factor genes associated with skin infections without consideration of a localized immune response. The numbers of *S aureus* carrying the

**STATISTICAL ANALYSIS**

The prevalence of specific toxin genes associated with the 72 total *S aureus* isolates from infected skin lesions was calculated without regard to associated WBC counts determined at the time of culture. The prevalence of the toxin genes carried by the 61 bacterial isolates from the *S aureus* only–infected lesions was determined in the low (<5 WBCs/LPF) and high (>5 WBCs/LPF) WBC groups and compared using χ² analysis. Significance was defined as P < .05.

**RESULTS**

*Staphylococcus aureus*, either exclusively or in combination with *Streptococcus pyogenes* (Lansfield group A streptococci [GAS]), group G streptococci (GGS), or group C streptococci (GCS) was isolated from 72 of 105 skin lesions determined to be infected by clinical evaluation (69%). Sixty-one of these lesions were determined to be infected with *S aureus* as a single causative organism (58%). White blood cell counts on the initial swab specimens taken for culture were determined per LPF for each lesion. Bacterial isolates were collected and correlated with the respective WBC count and separated into 2 groups, those associated with a low WBC count (0–5 WBC/LPF) and those associated with a high WBC count (>5 WBC/LPF). The presence or absence of *S aureus* genes associated with virulence and with the potential to modulate the host’s immune response were determined by real-time PCR using oligonucleotide primers specific for the genes of interest, and the results for all *S aureus* isolates are reported in eTable 2 (available at http://www.archdermatol.com). All 72 isolates were analyzed for the presence of *S aureus* virulence factor genes associated with skin infections without consideration of a localized immune response. The numbers of *S aureus* carrying the
genes for the exfoliative toxins ETA and ETB and PVL were increased ($P < .001$ for ETA and ETB and $P = .049$ for PVL) compared with the expected community prevalence, while the numbers of isolates encoding TSST ($P < .001$) and SEA ($P = .005$) were significantly decreased (Table).13-18 Coding for all other genes showed no significant difference in prevalence vs that previously reported for each. These data indicate that $S$ aureus associated with skin lesions are more likely to carry the genes for ETA, ETB, and PVL and less likely to carry the genes for SEA and TSST.

To determine if an association exists between $S$ aureus virulence factors and the local immune response as indicated by the number of WBCs in an infected skin lesion, the 61 bacterial isolates from $S$ aureus only–infected lesions were divided into 2 groups, those associated with low WBC counts and those associated with high WBC counts and compared. Comparison of the presence of virulence genes carried by the bacteria isolated from the lesions in the low WBC vs the high WBC group demonstrated a difference in these bacterial populations (Figure 1 A). $S$ aureus capable of producing ETA ($P = .006$) and ETB ($P = .002$) were significantly associated with infections with low WBC counts in the lesions, while those organisms capable of producing PVL ($P = .03$) were associated with infections with high WBC counts on initial gram stain of swabs for culture. Analysis of the low WBC population alone (44 isolates) showed that the number of $S$ aureus carrying the genes for ETA and ETB were significantly increased ($P < .001$ for both) in this subset, while the number of isolates encoding SEA ($P = .03$) were significantly decreased compared with the expected community prevalence Figure 1B. Similar analysis of the high WBC population alone (17 isolates) revealed no statistically significant differences in the prevalence of virulence factors in this population compared with the expected prevalence Figure 1C.

Comparisons of the clinical appearance of individual skin lesions associated with each WBC subset showed no apparent differences between the low and high WBC groups (Figure 2) despite the significant difference in associated infecting bacterial populations. Physical examination findings of all lesions were consistent with a significant bacterial skin infection, and so all lesions were

### Table. Prevalence of Virulence Factors of Staphylococcus aureus Isolated From Infected Skin Lesions Compared With Community Prevalence

<table>
<thead>
<tr>
<th>Source</th>
<th>Virulence Factor</th>
<th>Community, %</th>
<th>Study, % (No.) (N=72)</th>
<th>$P$ Value</th>
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</thead>
<tbody>
<tr>
<td>Larsen et al14 and Dancer and Noble15</td>
<td>ETA</td>
<td>5</td>
<td>43 (31)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Larsen et al14 and Dancer and Noble15</td>
<td>ETB</td>
<td>5</td>
<td>39 (28)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>Becker et al16</td>
<td>SEB</td>
<td>7</td>
<td>13 (9)</td>
<td>.26</td>
</tr>
<tr>
<td>Prevost et al17</td>
<td>PVL</td>
<td>2</td>
<td>11 (8)</td>
<td>.049</td>
</tr>
<tr>
<td>Peacock et al18</td>
<td>SEA</td>
<td>17</td>
<td>3 (2)</td>
<td>.005</td>
</tr>
<tr>
<td>Peacock et al18</td>
<td>TSST</td>
<td>25</td>
<td>4 (3)</td>
<td>$&lt; .001$</td>
</tr>
<tr>
<td>de Haas et al13</td>
<td>CHIP</td>
<td>62</td>
<td>75 (54)</td>
<td>.11</td>
</tr>
</tbody>
</table>

Abbreviations: CHIP, chemotaxis-inhibiting protein; ETA, exfoliative toxin A; ETB, exfoliative toxin B; PVL, Panton-Valentine leukocidin; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; TSST, toxic shock syndrome toxin.
selected for culture and gram staining. Of the 105 total lesions sampled, 21 (20%) failed to have any associated bacteria by culture. Of the 80% of bacteria-positive lesions, 85% grew *S aureus* either alone or in combination with a *Streptococcus* species. Overall, of the skin lesions identified clinically as infected, 69% (n=72) were associated with growth of any *S aureus*, and 58% (n=61) were infected exclusively with *S aureus*.

**COMMENT**

*Staphylococcus aureus* is a common cause of local skin infections as well as many other serious infections. Infections caused by *S aureus* have been linked to a number of potential virulence factors made by the organism. These associations range from superficial skin infections such as bullous impetigo, associated with ETA and ETB, to the multiple-organ system failure associated with toxic shock syndrome and the organisms capable of making TSST. Many of the toxins and virulence factors of *S aureus* are known to have effects on the immune response, either directly by lysing WBCs (as in the actions of leukotoxins such as PVL) or indirectly by the actions of superantigens (such as TSST and several enterotoxins) stimulating the release of abnormally high concentrations of cytokines and chemokines and potentially leading to multiple-organ system failure. Other virulence factors (eg, CHIPS and *Staphylococcus complement inhibitor*13,19) function to prevent the influx of WBCs into an infected site.

In the present study we describe for the first time to our knowledge a direct association between the number of WBCs in a local skin infection and the toxin genes that the infecting *S aureus* carry. In this population taken as a whole, and as has been previously reported,6,7 there is a significant association of exfoliative toxin genes and *pvl* with skin infections. In addition, we demonstrate for the first time to our knowledge that this association can be categorized into 2 distinct infection groups: those with few to no WBCs in the skin lesions at the time the bacterial cultures were obtained (≤ 5 WBCs/LPF) and those with many WBCs associated with the lesions. We determined that the lesions with the fewest WBCs were more likely to be infected with *S aureus* capable of producing ETA or ETB, while the lesions with the most WBCs were more likely to be infected with an organism capable of producing PVL.

Comparisons of the physical appearance of the lesions associated with each WBC subset showed no apparent differences between the low WBC and high WBC groups. The appearances of all lesions were determined to be consistent with significant infections when the initial lesions were chosen for obtaining swabs for culture, and therefore appearance alone is not a good indicator of inflammatory cell involvement. Common dogma holds that for a superficial bacterial skin infection to be deemed significant it must be associated with a high WBC count from the lesion at the time the bacterial cultures are obtained.20 Findings of the present study indicate that the particular bacterial population involved in an infection might contribute greatly to the severity and quality of the local immune response and that the population of infecting bacteria with its associated repertoire of potential virulence factors contributes to the robustness of the immune response.

The relationship between the genes encoding ETA and ETB and the lack of WBCs in some of the lesions is not understood, and the exact mechanisms by which these toxins may be acting to either eliminate WBCs from the lesions or prevent their accumulation is likewise not known. The action of the exfoliative toxins to cause exfoliation of the skin by the cleavage of the cadherin family member protein desmoglein 1,2 thereby disrupting the desmosome
and destroying the cell-cell integrity in the upper epidermis, does not directly explain these findings. However, cadherin family member proteins are involved in a variety of cell signaling processes. It is possible that the cleavage of desmoglein 1 is directly or indirectly involved in modifying the signaling pathways that affect the local immune response. It has also been shown that ETA is capable of stimulating a specific population of murine T cells, which could also contribute to cytokine release and affect the local immune response.

An additional possibility is that the associated toxin genes and their products are not involved at all but serve as genetic markers for other virulence factors that are responsible. Such a situation exists for PVL and its association with necrotizing infections: under certain conditions it is clearly not always an accurate estimate of the seriousness of an infection—a major virulence factor contributing to disease, while in other infections it serves as a genetic marker for other virulence factors or specific bacterial populations. Given that these bacteria have the potential to express a number of immunomodulating factors, we argue that the measurement of the local immune response (WBC count) is not an accurate estimate of the seriousness of an infection in patients with staphylococcal toxic shock syndrome and staphylococcal scarlet fever.

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Author Contributions: Ms Mertz and Dr Plano had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mertz and Plano.

Acquisition of data: Cardenas, Snyder, Kinney, Davis, and Plano. Analysis and interpretation of data: Mertz, Cardenas, Snyder, and Plano. Drafting of the manuscript: Mertz and Plano. Critical revision of the manuscript for important intellectual content: Davis and Plano. Statistical analysis: Cardenas and Plano. Obtained funding: Plano. Administrative, technical, or material support: Cardenas. Study supervision: Mertz, Davis, and Plano.

Financial Disclosure: None reported.

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Additional Information: eTable 1 and eTable 2 are available at http://www.archdermatol.com.

Additional Contributions: Yvette Piovannetti, MD, Maria D. Ordriozola, MD, Kamara Mertz-Rivera, MS, CCRC, and Juan B Rivera, AA, collected the clinical samples.

REFERENCES

25. Mertz, Cardenas and Plano.
### eTable 1. Virulence Factors With Corresponding Sequences of Oligonucleotide Primers and Melting Temperatures Used for Real-Time PCR Determination of the Presence of the Corresponding Genes From *Staphylococcus aureus* Isolated From Infected Skin Lesions

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Abbreviations: CHIP, chemotaxis-inhibiting protein; ETA, exfoliative toxin A; ETB, exfoliative toxin B; gyrA, gyrase; HLA, α-hemolysin; LukD-E, leukocidin D-E; mecA, methicillin resistance; PCR, polymerase chain reaction; PVL, Panton-Valentine leukocidin; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; temp, temperature; TSST, toxic shock syndrome toxin.
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(continued)
### Table 2. Gene Distribution in *Staphylococcus aureus* from Infected Skin Lesions (cont)

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<th>CPM</th>
<th>WBC</th>
<th><em>hla</em> (HLA)</th>
<th><em>pvl</em> (PVL)</th>
<th><em>luk</em> D-E (LukD-E)</th>
<th><em>eta</em> (ETA)</th>
<th><em>etb</em> (ETB)</th>
<th><em>sea</em> (SEA)</th>
<th><em>seb</em> (SEB)</th>
<th><em>tst</em> (TSST)</th>
<th><em>chs</em> (CHIP)</th>
<th><em>mecA</em></th>
<th><em>gyrA</em></th>
<th>Bacteria</th>
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Abbreviations: CHIP, chemotaxis-inhibiting protein; CPM, letter designation for this bacterial population; ETA, exfoliative toxin A; ETB, exfoliative toxin B; GGS, group G streptococci; gyrA, gyrase; HLA, α-hemolysin; LPF, low-power field; LukD-E, leukocidin D-E; mecA, methicillin resistance; MGAS, multiple organisms group A streptococci; MGCS, multiple organisms group C streptococci; MGGS, multiple organisms group G streptococci; NEG, negative findings; POS, positive findings; PVL, Panton-Valentine leukocidin; S, *Staphylococcus aureus*; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; TSST, Toxic shock syndrome toxin; WBC, white blood cell count.

*Yellow indicates low WBC count; blue, high WBC; green, gene presence; red, gene absence.*
Wound Complications Following Diagnostic Skin Biopsies in Dermatology Inpatients

Shyam Wahie, MB, MRCP; Clifford M. Lawrence, MD, FRCP

**Objectives:** To prospectively determine the wound complication rate for dermatology inpatients undergoing diagnostic skin biopsies during their admission and to determine significant host and procedural risk factors.

**Design:** Prospective assessment, by a single observer, of 100 postdiagnostic skin biopsy wounds in dermatology inpatients. The following data were recorded for each patient: age and sex, presence of comorbidities, smoking status, dermatologic diagnosis, use of immunosuppressive or antibiotic therapy, place of biopsy (whether in the operation theater or in the ward), grade of physician performing biopsy, biopsy site on the body, type of biopsy (whether elliptical incision, punch, shave, or curettage), and wound closure technique.

**Main Outcome Measure:** Wounds were designated as having had no complication or as being complicated by infection, dehiscence, and/or hematoma.

**Setting:** A dedicated dermatology inpatient ward in a university teaching hospital.

**Results:** Wound complications occurred in 29 (29%) biopsies, 27 (93%) of which were the result of wound infection. Complications occurred significantly more frequently when biopsies were performed below the waist compared with above the waist ($P < .02$), in the ward compared with the outpatient operating theater ($P < .001$), in smokers compared with nonsmokers ($P < .001$), and in those taking corticosteroids compared with those who were not ($P < .001$). In addition, elliptical incisional biopsies developed complications more frequently when subcutaneous sutures were not used compared with when they had been used ($P < .001$).

**Conclusions:** This study has demonstrated a high rate of wound complications after diagnostic dermatologic surgery on dermatology inpatients with significant host and procedural risk factors. These findings are relevant for other centers with inpatient units where diagnostic biopsies are performed.

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**Methods**

The study protocol was reviewed and approved by an independent review board and all study participants gave oral consent.

**Ward and Study Population**

The prospective study took place in the dermatology ward of the Newcastle-upon-Tyne Hospitals National Health Service Trust between January 15 and September 15, 2006. The ward is a 16-bed unit for adult patients with dermatologic disease, with dedicated cubicles for those colonized with methicillin-resistant *Staphylococcus aureus* (MRSA). Patients are admitted either electively or on an emergency basis after consultation with a dermatologist.

**Surveillance**

All dermatology inpatients who underwent diagnostic incisional and excisional skin biopsies during their hospital admission were prospectively assessed for postoperative wound...
complications. Diagnostic skin biopsies surveyed included elliptical incisions, punch incisions, shave biopsies, or curettage and cautery.

The following data were recorded by the operating physician for each patient: age and sex, presence of comorbidities (diabetes mellitus, MRSA, leg edema, obesity), smoking status, dermatologic diagnosis, and the use of immunosuppressive or antibiotic therapy at the time of the biopsy.

The following procedural data were also recorded: place of biopsy (whether in an examination room in the dermatology ward or in a dedicated outpatient operation theater), grade of physician performing biopsy (whether senior house officer, specialist registrar, or consultant), biopsy site on the body, type of biopsy (whether elliptical incision, punch, shave, or curettage), wound closure technique, and whether senior advice was given to the operating physician (on the type or site of biopsy or on wound closure).

One of us (S.W.) inspected and assessed each postoperative wound every 3 days until hospital discharge. Wounds were designated as having had either no complications or complications classified as wound infection (manifested by erythema, edema, warmth, and discharge of pus), wound dehiscence, and/or hemorrhoma.

Medical notes, microbiology reports, temperature, and treatment charts were also reviewed. At discharge, the dermatologist recorded whether the wound site had reepithelialized or required ongoing treatment in the community. Wounds were not routinely surveyed after discharge.

STATISTICAL ANALYSIS

A binomial test of 2 proportions was used to determine if independent variables were significantly associated with the development of wound complication. A multivariate analysis using binomial logistic regression was performed (using SPSS software version 12 [SPSS Inc, Chicago, Illinois]). All variables were fitted into a multivariate model and kept if they remained significantly associated with wound complication after adjusting for other factors in the model.

RESULTS

A total of 301 patients were admitted to the dermatology ward during the 8-month survey period and 75 of these patients (40 men and 35 women; median age, 62 years; range, 18-94 years) had a total of 100 diagnostic biopsies.

Twenty of the 100 diagnostic biopsies were performed on patients with diabetes, 22 on individuals colonized with MRSA, 5 on those with leg edema, 4 on obese individuals, 33 on smokers, and 19 on patients taking prednisolone at a dosage of more than 0.5 mg/kg/d. Twelve biopsies were performed on patients taking oral floxicillin or amoxicillin, which had been prescribed by their general practitioner before admission.

The dermatologic diagnosis was defined at the end of a patient’s admission. Twenty-eight biopsies were performed on patients with autoimmune blistering diseases, such as bullous pemphigoid (n = 23), pemphigus (n = 3), and linear IgA disease (n = 2). The remainder of the biopsies were performed for nonblistering conditions, such as eczema (n = 29), psoriasis (n = 25), leukocytoclastic vasculitis (n = 9), drug-induced eruptions (n = 5), skin cancers (n = 3), and lymphoma (n = 1).

Biopsies were performed in a dedicated examination room in the dermatology ward using a portable biopsy kit in 34 cases and in 1 of 3 dedicated outpatient operation theaters in the remaining 66 cases. The grade of physician carrying out the diagnostic biopsy included a senior house officer in the first month of dermatology training (23 biopsies), a senior house officer in the second to fourth month of dermatology training (55 biopsies), a specialist registrar with more than 24 months’ experience (18 biopsies), and a consultant (4 biopsies). Of the 100 biopsies, 75 were performed on sites above the waist (57 on the arm, 10 on the back, 5 on the chest, and 3 on the head and neck) and 25 were performed on sites below the waist (21 on the leg and 4 on the groin and genitals).

Fifty-six procedures were punch biopsies, 40 were elliptical incisions, 3 were shave biopsies, and 1 was a curettage. All punch and elliptical incisional biopsies were closed with interrupted surface sutures, but subcutaneous sutures were only used in 13 (33%) of the elliptical biopsies. The operating physicians indicated that senior advice, on either the type or site of biopsy or wound closure technique, was given in 35 of 90 cases. In 10 cases, these data were missing.

POSTBIOXY WOUND COMPLICATIONS

Wound complications occurred in 29 of the 100 diagnostic biopsies performed. Twenty-two wounds demonstrated clinical signs of infection alone, 2 of dehiscence alone, and 5 had signs of both infection and dehiscence. No wounds were complicated by hematoma.

In the 27 cases in which infection was clinically evident, positive bacterial isolates from wound swabs were isolated in 24 (S aureus in 15, Streptococcus species in 4, and MRSA in 5 cases). Of the 5 patients with MRSA wound infections, 4 were colonized with MRSA on admission. Twelve biopsies (6 ellipses and 6 punches) were performed on patients already taking antibiotics, of which half subsequently developed wound infections.

All 27 patients with wound infections were treated with topical and oral antibiotics according to the sensitivities from wound swabs. Consequently, 2 developed abnormal liver function, 2 developed noninfectious diarrhea; all 4 patients experienced a delay in their discharge. At discharge, 4 of 29 wounds that had developed a complication after the procedure still required treatment in the community.

The Table records the univariate analysis findings on the incidence and characteristics associated with all wound complications. Wound complications occurred significantly more frequently when biopsies were performed below the waist compared with above the waist (48% vs 23%, 95% confidence interval [CI] for difference, 36%-47%; P < .02); in the ward compared with the outpatient operation theater (53% vs 17%, 95% CI for difference, 17%-55%; P < .001); in smokers compared with nonsmokers (64% vs 12%, 95% CI for difference, 34%-70%; P < .001); and in those taking corticosteroids compared with those who were not (63% vs 21%, 95% CI for difference, 19%-66%; P < .001). In addition, elliptical incisional biopsies developed complications more fre-
quently when subcutaneous sutures were not used compared with when they had been used (70% vs 15%, 95% CI for difference, 29%-81%; \( P < .001 \)). Biopsies performed by senior house officers developed wound complications more frequently than those performed by specialist registrars and consultants (33% vs 14%, 95% CI for difference, 19%-37%) but the Fisher exact test did not show this difference to be statistically significant \( (P = .11) \).

No statistically significant correlations were demonstrated between wound complication and the age or sex of the patient, comorbidities (ie, MRSA, diabetes, leg edema, obesity) or dermatologic diagnosis. Similarly, no links were established between complications occurring and the provision of senior advice or the use of antibiotics.

Multivariate analysis by logistic regression did not demonstrate any single variable that was a significant risk fac-

### Table. Univariate Analysis of Characteristics Associated With Wound Complications

<table>
<thead>
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<th>Biopsy Sample</th>
<th>No. of Wound Complications (n = 29)</th>
<th>No. of Biopsies (n= 100)</th>
<th>Sample Proportions</th>
<th>95% Confidence Interval for Difference</th>
<th>Test for Difference</th>
<th>Fisher Exact Test (for Small Samples)</th>
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<td>Below waist</td>
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<td>0.48</td>
<td>0.04 to 0.47</td>
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<td>In ward</td>
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<td>0.17 to 0.55</td>
<td>&lt; .001</td>
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<td>0.02 to 0.37</td>
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<tr>
<td><strong>Elliptical biopsy</strong></td>
<td></td>
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</tr>
<tr>
<td>Without subcutaneous sutures</td>
<td>19</td>
<td>27</td>
<td>0.70</td>
<td>0.29 to 0.81</td>
<td>&lt; .001</td>
<td>.002</td>
</tr>
<tr>
<td>With subcutaneous sutures</td>
<td>2</td>
<td>13</td>
<td>0.15</td>
<td></td>
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<tr>
<td><strong>Smoking status</strong></td>
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<tr>
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<td>21</td>
<td>33</td>
<td>0.64</td>
<td>0.34 to 0.70</td>
<td>&lt; .001</td>
<td>NA</td>
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<td>Nonsmoker</td>
<td>8</td>
<td>67</td>
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<td><strong>Corticosteroid therapy</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Yes</td>
<td>12</td>
<td>19</td>
<td>0.63</td>
<td>0.19 to 0.66</td>
<td>&lt; .001</td>
<td>NA</td>
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<tr>
<td>No</td>
<td>17</td>
<td>81</td>
<td>0.21</td>
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<tr>
<td><strong>Advice to operator</strong></td>
<td></td>
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<tr>
<td>No senior advice</td>
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<td>55</td>
<td>0.35</td>
<td>-0.10 to 0.28</td>
<td>.37</td>
<td>NA</td>
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<td>Senior advice</td>
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<td>35</td>
<td>0.26</td>
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<tr>
<td><strong>Age, y</strong></td>
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<tr>
<td>( \geq 60 )</td>
<td>25</td>
<td>80</td>
<td>0.31</td>
<td>-0.09 to 0.32</td>
<td>.28</td>
<td>.42</td>
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<td>( &lt; 60 )</td>
<td>4</td>
<td>20</td>
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<tr>
<td><strong>MRSA</strong></td>
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<tr>
<td>Positive</td>
<td>5</td>
<td>22</td>
<td>0.23</td>
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<td>0.31</td>
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<td>Yes</td>
<td>3</td>
<td>20</td>
<td>0.15</td>
<td>-0.36 to 0.01</td>
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<td>.17</td>
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<td>No</td>
<td>26</td>
<td>80</td>
<td>0.33</td>
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<td><strong>Blistering disease</strong></td>
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<td>11</td>
<td>28</td>
<td>0.39</td>
<td>-0.07 to 0.35</td>
<td>.20</td>
<td>NA</td>
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<td>No</td>
<td>18</td>
<td>72</td>
<td>0.25</td>
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<td><strong>Obese</strong></td>
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<tr>
<td>Yes</td>
<td>2</td>
<td>4</td>
<td>0.50</td>
<td>-0.28 to 0.72</td>
<td>.39</td>
<td>.58</td>
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<tr>
<td>No</td>
<td>27</td>
<td>96</td>
<td>0.28</td>
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<td><strong>Antibiotic therapy</strong></td>
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<tr>
<td>Yes</td>
<td>6</td>
<td>12</td>
<td>0.50</td>
<td>-0.06 to 0.54</td>
<td>.12</td>
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<tr>
<td>No</td>
<td>23</td>
<td>88</td>
<td>0.26</td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
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<tr>
<td>Female</td>
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<td>55</td>
<td>0.26</td>
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<tr>
<td><strong>Leg edema</strong></td>
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<tr>
<td>Present</td>
<td>1</td>
<td>5</td>
<td>0.20</td>
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<td>.61</td>
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<tr>
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<td>28</td>
<td>95</td>
<td>0.30</td>
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</table>

Abbreviations: MRSA, methicillin-resistant Staphylococcus aureus; NA, not available.
tor for wound complications. This is likely to be explained by the low number of trial events (n=29) and the large number of variables being investigated.

COMMENT

To our knowledge, this is the first study describing the incidence and risk factors for wound complications after diagnostic skin biopsies in a dermatology inpatient population.

We have shown that 29 (29%) diagnostic biopsies performed on inpatients resulted in a postoperative complication, 27 (93%) of which were due to wound infection. All the infections resulted in the need for antibiotics and their use led to a delay in discharge in 4 (15%) treated patients.

Univariate analysis demonstrated that cigarette smoking and the use of corticosteroids appeared to be the most significant host risk factors contributing to the development of wound complications. The most significant procedural risk factors for wound complication were biopsy sites below the waist, performing the biopsy in the ward rather than in the operation theater, and not using subcutaneous sutures after elliptical procedures.

Logistic regression analysis showed no single significant risk factor, possibly because only 29 wound complications were identified. A larger study including more complications might have increased the power of the analysis.

Data were not collected on the duration of the biopsy procedure or on the use of antiplatelet or anticoagulant therapy; these factors may have also been relevant to the development of wound complications.

Smoking has been shown to be an important risk factor for wound complications after mastectomy, abdominalplasty, and full-thickness skin grafts, with heavy smokers being most at risk. Nicotine in cigarette smoke is a vasoconstrictor that causes tissue ischemia and impairs healing of injured tissue. Amici et al noted a significant association between immunosuppressants and wound complications after excisional dermatologic surgery, but did not specify which immunosuppressant drugs were involved.

Our study investigated wound complications solely associated with diagnostic skin biopsies. Previous authors have concentrated predominantly on the complications of excisional surgery (eg, for melanomas and nonmelanoma skin cancers) performed in an outpatient department setting. Dermatology inpatients differ significantly from outpatients in that inpatients are more likely to have widespread skin disease possibly colonized with *S aureus* to be systemically unwell, and to require intensive topical therapy and observation. It is, therefore, not surprising that the rate of infectious complications in these studies of excisional surgery is far lower than in our present study. The preoperative state of the skin is clearly important. Weatherhead and Lawrence previously demonstrated (in a prospective case-control study of day-case patients) that 17% developed wound infection after excisional surgery when the overlying skin was ulcerated before surgery compared with 4% when the skin was intact.

### CONCLUSIONS

Our study has demonstrated a high rate of wound complications after diagnostic dermatologic surgery performed on inpatients with significant host and procedural risk factors. These findings may be relevant for other regional centers with inpatient units in which diagnostic biopsies are frequently performed by junior physicians. Further larger studies will be necessary to confirm these results and establish local (and possibly even national) guidelines regarding diagnostic biopsies in dermatology inpatients.

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Author Contributions: Study concept and design: Wahie and Lawrence. Acquisition of data: Wahie. Analysis and interpretation of data: Wahie and Lawrence. Drafting of the manuscript: Wahie and Lawrence. Critical revision of the manuscript for important intellectual content: Wahie and Lawrence. Statistical analysis: Wahie. Study supervision: Lawrence.

Financial Disclosure: None reported.

Additional Contributions: Tom Chadwick, PhD, Institute of Health and Society, Newcastle University, gave advice on analysis of data.
REFERENCES


Association Between the Use of β-Adrenergic Receptor Agents and the Development of Venous Leg Ulcers

David J. Margolis, MD, PhD; Ole Hoffstad, MA; R. Rivkah Isseroff, MD

Objective: To explore an association between the use of β-adrenergic receptor agonists or antagonists and the onset of venous leg ulcers (VLUs).

Design: Retrospective cohort study.

Setting: Ambulatory setting of general practice in the United Kingdom.

Patients: Patients followed by participating physicians.

Main Outcome Measure: Onset of VLU.

Results: A total of 414,887 patients registered in the General Practice Research Database met our study criteria for eligibility. Of these individuals, 62,886 were exposed to a β-adrenergic receptor agonist and 54,861 were exposed to a β-adrenergic receptor antagonist (6,620 used both β-adrenergic receptor antagonists and agonists). Of those exposed to a β-adrenergic receptor agonist, 15.5% developed a VLU, whereas 18.4% of those who were not exposed developed a VLU. Of those exposed to a β-adrenergic receptor antagonist, 18.2% developed a VLU, whereas 19.9% of those not exposed developed a VLU. The odds ratio (OR) of association between β-adrenergic receptor antagonist and VLUs was 1.02 (95% confidence interval [CI], 0.99-1.04); for the association between β-adrenergic receptor agonist and VLUs, 0.84 (95% CI, 0.82-0.86). The fully adjusted ORs were 1.04 (95% CI, 0.98-1.11) and 0.44 (95% CI, 0.42-0.45), respectively. Furthermore, using propensity score models, we were able to confirm the association for β-adrenergic receptor agonist users. In addition, β-adrenergic receptor antagonist users in many of the propensity score quintiles were also protected from developing VLUs.

Conclusions: A protective association between β-adrenergic receptor agonists and perhaps β-adrenergic receptor antagonists and VLUs exists. There is strong laboratory evidence to support these epidemiologic findings. The evidence in this study should not be used as a rationale for treatment of VLUs with β-adrenergic receptor agents but should be compelling for the consideration of a randomized clinical trial.

Arch Dermatol. 2007;143(10):1275-1280
Recent laboratory work has provided evidence to support a role for the β-adrenergic receptor in cutaneous wound repair. Specifically, β-adrenergic receptor agonists decrease the rate of keratinocyte migration in vitro, impair the ability of cultured keratinocytes to repair a scratch wound in a confluent monolayer, delay wound epithelialization in organ-cultured human skin wounds, and inhibit wound healing in vivo in a murine wound model.4 5 β-Adrenergic receptor antagonists, however, increase cultured keratinocytes’ migratory speed and their ability to heal a scratch wound in vitro, speed up wound healing in organ-cultured human skin, and improve wound epithelialization in vivo in murine wounds.9,10

Thus, one might anticipate that in patients who use β-adrenergic receptor agonists, there might be a deleterious effect on the propensity of those patients to heal wounds and, therefore, an increased incidence of chronic, nonhealing wounds. However, complicating the assumed association is the additional finding that although β-adrenergic receptor agonists impair many aspects that contribute to wound epithelialization, they can improve fibroblast function in the healing wound by increasing both fibroblast proliferation and migratory rates. Essentially, agonists have opposite effects on keratinocytes and dermal fibroblasts.8 Thus, one could also reasonably envision a clinical scenario, like lipodermatosclerosis, which is a skin sign associated with VLUs and is likely caused by chronic inflammation, destruction, wounding, and scarring of the dermis and fat layer, where wound repair is mostly dependent on fibroblast function. In this scenario, by virtue of their fibroblast stimulatory effects, administration of β-adrenergic receptor agonists might improve wound repair or prevent lipodermatosclerosis, thereby preventing the onset of a VLU. And, one would thus reasonably propose that systemic administration of either β-adrenergic receptor antagonists or agonists as commonly administered for the treatment of asthma, hypertension, or after a myocardial infarction might have an effect on the onset of nonhealing wounds, such as VLUs. In fact, in an earlier study12 on the incidence and prevalence of VLUs, we did notice unexplainable associations between patients with VLUs and those with asthma or congestive heart failure, angina, or myocardial infarction (diseases classically treated with β-adrenergic receptor agonists or antagonists) and the onset of a VLU.

Venous leg ulcers occur in about 1% of the population older than 45 years.12,13 Most are preceded by varicosities, leg edema, and lipodermatosclerosis.14 For those with lipodermatosclerosis, it is therefore likely that a VLU is really the outcome of repetitive wounding of the dermis that ultimately penetrates the epidermis. We have previously used this logic to demonstrate that estrogen, which have been shown in the laboratory to enhance wound repair, likely clinically promote healing too because those who use them are less likely to develop a VLU.15

Our current study was, therefore, undertaken to determine whether an epidemiologic association could be established in patients using β-adrenergic receptor agonists or antagonists and the incidence of chronic wounds.

STUDY POPULATION

This was a retrospective cohort study consisting of individuals registered in a large patient-record database called the General Practice Research Database (GPRD). Established in the United Kingdom in 1987, the GPRD is a medical records database used by general practitioners (GPs) as their primary means of tracking patient clinical information. We were provided access to the GPRD by the Epidemiology and Pharmacology Information Core (London, England). The GPRD GPs receive both financial inducements and penalties to ensure compliance with providing information in this electronic record. Approximately 1500 GPs representing 500 practices across the United Kingdom participated in the GPRD between 1987 and 2002. Patients were eligible to enroll in our study if they had been registered with a GPRD GP during this period. The total GPRD population available exceeds 9 million patients with over 35 million person-years of follow-up.

PATIENT ELIGIBILITY

A GPRD-registered patient was eligible for our study if (1) they received care from a GP who is a member of the GPRD, (2) they had at least 2 consultations with the GP while they were 40 to 95 years of age, and (3) they did not have a diagnosis of a VLU for the first 6 months after the commencement of their database record. The 6-month period was based on several lines of clinical evidence and was previously evaluated by us.12,13 Participants maintained their eligibility until they died or transferred out of the practice, or if the practice stopped contributing data to the GPRD.

DEFINITION OF OUTCOME, EXPOSURES, AND CONFOUNDERS

Diseases are classified in the GPRD database using a hierarchical coding system called Read codes. For this study, an eligible patient was considered to have a diagnosis of VLU using an explicit and previously evaluated (by direct query of the GP) algorithm consistent with the clinical diagnosis of VLU.12 This algorithm also excludes those with lower extremity peripheral arterial disease. For a VLU to be termed associated with the use of a β-adrenergic receptor agent, it must have occurred in an eligible study participant at least 90 days after exposure to the agent, and for a VLU to be an outcome in those who did not use a β-adrenergic receptor agent, once eligible, the participant had to have been followed for at least 120 days (minimum time between receipt of 2 prescriptions and 90-day period of association).13 A participant’s use of β-adrenergic receptor agonist or antagonist therapy was determined using the British National Formulary coding system. Separate variables were created for exposure to β-blocking antagonists and β-adrenergic receptor agonists. All individuals needed to have received at least 2 prescriptions separated by at least 30 days to be deemed exposed. All medications dispensed by a GPRD GP are coded in this system because GPs need to be compliant with NHS electronic prescription regulations.

β-Adrenergic receptor agents may be used to treat or prevent many medical conditions, and their use may vary by sex and age. These ailments and other illnesses were evaluated as potential confounders. As a result, the following variables were captured as potential confounders: age; sex; and history of angina, asthma, congestive heart failure, diabetes mellitus, emphysema, glaucoma, hypertension, or myocardial infarction.
Two-way interaction terms were also evaluated and were considered to be clinically important or statistically important variables (based on a P value of <.10 in the single-variable model) in a logistic model. Age was evaluated both as a continuous variable and in deciles. The effects on the OR were identical, and for simplicity they are reported only as a continuous variable. Two-way interaction terms were also evaluated and were considered to be statistically significant at P < .10. Reported P values are for the Wald statistic or z statistic, calculated as the estimated coefficient divided by its standard error. We used Mantel-Haenszel models to estimate relative risks (RRs).

Evaluation of the appropriateness of the fully adjusted model included analyses for outliers, collinearity, tolerance and covariance, goodness-of-fit, and discrimination. In all cases, the appropriateness of the logistic regression model was confirmed.

### Propensity Score

To further explore our observations and to attempt to control for treatment selection bias, we also used propensity score methods. Basically, because treatment selection in cohort studies is not random but rather determined by the GP, selection bias could arise if the choice of therapy depends on patient factors related to the probability that a wound will occur. For example, if clinically everyone with asthma who has leg edema uses drug A and leg edema is associated with a VLU, then treatment selection for drug A would be biased toward those with leg edema and also a VLU. One of the important reasons for performing a randomized controlled trial is that it can essentially eliminate treatment selection bias because selection is determined by the randomization procedure. The propensity score technique can be used to statistically model treatment selection, thereby minimizing selection bias attributable to observed covariates. Propensity score techniques mimic the random assignment of a randomized controlled trial by balancing important variables involved in the selection of a therapy between those who received and those who did not receive a treatment.\(^{16,17}\)

For the current study, separate covariates were included if they were hypothesized to affect the selection of a patient to receive either of the β-adrenergic receptor antagonists. All of the covariates listed in the “Definition of Outcome, Exposures, and Confounders” subsection as potential confounders were included in these models. The ability of the model to discriminate between those who received 1 of the 2 agents and those who did not was estimated by the area under the receiver operating characteristic curve.

Patients were stratified into quintiles based on the distribution of propensity scores. Quintile-specific rates for the development of a VLU were calculated for those who used a β-adrenergic receptor antagonist and those who did not. An overall estimate of the association of the agent with the onset of a VLU was then calculated by summarizing the stratum (quintile) specific RRUs using a Mantel-Haenszel technique. Before combining the quintile-specific data into a summary score, we used the Q-statistic for heterogeneity to determine whether the size of the treatment effect varied across quintiles. Finally, to estimate the summary of effectiveness in the setting of confounding and effect modification, multivariable logistic regression models were used.

Statistical analyses were conducted using Stata statistical software for Windows XP (version 9.2; StataCorp, College Station, Texas). This study was reviewed by the institutional review board of the University of Pennsylvania and previously reviewed by the Scientific and Ethical Advisory Group of the United Kingdom.

### Results

A total of 414,887 GPRD-registered patients met our study criteria for eligibility (Table 1). Their mean (SD) age was 61.8 (14.1) years (95% CI, 61.8-61.9) and the median age was 61 years (range, 49-73 years). With respect to sex, 240,592 (58%) were female, and 174,295 (42%) were male. Of these individuals, 62,886 were exposed to a β-adrenergic receptor antagonist and 54,861 were exposed to a β-adrenergic receptor agonist (6620 used both β-adrenergic receptor antagonists and agonists). Of those exposed to a β-adrenergic receptor agonist, 15.5% developed a VLU, whereas 18.4% of those not exposed developed a VLU (Table 1). Of those exposed to a β-adrenergic receptor antagonist, 15.5% developed a VLU, whereas 19.9% of those not exposed developed a VLU (Table 1). The OR of association between β-adrenergic receptor agonist use and VLUs was 1.02 (95% CI, 0.99-1.04). The OR of association between β-adrenergic receptor agonist and VLUs was 0.84 (95% CI, 0.82-0.86). As has been previously shown,\(^{12}\) those who developed a VLU were more likely to be older (the percentage with a VLU increased from younger to older age groups, P < .001) and female (P < .001).

Several multivariate analyses were conducted (Table 2). The relationship between β-adrenergic receptor antagonist use and VLUs was not notably confounded by (ie, altered point estimate by more than 10%) other covariates (Table 2) (see the “Definition of Outcome, Exposures, and Confounders” subsection in the “Methods” section for the listing of potential confounders). Indeed, the fully adjusted OR (adjusted for sex; age;
and history of myocardial infarction, hypertension, angina, or congestive heart failure) was 1.04 (95% CI, 0.98-1.11). The relationship between β-adrenergic receptor agonist use and VLUs was confounded (changed the point estimate of the unadjusted model by more than 10%) by asthma and prior oral or inhaled glucocorticoid use. The adjusted OR (adjusted by sex, age, and history of asthma and glucocorticoid use) was 0.44 (95% CI, 0.42-0.45), meaning that those who used β-adrenergic receptor agonists were about 66% less likely to develop a VLU. This indicates that the use of glucocorticoids and a history of asthma masked the protective association of β-adrenergic receptor agonist use on the onset of a VLU. Finally, the most frequently used β-adrenergic receptor agonist in our data set was salbutamol (also known as albuterol). The fully adjusted OR for comparing users of β-adrenergic receptor agonist had an area under the receiver operating characteristic curve of 0.83. Using the Mantel-Haenszel technique to combine the quintiles, the propensity score RR summary for β-adrenergic receptor agonist use was 0.76 (95% CI, 0.75-0.78). Clinically important heterogeneity was not noted. For both of our models, important covariates were equally balanced between groups within each quintile.

<table>
<thead>
<tr>
<th>Propensity Score</th>
<th>β-Adrenergic Receptor Agonist</th>
<th>β-Adrenergic Receptor Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile 1</td>
<td>0.59 (0.55-0.64)</td>
<td>0.93 (0.87-0.99)</td>
</tr>
<tr>
<td>Quintile 2</td>
<td>0.71 (0.65-0.78)</td>
<td>0.61 (0.56-0.66)</td>
</tr>
<tr>
<td>Quintile 3</td>
<td>0.50 (0.46-0.54)</td>
<td>0.64 (0.58-0.71)</td>
</tr>
<tr>
<td>Quintile 4</td>
<td>0.30 (0.45-0.56)</td>
<td>0.39 (0.35-0.43)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>0.87 (0.85-0.89)</td>
<td>1.52 (1.48-1.55)</td>
</tr>
<tr>
<td>Unadjusted RRb</td>
<td>0.84 (0.82-0.86)</td>
<td>1.02 (0.99-1.04)</td>
</tr>
<tr>
<td>Mantel-Haenszel combined RRsc</td>
<td>0.76 (0.74-0.78)</td>
<td>1.11 (1.09-1.14)</td>
</tr>
</tbody>
</table>

a Data are given as RR (95% confidence interval).

b The unadjusted RR is based on the full data set without grouping by propensity score strata.

c The Mantel-Haenszel technique to combine the RRs across strata.

However, there is notable heterogeneity in this estimate in that individuals in propensity quintile subgroups 1 to 4 did seem to have a protective association with respect to drug exposure and VLUs (Table 3) (eg, group 4: RR, 0.39 [95% CI, 0.35-0.43]). In group 5, which comprises those most likely to receive a β-adrenergic receptor antagonist, those who used a β-adrenergic antagonist were at increased risk for developing a VLU. For β-adrenergic receptor agonist use, our propensity score for the selection of exposure to a β-adrenergic receptor antagonist had an area under the receiver operating characteristic curve of 0.83. Using the Mantel-Haenszel technique to combine the quintiles, the propensity score RR summary for β-adrenergic receptor agonist use was 0.76 (95% CI, 0.75-0.78). Clinically important heterogeneity was not noted. For both of our models, important covariates were evenly balanced between groups within each quintile.

Table 2. Odds Ratios (ORs) for the Association Between the β-Adrenergic Receptor Agent and the Onset of a Venous Leg Ulcer

<table>
<thead>
<tr>
<th>Type of OR</th>
<th>β-Adrenergic Receptor Agonist</th>
<th>β-Adrenergic Receptor Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.84 (0.82-0.86)</td>
<td>1.02 (0.99-1.04)</td>
</tr>
<tr>
<td>Fully adjusted</td>
<td>0.44 (0.42-0.45)</td>
<td>1.04 (0.98-1.11)</td>
</tr>
</tbody>
</table>

a Data are given as OR (95% confidence interval); ORs were estimated using logistic regression.

b The fully adjusted OR for β-adrenergic receptor agonist use includes sex, age, and history of asthma and glucocorticoid use.

c The fully adjusted OR for β-adrenergic receptor antagonist use includes sex, age, and history of myocardial infarction, hypertension, angina, or congestive heart failure.

Laboratory investigations have suggested that β-adrenergic receptors may be involved in cutaneous wound repair. β-Adrenergic receptors are present on keratinocytes and fibroblasts of the skin; however, their effects on keratinocytes and fibroblasts differ.9,10 In our current study, we have shown that those exposed to β-adrenergic receptor agonists are less likely to develop a VLU. This effect was noted in a propensity score model as well. We were unable to find a consistent association between the use of β-adrenergic receptor antagonist using multivariable logistic regression and the onset of a VLU. However, in our propensity score model we were able to demonstrate that a protective effect was noted in many of the propensity deciles (Table 2). This suggests that in a subset of patients, β-adrenergic receptor antagonists may also provide some protective effect.

Previous work9,10 in our laboratory has shown that β-adrenergic receptor antagonists increase cultured keratinocyte migratory speed and their ability to heal a scratch wound in vitro, speed up wound healing in organ-cultured human skin, and improve wound epithelialization in vivo in murine skin wounds. Although we were able to show in our propensity score study that some individuals who received β-adrenergic receptor antagonists were less likely to develop a VLU (Table 3; 2, 3, and 4), our adjusted estimate does not show a protective effect. This apparent heterogeneity may have 2 simple clinical explanations. First, we and others 11,18,19 have previously shown that subtle peripheral vascular (arterial) disease of the lower extremity (eg, a lower limb ankle-brachial index of 0.7-0.9) is a risk factor for the development and healing of a VLU. As noted, the individuals in group 5 were the ones most likely to use β-adrenergic receptor antagonists, which means that they are also most likely to have hypertension and atherosclerotic vascular disease of the heart. These are also, therefore, individuals at highest risk for peripheral vascular disease, which, when subtle, we know from experience cannot be properly ascertained in this database.12 As a result, the RRs that we note in group 5 may be caused by residual confounding. Second, genetic polymorphisms commonly exist for β-ad-
renergic receptor agents. These polymorphisms have been shown to have an effect on the regulation of the receptor itself. It is entirely possible that the effects of this agent depend on the genetic polymorphism that is present and that our heterogeneity has a genetic basis.

However, β-adrenergic receptor agonists increase both the migration and proliferative rate of dermal fibroblasts, and it is likely that this cell type is the one that is initially damaged in patients with lipodermatosclerosis. Thus, β-adrenergic receptor agonists could be predicted to enhance the repair process of the woundlike environment of early lipodermatosclerotic lesions and thus prevent overlying ulceration. There is also evidence that implicates β-adrenergic receptor activation with enhancement of angiogenesis. Thus, in addition to their function on dermal fibroblasts, β-adrenergic receptor agonists could improve chronic wounds by up-regulating their vascularization. Furthermore, inflammation plays an important part in the pathogenesis of lipodermatosclerosis and chronic VLUs.11,14 Thus, β-adrenergic receptor agonists could improve chronic wounds by up-regulating their chemotaxis and recruitment, their ability to adhere to the endothelium, and their ability to generate reactive oxygen species and cytokine inflammatory mediators. Therefore, either by its effects on dermal fibroblasts, angiogenesis, or on the inflammatory process, the systemic administration of β-adrenergic receptor agonists may decrease the individual’s propensity to develop a nonhealing venous ulcer.

All observational studies may be limited by bias and confounding. Treatment selection bias is a critical concern when evaluating the efficacy of a medication in a study that does not randomly allocate treatment. Although the ultimate proof of the effectiveness of β-adrenergic receptor agents in wound repair will require a randomized clinical trial, we feel that treatment selection bias is less likely an issue in our study than in most observational studies. First, during the period of patient observation in this study (1987-2002), no one suspected that β-adrenergic receptor agents were likely to have clinically important effects on wound repair. More important, no one suspected that they had clinical activity with respect to the treatment of VLUs. Treatment selection with respect to these agents is likely based on the illnesses for which they are treatment options (eg, asthma, glaucoma, hypertension, myocardial infarction, and congestive heart failure). Second, with respect to β-adrenergic receptor agonists, the association of these agents and the association of asthma with respect to VLUs are in opposite directions. Although a decreased association with VLUs was noted in our unadjusted model, this effect was unmasked (more protective) once our models were adjusted for history of asthma and systemic glucocorticoid use. This effect was also noted across all strata using a propensity score model, which attempts to adjust for treatment selection bias. In essence, we have 2 different models that show that the use of β-adrenergic receptor agonists protects against the onset of VLUs. Finally, it is possible that our results are biased owing to confounding by indication. However, there are multiple different diseases associated with the use of these medications; our propensity scores, which are based on treatment selection, revealed similar results; and β-adrenergic receptor agents are used for illnesses both with an increased and decreased association with VLUs.12

Information bias is also problematic for observational studies. We have previously demonstrated our ability to use the GPRD to determine whether an individual has developed a VLU.12 Although we do not know if our participants actually used β-adrenergic receptor agents, we do know that they were prescribed more than once. Our definition of exposure to β-adrenergic receptor agents was based on at least 2 prescriptions to the agent, and for an outcome to be associated with 1 of these agents it must have occurred 90 days after receipt of the agent. In any event, if individuals received these agents and did not use them, then the direction of the information bias should have biased our results toward the null (no association). It is very unlikely that anyone would have used β-adrenergic receptor agents without knowledge of the participant’s GP, but again, if this did occur then the bias would have been toward the null (fewer unexposed individuals would have developed a VLU), and therefore our true effect estimate would have been even more protective.

In summary, we have shown a protective association between β-adrenergic receptor agonists and VLUs. There is strong laboratory evidence to support β-adrenergic receptor agonist-mediated modulation of dermal fibroblast function as the mechanism underpinning this epidemiologic finding. It is, however, possible that the benefit noted in our study is caused by another mechanism, such as local changes in arterial perfusion, and we encourage others to investigate this possibility. Although we were unable to find consistent evidence of an association between β-adrenergic receptor antagonist and VLUs, there was, however, a subgroup of patients who benefited from the use of these agents too. It may also be possible that individuals with specific illnesses, such as diabetes mellitus or congestive heart failure, might benefit more from these agents. This needs further study. It is important to realize that the evidence in this study should not be used as a rationale for treatment of VLUs with β-adrenergic receptor agents but rather should be compelling data for the consideration of a randomized clinical trial.

Accepted for Publication: November 9, 2006. Correspondence: David J. Margolis, MD, PhD, 815 Blockley Hall, 423 Guardian Dr, University of Pennsylvania, Philadelphia, PA 19104 (dmargoli@cccb.med.upenn.edu).

Author Contributions: Dr Margolis had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Margolis, Hoffstad, and Isseroff. Acquisition of data: Margolis and Hoffstad. Analysis and interpretation of data: Margolis, Hoffstad, and Isseroff. Drafting of the manuscript: Margolis, Hoffstad, and Isseroff. Critical revision of the manuscript for impor-
tant intellectual content: Margolis, Hoffstad, and Isseroff. Statistical analysis: Margolis and Hoffstad. Obtained funding: Margolis and Isseroff. Administrative, technical, or material support: Margolis, Hoffstad, and Isseroff. Study supervision: Margolis, Hoffstad, and Isseroff.

Financial Disclosures: Dr Isseroff has a patent application on the use of adrenergic agents in wound repair that both she and the University of California, Davis, are currently preparing.

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REFERENCES


Physical Activity and Adherence to Compression Therapy in Patients With Venous Leg Ulcers

Maud M. Heinen, PhD, RN; Carine van der Vleuten, MD, PhD; Michette J. M. de Rooij, MD, PhD; Caro J. T. Uden, PhD; Andrea W. M. Evers, PhD; Theo van Achterberg, PhD, RN

Objective: To assess levels of physical activity, particularly walking and leg exercises, among patients with venous leg ulcers and the extent to which patients adhere to compression therapy.

Design: Descriptive cross-sectional study.

Setting: Patients from 12 outpatient dermatology clinics were invited to participate in this study. When they agreed, they were asked to wear an accelerometer for a week and were then interviewed at the outpatient clinic.

Patients: A total of 150 patients with leg ulcers caused mainly by venous insufficiency.

Main Outcome Measures: The amount of moderately strenuous physical activity, the amount of walking, and adherence to compression therapy.

Results: In this study, 39% of the patients interviewed displayed adherence to compression therapy. Self-reported data validated by the use of an accelerometer indicated that the amount of moderately strenuous activity in the study group was low compared with that of the general Dutch population; 35% of the patients did not have a 10-minute walk even once a week.

Conclusions: Low levels of physical activity were established in a group of 150 patients with venous leg ulcers. Full adherence to compression therapy was reported in about 40% of the patients. Patients should be educated and encouraged to (1) enhance physical activity through walking and leg exercises and (2) increase adherence to compression therapy.

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IN 70% OF ALL PATIENTS WITH LEG ulcers, ulceration is caused by venous insufficiency. Physical activity and adherence to compression therapy are 2 vital factors in decreasing wound healing time and preventing wound recurrence. Leg exercises and physical activity stimulate the calf muscle pump, which supports venous circulation. Walking is particularly beneficial because it causes the calf muscles to contract and expand. This in turn results in increased pumping of blood from the lower leg upward toward the heart. A diminished pump function, or absence of the calf muscle pump, can contribute considerably to the development of edema in the lower legs and other chronic venous insufficiency symptoms. As a result, patients with leg ulcers should be encouraged to enhance calf muscle activity and to prevent the occurrence of edema by walking.

Exercises for the lower legs efficiently supplement daily physical activities and walking, especially when the opportunities to walk or engage in other physical activity are limited. Several studies show the positive effects of leg exercises on the calf muscle pump function. The tip-toe exercise in the standing position, as well as flexing and stretching of the feet in the sitting position, effectively stimulates the calf muscle and enhances venous return.

To effectively treat venous leg ulceration, compression therapy of the lower legs is essential. Patient adherence to compression therapy improves the effectiveness of the calf muscle pump, reduces venous volume, lowers venous pressure (only with high external pressure), increases current velocity, and improves the microcirculation. It also prevents the occurrence of edema and reduces the development of skin changes, especially after deep venous thrombosis. In addition, activation...
of the calf muscle in patients with chronic venous insufficiency is less effective when compression is not used.\(^9\) Compression therapy is applied by means of bandages or therapeutic elastic stockings. It is important that therapeutic elastic stockings be replaced regularly to ensure or therapeutic elastic stockings. It is important that therapeutic elastic stockings be replaced regularly to ensure that compression therapy is used.\(^9\) It is important that the patient has experience with therapeutic elastic stockings and/or bandages.

**Questions and scoring list to determine adherence with compression therapy.**

The interviewer was instructed to translate the given answers to the questions above into prestructured adherence categories. The following categories were used.

**Scoring Categories, Adherence With Therapeutic Elastic Stockings and/or Bandages**

1. The patient did not wear the therapeutic elastic stockings and/or bandages:
   - Every day, all day
   - Occasionally, for a somewhat shorter period (<2 hours shorter) than the recommended time period (all day, from the moment one arises until the moment one goes to bed), less than once a week
   - Regularly, for a considerably shorter period (<2 hours), at least once a week
   - Occasionally, for a considerably shorter period (>2 hours shorter), once a week
   - Regularly, for considerably shorter period (>2 hours shorter), at least once a week
   - Not wearing compression (for a whole day) occasionally (less often than once a month in the past 6 months)
   - Not wearing compression (for a whole day) on a regular basis, more often than once a month
   - Not wearing compression for several days in a row in the past 6 months
   - The patient had no experience yet (with therapeutic elastic stockings and/or bandages

**ASSESSMENTS AND OBSERVATIONS**

Data on wound characteristics and etiology and comorbidity were provided by the dermatologist or dermatology nurse. Patients were also asked to report comorbidity, the duration of the current wound, and the date of the first wound. In addition, patients were asked to report how they conducted daily tasks, the type of exercises, and how often they conducted these exercises. Six questions on adherence to compression therapy were presented to determine actual treatment adherence behavior. Answers were registered in prestructured categories. The questions and categories are displayed in the **Figure**. Additional remarks from the patients concerning their experiences with compression therapy were reported at the end of the interviews.

**METHODS**

Interviews of 150 patients were conducted by a team of 3 trained interviewers (1 of whom was M.M.H.). Patients from 12 hospital-based outpatient dermatology clinics in the Netherlands were included. The study was approved by the medical ethics committee of all participating hospitals.

Patients with leg ulcers who had received treatment at outpatient dermatology clinics during the 9-month inclusion period of the study were asked to participate (at the start of the study, patients who had been treated within the preceding month were also invited to participate). Only patients with leg ulceration based on venous etiology or a mixed etiology of venous and arterial or venous and arteriolar insufficiency were invited to participate. To be included in the study, patients had to be able to speak and understand the Dutch language. In addition, participants were required to provide written informed consent after they received written and oral information about the study. Exclusion criteria included arterial insufficiency with an ankle-brachial pressure index of less than 0.8 or full immobility.

Patients were interviewed at the outpatient dermatology clinic where they were being treated. All participants were initially approached by dermatology nurses and/or dermatologists and asked if they would be willing to participate in this study. Patients were asked to wear an accelerometer (hereinafter, PAM [physical activity monitor]) during the week prior to interview and were given instructions for its use.

**QUESTIONNAIRES AND PAM**

All patients completed the 7-day Physical Activity Recall questionnaire (PAR),\(^{10,17}\) which asks respondents to recall and report all physical activity in which they had engaged during the previous 7 days. A distinction was made between weekdays and weekends. The PAR requires respondents to report any moderately strenuous activities in the past week and the amount of time spent on these activities. To increase understanding of what
kinds of activities are considered moderately strenuous, ex-
amples were provided on the back of the questionnaire. Fur-
thermore, the amount of walking the patient had done in the
week prior to the interview was investigated using a question
derived from the International Physical Activity Question-
naire. This question asked patients how often in the previ-
ous week they had walked for a minimum of 10 minutes.
To measure actual physical activity, a PAM was used. The PAM is a small device that can be attached to the waist-
band of trousers or a skirt and contains a display that shows 2
different scores of physical activity, namely, a daily score and
a mean weekly score. The PAM was used as a control device for
overreporting of physical activity.

We used descriptive analysis to analyze the data in this study. Scores for self-reported physical activity were combined with
PAM scores to validate self-reported activity. Self-reported ad-
herence to compression was combined with dermatology nurses’
observations.

RESULTS

In total, 227 patients were invited to participate in our study. Of these, 77 (34%) chose not to participate for the follow-
ing reasons: (1) 29 patients considered participation in this study to be too much trouble (many of these patients were dependent on others for transportation to the hospital), (2) 16 patients were unable to participate because they or their partners were unwell, and (3) 11 did not have time to participate because of work com-
mitments or other activities. (Twenty-one patients did not provide a specific reason for not participating.)

PATIENT CHARACTERISTICS

Table 1 presents patient characteristics, wound character-
istics, and comorbidity. In 60% of the patients, the leg ulcer was the result of a mixed etiology of venous and arte-
rial or arteriolar insufficiency. All patients with dia-
abetes mellitus, heart failure, hypertension, or intermit-
tent claudication were also classified as patients with a
mixed etiology. Patients who had a leg ulcer based on a
pure venous etiology comprised 40% of the sample. Al-
most three-quarters of the patients had varicose veins
(71%), and more than one-third had a history of deep
venous thrombosis (35%). At the time of the interviews,
103 patients had a wound (69%). Forty-seven patients
had had a wound in the month prior to the interview
(31%). Almost one-fifth of the patients had wounds on more than 10 occasions (19%). The median duration of the wound was 4 months (range, 2 weeks to 5 years). Compression therapy was applied by short or long stretch bandages or therapeutic elastic stockings. Some pa-
patients had both because they had different types of com-
pression on each leg.

PHYSICAL ACTIVITY

In Table 2, the data for physical activity, walking, and leg exercises are displayed. The results of the PAR, cor-
rected for overreporting, showed that 56% of the pa-
tients had less than 2.5 hours of physical activity a week
and about half of these patients (26%) did not have any
moderately strenuous physical activity in the week prior
to the interview. The PAM scores of 17 patients (11%) were corrected for the amount of physical activity per week, and 12 (8%) were corrected for the amount of walk-
ing in the week previous to the interview. Patients who reported more than 2.5 hours on the PAR and had a score higher than 9 on the PAM were classified as the moder-
ately strenuous activity group.

Only 13% of the patients had walked for 30 minutes on at least 5 days of the week. The percentage of pa-
patients who did not walk for 10 minutes at least once in

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Table 1. Characteristics of 150 Patients, Wound Characteristics, and Comorbidity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, mean, median (range), y</td>
<td>67, 68 (27-91)</td>
</tr>
<tr>
<td>Female</td>
<td>93 (62)</td>
</tr>
<tr>
<td>Education, highest completed level</td>
<td></td>
</tr>
<tr>
<td>Elementary school</td>
<td>37 (25)</td>
</tr>
<tr>
<td>Lower secondary school</td>
<td>72 (48)</td>
</tr>
<tr>
<td>Vocational education</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Higher educational level</td>
<td>21 (14)</td>
</tr>
<tr>
<td>Paid outdoor occupation</td>
<td>30 (20)</td>
</tr>
<tr>
<td>BMI, mean, median (range)</td>
<td>30, 29 (20-53)</td>
</tr>
<tr>
<td>19-25 (normal)</td>
<td>34 (23)</td>
</tr>
<tr>
<td>25-30 (overweight)</td>
<td>57 (38)</td>
</tr>
<tr>
<td>&gt; 30 (obese)</td>
<td>59 (39)</td>
</tr>
<tr>
<td><strong>Wound Characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Duration, mean, median (range), mo</td>
<td>7.9, 4.0 (0.5-60.0)</td>
</tr>
<tr>
<td>First wound, mean, median (range), No. of years ago</td>
<td>23, 20 (1-76)</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>41 (27)</td>
</tr>
<tr>
<td>2</td>
<td>27 (18)</td>
</tr>
<tr>
<td>3-10</td>
<td>53 (36)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>29 (19)</td>
</tr>
<tr>
<td>Professional wound care, mean, median (range), frequency per month</td>
<td>8 (1-29)</td>
</tr>
<tr>
<td>Compression</td>
<td></td>
</tr>
<tr>
<td>Bandages, short stretch</td>
<td>69 (46)</td>
</tr>
<tr>
<td>Bandages, long stretch</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Therapeutic elastic stocking(s)</td>
<td>89 (59)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (15)</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Varicose veins</td>
<td>106 (71)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>59 (39)</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>53 (35)</td>
</tr>
<tr>
<td>Cardiac problem</td>
<td>29 (19)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td>12 (8)</td>
</tr>
<tr>
<td>Erysipelas</td>
<td>26 (17)</td>
</tr>
<tr>
<td>Eczema</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Arthritis or arthrosis</td>
<td>35 (23)</td>
</tr>
<tr>
<td>Hip, back, or knee pain and/or surgery</td>
<td>24 (16)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

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had experience with therapeutic elastic stockings, 33% as well as compression bandages. Of the 119 patients who fully adhered to the use of therapeutic elastic stockings, 39% of all 150 patients were seven patients had compression bandages or had had experience with them within the past 6 months. Ninety-six patients reported wearing their stockings everyday from the time they awoke until they went to bed at night. With respect to the use of bandages, 78 of the 97 patients who had experience with them (80%) reported being completely adherent to therapy.

Table 2. Amount of Moderately Strenuous Activity, Walking, and Leg Exercises in 150 Patientsa

<table>
<thead>
<tr>
<th>Physical Activity, PAR</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSA, ≥2.5 h</td>
<td>66 (44)b</td>
</tr>
<tr>
<td>No MSA</td>
<td>39 (26)</td>
</tr>
<tr>
<td>Walking</td>
<td></td>
</tr>
<tr>
<td>≥30 min on ≥5 d</td>
<td>19 (13)b,c</td>
</tr>
<tr>
<td>&lt;10 min on ≥1 d</td>
<td>52 (35)</td>
</tr>
<tr>
<td>Don’t know</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Leg and foot exercises</td>
<td></td>
</tr>
<tr>
<td>Leg exercises</td>
<td>53 (35)</td>
</tr>
<tr>
<td>Flexing and stretching the feet</td>
<td>30 (20)</td>
</tr>
<tr>
<td>Rotating the feet</td>
<td>35 (23)</td>
</tr>
<tr>
<td>Tip-toe exercise</td>
<td>11 (7)</td>
</tr>
</tbody>
</table>

Abbreviations: MSA, moderately strenuous activity; PAR, Physical Activity Recall Questionnaire.

a Defined as at least 2.5 hours per week.

b Self-reported data corrected for physical activity monitor (PAM) scores. The PAM corrections explained that at least 30 minutes of walking on at least 5 days per week, or at least 2.5 h of MSA, are not possible when the mean daily PAM score is 9 or less.

c A total of 26 patients with self-reported 2.5 hours or more of MSA per week had a mean weekly score on the PAM of less than 10, but 9 patients reported bicycling as MSA, so only 17 patients were corrected for PAM in their physical activity score because PAM scores are known to underestimate activity during bicycling.

Table 3. Adherence by 150 Patients to Compression Therapy Using Therapeutic Elastic Stockings and/or Bandagesa

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockings or Long Stretch Bandages (n = 119)</td>
<td></td>
</tr>
<tr>
<td>Fully adherent (on a daily basis, according to guidelines)</td>
<td>40 (33)</td>
</tr>
<tr>
<td>Moderately adherent (occasionally to regularly; a period &lt;2 h shorter rather than all day)</td>
<td>46 (38)</td>
</tr>
<tr>
<td>Nonadherent (occasionally, considerably shorter; a period &gt;2 h shorter rather than all day)</td>
<td>35 (29)</td>
</tr>
<tr>
<td>Short Stretch Bandages (n = 97)</td>
<td></td>
</tr>
<tr>
<td>Fully adherent (on a daily basis, according to guidelines)</td>
<td>78 (80)</td>
</tr>
<tr>
<td>Moderately adherent (occasionally to regularly; a period &lt;2 h shorter rather than all day)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Nonadherent (occasionally, considerably shorter; a period &gt;2 h shorter rather than all day)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>All Patientsb (n = 150)</td>
<td></td>
</tr>
<tr>
<td>Fully adherent (on a daily basis, according to guidelines)</td>
<td>59 (39)</td>
</tr>
<tr>
<td>Moderately adherent (occasionally to regularly; a period &lt;2 h shorter rather than all day)</td>
<td>54 (36)</td>
</tr>
<tr>
<td>Nonadherent (occasionally, considerably shorter; a period &gt;2 h shorter rather than all day)</td>
<td>37 (25)</td>
</tr>
</tbody>
</table>

a Data are given as number (percentage) of patients.
b Regardless of the kind of compression.

The week prior to the interview was 35%. Only 35% of the patients did the exercises for the lower legs.

In Table 3, data for adherence to compression therapy are given. Of 150 patients, 119 had therapeutic compression stockings at the time of the interview or had had experience with them within the past 6 months. Ninety-seven patients had compression bandages or had had experience with them in the past 6 months. With respect to treatment adherence, 39% of all 150 patients were fully adherent to the use of therapeutic elastic stockings as well as compression bandages. Of the 119 patients who had experience with therapeutic elastic stockings, 33% reported wearing their stockings everyday from the time they awoke until they went to bed at night. With respect to the use of bandages, 78 of the 97 patients who had experience with them (80%) reported being completely adherent to therapy.

Activation of the calf muscle pump function combined with compression therapy is the most effective noninvasive component of venous leg ulceration treatment.22 This study provides insight into levels of physical activity among patients with venous leg ulcers, particularly walking and leg exercises, and patient adherence to compression therapy. The results of this study show that moderately strenuous activity levels in patients with venous leg ulcer are low. A substantial number of patients do not engage in even 10 minutes of walking per week. In addition, this study shows that only one-third of the patients conducted leg exercises. The rate of adherence to compression therapy was also low, with less than half of the patients reporting full adherence to therapy.

To our knowledge, there are no studies in the international literature that report on the physical activity and walking behavior of patients with venous leg ulcers. There was, however, a study23 in the Netherlands (where our patient sample was obtained) in which 8000 members of the general population were questioned about their physical activity. The patients in our sample showed lower physical activity levels compared with the sample surveyed among the general Dutch population, thereby indicating that our sample was comparatively more inactive. In the Dutch adult population, more than 50% were sufficiently physically active compared with 44% of the patients in our sample. Furthermore, in the Dutch study, only 8% of the sample were completely inactive compared with 26% of the patients in our sample.

Clearly, patients with venous leg ulcers have low levels of physical activity and spend little time walking even though walking activates the calf muscle pump and reduces venous hypertension when combined with compression therapy. There are, however, no guidelines that indicate the amount of walking necessary to improve venous insufficiency. In the study reported herein, the actual amount of walking was assessed using reports of 10-minute walking periods, because 10-minute walking periods ensure that the calf muscle is sufficiently activated. A study by Uden et al4 established that walking faster is more effective in promoting venous circulation of the lower legs. The amount of walking to achieve beneficial effects with respect to decreasing venous leg ulceration needs to be further established by future research.

Most patients in our study were classified as moderately adherent to compression therapy. A smaller group was categorized as nonadherent. In a study by Mayberry et al12 nonadherence was established for only 9.7% of the patients. However, at follow-up, this number increased to 20.5%. Erickson et al10 showed that strict adherence was established in 32% of the cases in their study, which is more on par with the results of our study. Ob-
viously, adherence or adherence rates are influenced by the methods used to obtain results. The patients in the studies by Mayberry et al12 and Erickson et al13 were considered to be adherent to therapy when they did not consistently refuse to use ambulatory elastic compression or when they kept 100% of their appointments, adhered completely to prescribed compression therapy, and followed all instructions for wound and extremity care. Kjaer et al11 stated that the indicator used to determine adherence is susceptible to bias. In our study, adherence was assessed by questioning the patients on their daily habits concerning compression therapy. Patients were invited and encouraged to tell the interviewer about their experiences with their compression bandages and stockings. In many cases, when the interviewer asked patients specifically about their habits concerning compression therapy, many reported a lower adherence level than what they had initially reported. Evidently, by discussing experiences and habits concerning compression in a nonjudgmental way, the provision of socially desirable answers was diminished.

Several studies10-13 have concluded that patients who display strict adherence with their treatment regimen show considerably faster healing rates and fewer recurrences compared with patients who are less adherent or nonadherent. A high level of adherence is, according to the World Health Organization review (Sabate25), associated with more severe symptoms or illness, knowledge about and belief in efficacy of treatment, adequate social support, and trust in the physician.14 Renzi et al,26 in a study of patients being treated for dermatologic concerns, concluded that dissatisfaction with care was associated with poor adherence to treatment. Unfortunately, few studies report on the determinants of nonadherence with compression therapy. A study by Edwards27 concluded that many patients do not have a clear understanding of their condition or the treatment regimes prescribed. In addition, Edwards27 indicated that concurrent problems associated with compression bandaging (eg, pain, leakage of exudates, and skin irritation) contribute to nonadherence. In a study by Kiev et al,28 socioeconomic factors, cosmetic reasons, concerns about discomfort, and difficulty in putting on the stockings were identified as primary reasons for nonadherence.

A limitation of our study is the fact that a relatively large number of patients declined participation. It is possible that this created a selection bias. Another limitation is related to the fact that the sample of patients with venous leg ulcers in our study was obtained from outpatient dermatology clinics. In the Netherlands, most patients with uncomplicated venous leg ulceration are treated by general practitioners and/or nurses from home health care organizations. Patients with poorly healing wounds, recurrent wounds, or wounds related to more complicated etiology are referred to outpatient dermatology clinics. As a result, the generalizability of our findings is probably limited to patients with more severe venous leg ulceration concerns. However, generalizability of our results is likely enlarged because the patients included were recruited from a large number of outpatient dermatology clinics in both academic and general hospitals in the Netherlands.

The validity of this study is strengthened by the use of several methods, such as self-reported data, validated questionnaires, data from the medical files, observational data from dermatology nurses, and interviewers and the use of a PAM. Using a PAM allowed us to objectively measure actual physical activity along with self-reported physical activity. In our study, the PAM was used specifically to control for overreporting of physical activity by the patients rather than to measure the total amount of physical activity.

In conclusion, patients with venous leg ulcers treated with ambulant compression therapy have low levels of physical activity and spend little time walking. Levels of full adherence with compression therapy are low. Physical activity through walking and leg exercise, combined with compression therapy, is the most effective element of conservative leg ulceration treatment. Patients should be encouraged to enhance physical activity that aims to activate the calf muscle pump. Patients should be stimulated to increase adherence to treatment with compression bandages or stockings. Determinants for enhancing adherence and physical activity levels need to be further explored and anticipated at as a part of professional care.

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Author Contributions: Study concept and design: Heinen, de Rooij, Uden, Evers, and van Achterberg. Acquisition of data: Heinen, van der Vleuten, and van Rooij. Analysis and interpretation of data: Heinen and van Achterberg. Drafting of the manuscript: Heinen, de Rooij, and Uden. Critical revision of the manuscript for important intellectual content: Heinen, van der Vleuten, Evers, and van Achterberg. Statistical analysis: van Achterberg. Obtained funding: Heinen and van Achterberg. Study supervision: van der Vleuten, de Rooij, Evers, and van Achterberg.

Financial Disclosure: None reported.

Funding/Support: This study was funded by a grant from ZonMw, the Netherlands’ organization for Health Research and Development.

Role of the Sponsor: The funding organization did not have a role in the design and conduct of the study or in the approval of this manuscript.

REFERENCES

CONSENSUS STATEMENT

Consensus Panel Recommendations for Chronic and Acute Wound Dressings

Michel Vaneau, PharmD; Guillaume Chaby, MD; Bernard Guillot, MD; Philippe Martel, MD; Patricia Senet, MD; Luc Teot, MD, PhD; Olivier Chosidow, MD, PhD

Objective: To seek a consensus on recommendations that would help health professionals choose appropriate wound dressings in daily practice, since a systematic review found only limited evidence to support reported indications for modern wound dressings.

Participants: A steering committee selected a panel of 27 experts with no declared conflicts of interest from lists of nursing staff and physicians (specialists or general practitioners) with long-standing experience of wound care. The lists were put forward by 15 French learned societies.

Evidence: The panelists received a recent systematic review of the literature, a classification of indications established by a working group, and definitions for the dressings.

Consensus Process: The steering committee designed questionnaires on chronic wounds and on acute wounds for each of the 2 panels. The consensus method was derived from the nominal group technique adapted by RAND/UCLA. Panelists rated the relevance of each possible dressing-indication combination on the basis of the published evidence and their own experience. After the first round of rating, they met to discuss results and propose recommendations before taking part in a second round of rating. The working group peer reviewed the final recommendations.

Conclusions: A strong consensus was reached for use of the following combinations: for chronic wounds, (1) debridement stage, hydrogels; (2) granulation stage, foam and low-adherence dressings; and (3) epithelialization stage, hydrocolloid and low-adherence dressings; and for the epithelialization stage of acute wounds, low-adherence dressings. For specific situations, the following dressings were favored: for fragile skin, low-adherence dressings; for hemorrhagic wounds, alginates; and for malodorous wounds, activated charcoal.

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Published systematic reviews of the value of different types of dressing in the management of acute and chronic wounds provide only weak levels of evidence for their clinical efficacy.1-3 An updated systematic review by our team has confirmed the lack of high-evidence-level data (see companion article [Chaby et al4]).

The best evidence in our review suggests that hydrocolloid dressings and alginate dressings are effective in the treatment of chronic wounds, and foam dressings and hydrofiber dressings are effective in the treatment of acute wounds, regardless of healing stage. Alginate dressings are for use at the debridement stage of chronic wounds. However, it was only for these 3 types of wound dressing that the evidence was good enough to reach a firm conclusion. Evidence is still scant for the relative efficacy of other types of dressing. This is why we decided to set up a formal consensus process to establish which dressings are most commonly accepted and recommended by physicians and nurses and to provide recommended indications for each type of dressing. Our assumption was that, depending on the kind of wound and the healing stage, it should be possible to provide appropriate, pragmatic criteria for choosing a particular dressing.

Participants

The consensus process (March-September 2006) was sponsored by Haute Autorité de Santé (HAS), the French National Authority for Health. In 2004, the sponsor nominated the chairman of a working group (O.C.), who selected, together with

Author Affiliations: Haute Autorité de Santé, Saint Denis, France (Drs Vaneau and Martel); Department of Dermatology, Centre Hospitalier Universitaire (CHU) d’Amiens, Amiens, France (Dr Chaby); Department of Dermatology, CHU de Montpellier, Montpellier, France (Dr Guillot); Department of Geriatrics, Hôpital Charles Foix, Ivry/Seine, France (Dr Senet); Department of Plastic and Reconstructive Surgery, Hôpital La Pérouse, Montpellier (Dr Teot); and Université Pierre-et-Marie-Curie-Paris 6 and Department of Dermatology and Allergy, Assistance Publique–Hôpitaux de Paris, Hôpital Tenon, Paris, France (Dr Chosidow).
the sponsor, 20 working group members (pharmacists, dermatologists, and other physicians specializing in wound care), who were to perform and discuss a systematic review of the literature on dressings for wound care. Because this review found only limited evidence to support the proposed indications for wound dressings (see Chaby et al⁴), the decision was taken to carry out a formal consensus process. It was set up and run by a steering committee of 7 members (the authors of the present article) chosen by the chairman (O.C.) from among the working group members. To select consensus panel participants, the steering committee asked 15 learned societies to each submit a list of 4 to 6 experts (nursing staff and physicians and either specialists or general practitioners) with experience in wound care. Fourteen societies responded (available in an eTable [http://www.archdermatol.com]) and proposed the names of 78 experts. The steering committee ranked these experts on the basis of their suitability for inclusion in 1 of 2 panels (one on chronic wounds and the other on acute wounds). If there was no expert with the required experience in a specific field, the steering committee consulted lists of experts with similar experience maintained by HAS. Written declarations of interest were obtained by HAS from all participants. Experts declaring any permanent link with industry, ongoing clinical work sponsored by industry, or who were not available for the panel meeting were excluded. At the end of the selection process, 14 experts were assigned to the chronic wounds panel and 13 to the acute wounds panel.

EVIDENCE

Evidence for the relative efficiency of dressings was from a systematic review of the literature conducted by the second author (G.C., see Chaby et al⁴).

We used a consensus method adapted from the RAND/UCLA nominal group technique method (Figure 1). The steering committee designed 2 questionnaires (222 items for the chronic wound questionnaire and 263 for the acute wound questionnaire) and wrote the instructions for completing them. Apart from the relevant questionnaire, the expert panelists received a report describing the findings of the systematic review, a classification of indications established by the working group, and a list of the different types of dressing under consideration with explanatory comments (Figure 2). In the questionnaires, indications were listed from the most specific to the least specific (eg, infected before unspecified chronic wounds) so that panelists would not be tempted to provide answers relating to specific situations to questions that were of a more general nature. The questionnaire did not address dressing selection in relation to the amount of exudates or wound area because these factors are highly dependent on the stage of healing and/or vary considerably over time. Panelists could choose any dressing appropriate for a particular wound stage (eg, absorbent foam dressings).

Panelists were asked to rank the dressings that were “most often useful” in any given indication first, followed by the dressings that “may be used in some cases.” They had to rate the dressing in the light of clinical efficiency as given by the available evidence and their own experience on a scale from 1 (totally inappropriate) to 9 (totally appropriate). A rating of 5 reflected indecision. In addition, they had to answer general questions on usefulness criteria in selecting dressings. We made every effort to retrieve any missing ratings.

The panelists met between the 2 rounds of the consensus process. They were informed of the results of the first round, commented on their own ratings, and suggested amendments to the questionnaires. If the ratings for a given question were in the 1 to 3 range or in the 7 to 9 range, and there were no missing ratings, this was considered to be a sign of strong disagreement or of strong agreement. These proposals were not reassessed in the
second round. For all the other proposals, the steering committee used all the information from the first round and from the between-round discussion to design a second set of questionnaires for submission to the panelists in the second round (196 items for chronic wounds and 255 items for acute wounds). We applied the same decision rules in the second round, after deleting the highest and the lowest ratings (whenever there were no missing data), to discard incongruent responses.

The questionnaires for the first round were sent out on June 1, 2006, and for the second round, on July 11, 2006. All panelists completed both rounds (1 first-round questionnaire was retrieved after the panel meeting). The acute wounds panel meeting (June 19, 2006) was attended by 12 of 13 panelists, and the chronic wounds panel meeting (June 26, 2006), by 12 of 14 panelists. Data retrieval was complete on September 20, 2006. Results are given in Table 1. There was no agreement in the second round on any of the proposals with missing responses. However, even if the missing rating had always been a maximum of 9, none of these proposals would have fallen in the strong agreement category. The steering group only reported proposals on which there was strong or relatively strong agreement in favor of a given indication-dressing combination to the working group, which met on September 27, 2006, to review and approve the final consensus statements.

CONCLUSIONS

The consensus statements on which there was strong agreement on the “most often useful” dressing type for a given indication are summarized in Table 2. The most suitable dressings for chronic wounds were considered to be hydrogel dressings at the debridement stage, foam and low-adherent dressings at the granulation stage, and hydrocolloid and low-adherent dressings at the epithelialization stage (see dressing definitions in Figure 2). Low-adherent dressings were favored at the epithelialization stage of acute wounds. Certain dressings were appropriate for specific situations: low-adherent dressings for fragile skin, alginates for hemorrhagic wounds, and activated charcoal for malodorous wounds. The amount of wound exudates was not investigated. However, both panels agreed that the following criteria were useful when choosing a dressing: pain on application and removal, management of exudates, and dressing tolerance.

Interestingly, the consensus statements giving rise to strong agreement did not confirm the highest level (level B) evidence from the literature, possibly because the indications defined in published clinical trials are only of limited relevance to real-life situations in which considerations such as the stage of the healing process or the specific nature of the case (eg, hemorrhagic or malodorous wounds) tend to prevail.

There was no evidence nor consensus for claims that certain dressings (eg, silver-containing antibacterial dressings) are given in Table 2.

---

Table 1. Results of the 2 Rounds

<table>
<thead>
<tr>
<th>Round</th>
<th>Chronic Wound Questionnaire</th>
<th>Acute Wound Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>222 items</td>
<td>263 items</td>
</tr>
<tr>
<td>Strong agreement at issue of first round</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Strong disagreement at issue of first round</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Total of strong agreements or disagreements in the first round</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Second</td>
<td>196 items</td>
<td>255 items</td>
</tr>
<tr>
<td>No missing responses</td>
<td>190</td>
<td>238</td>
</tr>
<tr>
<td>A single missing response</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>More than 1 missing response</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Strong agreement at issue of second round</td>
<td>14</td>
<td>22</td>
</tr>
<tr>
<td>Strong disagreement at issue of second round</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Total of strong agreements or disagreements in second round</td>
<td>50</td>
<td>53</td>
</tr>
</tbody>
</table>

*There were 255 instead of 256 items because 6 items considered to be irrelevant by the panel were deleted and 5 new items were added.

---

Table 2. Evidence for and Opinion on Use of Different Types of Dressing at Different Stages of Care for Chronic and Acute Wounds

<table>
<thead>
<tr>
<th>Variable</th>
<th>Wound Typea or Cause</th>
<th>Level B Evidence (Literature Review)</th>
<th>Strong Agreement (Formal Consensus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debridementb</td>
<td>Chronic</td>
<td>Acute</td>
<td>None</td>
</tr>
<tr>
<td>Granulationc</td>
<td>Chronic</td>
<td>Alginate</td>
<td>None</td>
</tr>
<tr>
<td>Epithelializationd</td>
<td>Acute</td>
<td>Chronic</td>
<td>None</td>
</tr>
<tr>
<td>Specific cases</td>
<td>Fragile skin</td>
<td>Epidermolysis</td>
<td>None</td>
</tr>
<tr>
<td>Prevention of infection</td>
<td>Any cause</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Infected wound</td>
<td>Any cause</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hemorrhagic wound</td>
<td>Any cause</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Malodorous wound</td>
<td>Carcinoma</td>
<td>None</td>
<td>Activated charcoal</td>
</tr>
</tbody>
</table>

*a Chronic wounds were defined as wounds expected to take time to heal because of 1 or more factors delaying healing. Depending on the cause of the wound, wounds taking more than 4 to 6 weeks to heal were considered to be chronic. They included venous leg ulcers, pressure ulcers, diabetic foot ulcers, extended burns, and amputation wounds. Acute wounds were defined as wounds expected to heal in the usual time with no local or general factor delaying healing (eg, burns, split-skin donor grafts, skin graft donor site, sacrococcygeal cysts, bites, frostbites, deep dermabrasions, and postoperative guided tissue regeneration).

*b Debridement stage is defined as the wound stage at which debridement is required.

*c Granulation stage is defined as the wound stage at which the wound is recovered by a newly formed tissue of pink granular appearance (granulation tissue).

*d Epithelialization stage is defined as the wound stage at which migration of the keratinocytes across the wound surface occurs.
ings) are best suited to specified indications, such as care of infected wounds or prevention of infection. Nor was any consensus reached on classic paraffin gauzes despite their widespread use. Paradoxically, many panelists used paraffin gauzes, often combined with other topical agents, either in their routine daily practice or in specialized treatment protocols (eg, specific surgical procedures or care of extensive burns), even though they could not come to any agreement on their clinical value. Cost may be a factor to be taken into consideration here. Our questionnaires did not address highly specialized treatment protocols. Exploring such indications would require more detailed descriptions of wounds that include a consideration of their cause and healing stage and would need the contribution of experts in wound etiology.

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Author Contributions: Study concept and design: Vaneau, Senet, Teot, and Chosidow. Acquisition of data: Vaneau, Guillot, Martel, and Chosidow. Analysis and interpretation of data: Vaneau, Chaby, Guillot, Martel, Senet, and Chosidow. Drafting of the manuscript: Vaneau. Critical revision of the manuscript for important intellectual content: Chaby, Guillot, Martel, Senet, Teot, and Chosidow. Statistical analysis: Martel. Obtained funding: Vaneau. Administrative, technical, and material support: Vaneau and Martel. Study supervision: Vaneau, Guillot, Senet, and Chosidow.

Financial Disclosure: Drs Chosidow and Senet are presently involved in building a protocol using DermaGen, a dermal substitute (a cell therapy product) in diabetic foot ulcers. DermaGen is developed by Genevriér (Sophia Antipolis, France), which also sells hyaluronic acid–associated dressings. Dr Teot is involved in the following collaborations and partnerships: scientific collaboration on wound dressings with Braun (randomized trial on Calgitrol [a silver alginic acid dressing] [Magnus Bio-Medical Technologies] vs alginate in infected wounds) and Kinetic Concepts Inc (KCI) (and the French Ministry of Health) on a medical-economic study of the effects of vacuum-assisted closure (KCI); editorial collaboration with Molnlycke Products (pain and dressing changes for acute wounds), KCI (on technical considerations on vacuum-assisted closure [World Union of Wound Healing Societies statement]), and Coloplast (on pain management of wounds); and educational partnerships with Smith & Nephew, Johnson & Johnson, and Urgo.

Additional Information: The eTable is available at http://www.archdermatol.com.

Additional Contributions: The authors were all members of the steering committee. The working group who participated in peer reviewing the consensus statements included Helène Bachelet, pharmacist, Lille; Hervé Carpin, burns specialist, Clamart; Clélia Debure, dermatologist, Paris; Catherine Denis, endocrinologist and gynecologist, Saint Denis; Anne Dompmartin, dermatologist, Caen; Serge Grau-Ortiz, general practitioner, Auterive; Jean-Claude Guillaume, dermatologist, Colmar; Véronique Matz, pharmacist, Bar-le-Duc; Sylvie Meaume, gériatrician, Ivry sur Seine; Jean-Louis Richard, diabetologist, Le Grau du Roi; Jean-Michel Rochet, specialist in physical and rehabilitation medicine, Coubert; Nathalie Sales-Ausias, pharmacist, Marseille; and Anne Zagnoli, dermatologist, Brest, France. The members of the chronic wounds expert panel included Francis Ane, general practitioner, Montpellier; Hermine Arzt, specialist in physical and rehabilitation medicine, Amiens; Sophie Beyrand, nurse, Panazol; Sophie Blaise, dermatologist and specialist in vascular medicine, Grenoble; Maxime Chahim, phlebologist and angiologist, Paris; Catherine Gilbert, nurse, Paris; Georges Ha Van, specialist in physical and rehabilitation medicine, Paris; Chantal Le Goff, nursing manager (geriatrics), Le Mans; Laurent Machet, dermatologist, Tours; Philippe Nicolini, vascular surgeon, Lyon; Vincent Ould-Aoudia, gériatrician, Nantes; Nathalie Salles, gériatrician, Pessac; François Truchetet, dermatologist, Thionville; and Loïc Vaillant, dermatologist and lymphologist, Tours, France. The members of the acute wounds expert panel included Serge Baux, burns specialist, Paris; Françoise Blech, hygiene specialist, Nancy; Fabienne Brayé, burns specialist, Lyon; José Clavero, general practitioner, Paris; Nadine Favier, nurse, Montpellier; Ciprien Isacu, burns specialist, Bordeaux; Eric Jelele, emergency physician, Clermont-Ferrand; Laurent Lantieri, specialist in plastic and reconstructive surgery, Créteil; Jean-Louis Lorin, gastrointestinal surgeon, Bourg-Péage; Denis Pouchain, general practitioner, Vincennes; Michel Scepi, emergency physician, Poitiers; Claude Soulrier, nurse, Nîmes; and Jean-Paul Viand, general practitioner, Paris; France. Frédéric De Bels, pharmacist, Haute Autorité de Santé, Saint Denis, France, contributed to the design of the consensus process and questionnaires.

REFERENCES

## eTable. Collaborating Learned Societies

<table>
<thead>
<tr>
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<th>Name</th>
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</thead>
<tbody>
<tr>
<td>Angiology</td>
<td>Société Française d’Angiologie (SFA)</td>
</tr>
<tr>
<td>Burns</td>
<td>Société Française d’Etude et de Traitement de la Brûlure (SFETB)</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Société Française de Dermatologie (SFD)</td>
</tr>
<tr>
<td>General practice</td>
<td>Société Française de Médecine Générale (SFMG)</td>
</tr>
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<td>Gerontology</td>
<td>Société Française de Gériatrie et de Gériologie (SFGG)</td>
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<td>Lymphology</td>
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<td>Nursing</td>
<td>Fédération Nationale des Infirmiers (FNI)</td>
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<tr>
<td>Physical and rehabilitation medicine</td>
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<tr>
<td>Phlebology</td>
<td>Société Française de Phlébologie (SFP)</td>
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<tr>
<td>Vascular surgery</td>
<td>Société de Chirurgie Vasculaire de Langue Française (SCVLF); Société Française de Médecine Vasculaire (SFMV)</td>
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<tr>
<td>Wound care</td>
<td>Société Française et Francophone des Plaies et Cicatrisations (SFFPC)</td>
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<tr>
<td>Hygiene</td>
<td>Société Française d’Hygiène Hospitalière (SFHH)</td>
</tr>
<tr>
<td>Emergency medicine</td>
<td>Société Francophone de Médecine d’Urgence (SFMU)</td>
</tr>
</tbody>
</table>
Dressings for Acute and Chronic Wounds

A Systematic Review

Guillaume Chaby, MD; Patricia Senet, MD; Michel Vaneau, PharmD; Philippe Martel, MD; Jean-Claude Guillaume, MD; Sylvie Meaume, MD; Luc Téot, MD, PhD; Clélia Debure, MD; Anne Dompmartin, MD; Catherine Denis, MD; Bernard Guillot, MD; Olivier Chosidow, MD, PhD

Objective: To critically review the literature on the efficacy of modern dressings in healing chronic and acute wounds by secondary intention.

Data Sources: Search of 3 databases (MEDLINE, EMBASE, and the Cochrane Controlled Clinical Trials Register) from January 1990 to June 2006, completed by manual research, for articles in English and in French.

Study Selection: The end points for selecting studies were the rate of complete healing, time to complete healing, rate of change in wound area, and general performance criteria (eg, pain, ease of use, avoidance of wound trauma on dressing removal, ability to absorb and contain exudates). Studies were selected by a single reviewer. Overall, 99 studies met the selection criteria (89 randomized controlled trials [RCTs], 3 meta-analyses [1 of which came from 1 of the selected systematic reviews], 7 systematic reviews, and 1 cost-effectiveness study).

Data Extraction: The RCTs, meta-analyses, and cost-effectiveness studies were critically appraised by 2 reviewers to assess the clinical evidence level according to a modification of Sackett’s 1989 criteria. Ninety-three articles were finally graded.

Data Synthesis: We found no level A studies, 14 level B studies (11 RCTs and 3 meta-analyses), and 79 level C studies. Hydrocolloid dressings proved superior to saline gauze or paraffin gauze dressings for the complete healing of chronic wounds, and alginates were better than other modern dressings for debriding necrotic wounds. Hydrofiber and foam dressings, when compared with other traditional dressings or a silver-coated dressing, respectively, reduced time to healing of acute wounds.

Conclusions: Our systematic review provided only weak levels of evidence on the clinical efficacy of modern dressings compared with saline or paraffin gauze in terms of healing, with the exception of hydrocolloids. There was no evidence that any of the modern dressings was better than another, or better than saline or paraffin gauze, in terms of general performance criteria. More wound care research providing level A evidence is needed.

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WOUNDS ARE A MAJOR cause of morbidity and impaired quality of life and take up substantial health care resources in developed countries. Each year in the United States, over 1.25 million people experience burns, and 6.5 million have chronic skin ulcers caused by pressure, venous stasis, or diabetes mellitus.

Since the 1960s, it has been accepted that wound healing is optimal when the wound is kept in a moist environment rather than air dried. Occlusive or semi-occlusive dressings that promote reepithelialization and wound closure have been developed for chronic and acute wounds to reduce pain and healing time, absorb blood and tissue fluids, and to be painless on application and removal. The main occlusive or semi-occlusive dressings are hydrocolloid dressings (HCDs), alginates, hydrogels, foam dressings (FDs), hydrofiber dressings (HFDs), and paraffin gauze and nonadherent dressings. Recent products that are reported to induce angiogenesis or reduce infection are hyaluronic acid (HA) cream or dressings and dressings supplemented with activated charcoal or silver.

Current clinical practice guidelines on the treatment of pressure ulcers, leg ul-
ance of wound trauma on dressing removal, ability to ab-
complete healing or aspects such as pain, ease of use, avoid-
dence in support of the efficacy of modern dressings for
roversial. We assessed the level of published clinical evi-
designed using the full versions of the articles. Additional refer-
ers were excluded. The reviewer checked study relevance and
relevance and selection criteria to compare dressings. Case reports and case
teria are given in Table 1. From the list of retrieved titles and
reviewer (G.C.) selected the studies that used these
selection criteria to compare dressings. Case reports and case
eries were retrieved by manual searches.

Table 1. Keywords and Selection Criteria

<table>
<thead>
<tr>
<th>Key Words</th>
<th>MEDLINE</th>
<th>EMBASE</th>
<th>Selection Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trials, or meta-analysis, or review, or review-literature, or guidelines, or consensus, or consensus-development-conferences or congresses or recommendation(s) in combination with bandages, including hydrocolloid dressings, hydrocollular or polyurethane foams, alginate dressings, hydrogels, hydrofiber dressings, dextranomer, paraffin dressing, nonadherent dressings, dressings containing hyaluronic acid, silver-coated dressing or activated charcoal dressing, protease-modulating matrix (Promogran™) in combination with wound healing or vacuum or vacuum-assisted closure or negative pressure wound therapy, or topical negative pressure or leg ulcer or therapy, drug therapy, nursing, surgery or decubitus ulcer or therapy, drug therapy, nursing and surgery or chronic disease or therapy, drug therapy, nursing and surgery or surgical wound-dehiscence or therapy, drug therapy, nursing and surgery or surgical wound infection or therapy, drug therapy, nursing and surgery or skin transplantation or therapy, drug therapy, nursing and surgery or skin diseases vesiculobullous or therapy, drug therapy, nursing, and surgery or nursing or surgery or burns or skin graft or donor site or skin ulcer or pressure or diabetic with ulcer or therapy or nursing or therapy</td>
<td>Review or systematic review or meta-analysis or practice guideline or consensus or conference-paper or recommendation(s) or randomized-controlled-trial in combination with bandages-and-dressings, or wound-dressing or colloid or hydrogel or calcium-alginates or polyurethane or charcoal or silver or hyaluronic-acid in combination with leg-ulcer or decubitus or skin-ulcer or donor-site or bullous-skin-disease or trauma(tism) with wound(ing) or pressure or diabetic with ulcer or surgery or drug therapy or nursing or therapy</td>
<td>Complete healing measured by an objective method: rate of complete healing or rate of change in wound area and/or volume; pain or ease of use or avoidance of wound trauma on dressing removal or ability to absorb and contain exudates or prevention of infection or cost</td>
<td></td>
</tr>
</tbody>
</table>

Overall, 2330 studies were retrieved by electronic (n=2305) and manual (n=25) searching (Figure). Of these, 141 were considered relevant on the basis of title and/or abstract. However, only 99 full-text articles met our selection criteria (89 RCTs, 3 meta-analyses [1 of the meta-analyses came from 1 of the selected systematic reviews], 7 systematic reviews, and 1 cost-effectiveness study). The ref-

**METHODS**

**DATA SOURCES AND SELECTION CRITERIA**

Three bibliographic databases were searched from January 1990 to June 2006: MEDLINE, EMBASE, and the Cochrane Controlled Clinical Trials Register. The search was restricted to publications in English and in French. Keywords and selection criteria are given in Table 1. From the list of retrieved titles and abstracts, 1 reviewer (G.C.) selected the studies that used these selection criteria to compare dressings. Case reports and case series were excluded. The reviewer checked study relevance and design using the full versions of the articles. Additional references were retrieved by manual searches.

Wounds were considered to be chronic if time to healing was delayed as a result of impaired tissue repair due to poor oxygenation, malnutrition, or infection. Chronic wounds include leg ulcers, pressure sores, and diabetic foot ulcers. Acute wounds, however, tend to undergo an orderly and timely repair process that results in sustained restoration of anatomic and functional integrity. They include skin graft donor sites, partial-thickness burns, and posttraumatic and surgical wounds that heal by secondary intention. Studies on deep partial- and full-thickness burns were excluded.

**CRITICAL APPRAISAL OF SELECTED STUDIES**

Selected studies were distributed among 19 reviewers who were asked to grade trials using a checklist of items for methodological quality based on a modified version of Sackett’s criteria for clinical evidence. Each trial was graded by 2 reviewers (G.C. and 1 other reviewer). The 2 modifications to Sackett’s criteria were as follows: (1) meta-analyses that included level C randomized controlled trials (RCTs) were downgraded from level A to level B, and (2) RCTs were as graded level C if they had 1 or more of the following methodological shortcomings: evaluation of primary outcome was not blind, randomization method was performed incorrectly when it was described, primary and secondary objectives were not clearly defined, objective or subjective measures of dressing performance were not described, and patient groups were not comparable at baseline. The criteria we used for clinical evidence are given in Table 2.

Table 2. Criteria for Assessing Clinical Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Large, randomized, double-blind, controlled studies with low false-positive (α) and low false-negative (β) errors; MAs of RCTs</td>
</tr>
<tr>
<td>B</td>
<td>RCTs including a small number of patients, thereby increasing the likelihood of high false-positive and/or false-negative errors; MAs that include low-evidence RCTs (level C)</td>
</tr>
<tr>
<td>C</td>
<td>Trials that lack 1 or more of the following criteria: evaluation of primary outcome blind, randomized method performed correctly when described, primary and secondary objectives clearly defined, objective or subjective measures of dressing performance described, and patient groups comparable at baseline; case reports; case series</td>
</tr>
</tbody>
</table>

Abbreviations: MAs, meta-analyses; RCTs, randomized controlled trials. *According to the criteria of Bouvenot and Vray. †According to modifications to Sackett’s criteria.\(^{15,16}\)

---

![Flowchart](chart.png)

2305 References came from electronic search (MEDLINE, EMBASE, Cochrane Controlled Clinical Trials Register)

141 Potentially relevant articles (according to title on abstract)

25 Potentially relevant articles came from manual search

99 Selected articles

89 RCTs 3 MAs*

1 Cost-effectiveness study

7 Systematic reviews, consensus, and guidelines

93 Graded articles†

0 Evidence level A studies

14 Evidence level B studies 11 RCTs 3 MAs

79 Evidence level C studies 78 RCTs 1 Cost-effectiveness study

---

Table 3. Selected Studies by Type of Dressing

<table>
<thead>
<tr>
<th>Type of Dressing</th>
<th>RCTs</th>
<th>CES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocolloids(^{18-54})</td>
<td>34 + 3</td>
<td>2</td>
</tr>
<tr>
<td>Hydrocellular or polyurethane foam(^{18,20,30-37,55-69})</td>
<td>22 + 2</td>
<td>2</td>
</tr>
<tr>
<td>Alginate(^{30-40,53,55-59,64-64})</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Hydrogels(^{34,50-52})</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Hydrofiber(^{31,78,95})</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Dextranomer(^{60,81,55,56,97})</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Paraffin gauze(^{60,81,27,29,37,69,71,73,74,92})</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Hyaluronic acid–impregnated(^{97,102,103})</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Silver-coated(^{60,81,55,84,104,105})</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Activated charcoal(^{10})</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Protease-modulating matrix (Promogran(^{101,106-107}))</td>
<td>2 + 1 CES</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CES, cost-effectiveness study; MAs, meta-analyses; RCTs, randomized controlled trials. *Data are given as number of selected studies (we found no level A studies). †Johnson & Johnson, Issy-les-Moulineaux, France.

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**CHRONIC WOUND CARE**

Treatment with HCD resulted in a statistically significant improvement in the complete healing rate of leg ulcers and pressure sores according to 3 meta-analyses\(^{18-20}\) comparing HCD with paraffin gauze and wet-to-dry gauze dressings (odds ratio, 2.57 [95% confidence interval, 1.58-4.18]\(^{18}\); odds ratio, 2.45 [95% confidence interval, 1.18-5.12], \(P = .0219\); number needed to treat, 7 [95% confidence interval, 4-16]\(^{20}\)). However, there was no difference between the healing rates of HCDs and FDs whether for pressure sores or leg ulcers. An RCT\(^{101}\) comparing Promogran (Johnson & Johnson, Issy-les-Moulineaux, France) with a nonadherent dressing reported no difference in the complete healing rate of leg ulcers. In brief, for the complete healing of chronic wounds, HCD seems to be more effective than paraffin gauze and wet-to-dry gauze dressings, and there is no difference between FD and HCD in terms of optimizing complete healing rate.

Alginates considerably reduced chronic wound area in full-thickness pressure ulcers when used sequentially with HCD (alginites for the first 4 weeks and HCD for the next 4 weeks compared with HCD alone) and when compared with dextranomer.\(^{31,32}\) Pain on removal of a dressing, although never evaluated as a primary outcome, was lower for a nonadherent dressing than for HCD in a study of leg ulcers.\(^{33}\) Maceration and odor were also less marked.\(^{33}\) Scores on pain when changing a dressing were lower with an alginate than paraffin dressing in diabetic foot lesions.\(^{73}\)

**ACUTE WOUND CARE**

There was no difference in the efficacy of FD, a paraffin gauze dressing, polyethane film, or polyurethane film on...
The time to complete healing of these sites was lower with the FD than a silver-coated dressing (SCD), and with an HFD than with paraffin gauze. There was no difference in the complete healing rates of HFD and wet-to-dry gauze for surgical wounds. The HA-impregnated dressings delayed time to complete healing of skin graft donor sites when compared with a glycerine-impregnated dressing. In brief, FD seems to be more effective than an SCD in hastening complete healing of acute wounds, and HFD seems more effective than paraffin gauze.

Pain on dressing change was the primary outcome in 1 study only, which compared HFDs and alginates in surgical wound care and found no difference between these 2 types of dressing. When pain was a secondary outcome, HFD was superior to paraffin gauze for pain scores in split-thickness skin graft donor sites. No difference

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Design</th>
<th>Type of Dressing</th>
<th>Type of Wound</th>
<th>Patients (Wounds), No.</th>
<th>Primary End Point and Outcome</th>
<th>P Value</th>
<th>Area Reduction and/or Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley et al</td>
<td>Review (included MA of 5 RCTs); review (included MA of 2 RCTs)</td>
<td>HCD vs SG or DS; FD vs HCD</td>
<td>Pressure sores; leg ulcers</td>
<td>NA</td>
<td>Complete healing, 51% vs 31%; complete healing, OR 2.57 (95% CI, 1.58-4.18)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Singh et al</td>
<td>MA of 12 RCTs</td>
<td>HCD vs SG, PGD</td>
<td>Leg ulcers</td>
<td>683 (819)</td>
<td>Complete healing, 51% vs 31%, P=.02; OR, 2.45 (95% CI, 1.18-5.12)</td>
<td>.02</td>
<td>NA</td>
</tr>
<tr>
<td>Bouza et al</td>
<td>MA of 6 RCTs; MA of 5 RCTs</td>
<td>HCD vs SG, PGD, CD; FD vs HCD</td>
<td>Pressures sores; pressure sores</td>
<td>NA</td>
<td>Complete healing, HD &gt; TD; NNT, 7; complete healing (95% CI, 4-16)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vin et al</td>
<td>RCT</td>
<td>Pr vs ND</td>
<td>Leg ulcers</td>
<td>73 (73)</td>
<td>Complete healing, NS</td>
<td>.37</td>
<td>Mean (SD) surface decrease: 36.5% (11.4%) (ND) vs 54.4% (10.9%) (Pr), P&lt;.001; 20% surface area reduction: 42% (ND) vs 19% (Pr), P=.03; Ease of use, P=.10; mean dressing acceptability score, P=.17 (investigators) and P=.06 (patients)</td>
</tr>
<tr>
<td>Belmin et al</td>
<td>RCT</td>
<td>Alg and HCD vs HCD</td>
<td>Pressure sores</td>
<td>110 (110)</td>
<td>SAR and percentage of patients with ≥40% SAR at 4 and 8 wk; mean (SD) SAR: 7.6 (7.1) cm² vs 3.1 (2.7) cm² at 8 wk; SAR 40: 74.4% vs 58.5% at 8 wk</td>
<td>.001</td>
<td>Pain during dressing change, P=.03; ease of use, P=.11</td>
</tr>
<tr>
<td>Sayag et al</td>
<td>RCT</td>
<td>Alg vs D</td>
<td>Fibrous pressure sores</td>
<td>92 (92)</td>
<td>Time to achieve ≥40% SAR, plus granulation tissue uniformly covering the wound bed; median of 4 wk vs &gt;8 wk</td>
<td>&lt;.001</td>
<td>Mean surface area reduction per week: 2.39 cm² (Alg) vs 0.27 cm² (D), P&lt;.001; minimum 40% reduction in wound surface: 74% (Alg) vs 42% (D), P=.002</td>
</tr>
<tr>
<td>Lalau et al</td>
<td>RCT</td>
<td>Alg vs PGD</td>
<td>Diabetic foot lesions</td>
<td>77 (77)</td>
<td>Percentage of patients with granulation tissue over 75% of wound area and 40% SAR at 6 wk, NS</td>
<td>NA</td>
<td>Pain during dressing change: lower in Alg group, P=.047</td>
</tr>
<tr>
<td>Meaume et al</td>
<td>RCT</td>
<td>HCD vs ND</td>
<td>Leg ulcers</td>
<td>91 (91)</td>
<td>SAR at 8 wk, NS</td>
<td>NA</td>
<td>Pain during dressing removal, maceration and odor: better acceptability of ND, P&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: Alg, alginate; CD, cotton dressing; CI, confidence interval; D, dextranomer; FD, foam dressing; HCD, hydrocolloid dressing; MA, meta-analysis; NA, not available; ND, nonadherent dressing; NNT, number needed to treat; NS, not significant; OR, odds ratio; PGD, paraffin gauze dressing; Pr, Promogran (Johnson & Johnson, Issy-les-Moulineaux, France); RCT, randomized control trial; SAR, surface area reduction; SG, saline gauze; WDG, wet-to-dry gauze.

Level B studies were defined as (1) RCTs including few patients but with primary outcomes evaluated blindly, randomization method performed correctly, primary and secondary objectives clearly defined, and patient groups comparable at baseline or (2) meta-analyses including level C RCTs.

General performance criteria are pain, ease of use, avoidance of wound trauma on dressing removal, and ability to absorb and contain exudates.
between SCD and FD was found in the incidence of positive bacterial cultures.65

**COMMENT**

According to our systematic review, the methodological quality of most studies of wound dressings is poor (level C). There is little evidence to indicate which dressings are the most effective in chronic and acute local wound care in terms of complete healing, comfort, and prevention of infection. Most studies had several of the following limitations: (1) the number of patients was not based on a sample size calculation performed beforehand; (2) the randomization method was not described; (3) assessment of outcomes was not blinded to treatment or was not completely objective; (4) an intention-to-treat analysis was not always used; (5) assessment of objective or subjective measures of dressing performance was not always clearly described; (6) the study population was heterogeneous, particularly in studies of leg ulcers; (7) whether adjuvant treatments, such as pressure-relieving surfaces for pressure sores or off-loading devices for neuropathic diabetic foot ulcers, were used in each treatment group was not specified; and (8) a small sample size was combined with multiple outcome measures. There is, however, good (level B) evidence to suggest that, for chronic wounds, HCD dressings are better than saline gauze or paraffin gauze for complete healing and that alginates, used either singly or in combination with other dressings, are better than saline gauze or paraffin gauze for complete healing and that alginates, used either singly or in combination with other dressings, are better than saline gauze or paraffin gauze for complete healing. Other performance factors should be evaluated independently of any potential effect on healing. Intermediate goals in wound management strategy (ie, primary end points such as complete wound debridement for hydrogel dressings and lowering of systemic infection and prescription of antibiotics for SCDs) might be worth test-
ing. Other end points could be evaluated in specific situations (eg, when there is a need to control bleeding in hemorrhagic wounds or avoid trauma in cases of fragile skin).

In conclusion, available systematic reviews of the value of different types of dressing in the management of acute and chronic wounds provide only weak levels of evidence on clinical efficacy.\textsuperscript{10-12,18} The review by Palfreyman et al\textsuperscript{12} identified 42 RCTs that evaluated dressings for the treatment of venous leg ulcers but found that no dressing was better than any other in terms of number of ulcers healed.\textsuperscript{12} In our review, the studies with the best level of evidence underline the potential interest of some modern dressings (ie, use of HCDs and FDS) in optimizing the complete healing rate of chronic wounds, of alginites for the debridement of necrotic tissue from chronic wounds, and of HFDs for hastening the healing of acute wounds. However, our review also stresses the need for more wound care research providing level A evidence. Health care professionals require more detailed recommendations on the use of dressings. A discussion of our review by an expert panel would be useful in achieving professional agreement on the recommended use of dressings.

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Author Contributions: Study concept and design: Chaby, Senet, Vaneau, Meaume, Téot, Dompmartin, Denis, and Chosidow. Acquisition of data: Chaby, Martel, Guillaume, Meaume, Debure, Dompmartin, Guillot, and Chosidow. Analysis and interpretation of data: Chaby, Senet, Martel, Guillaume, Meaume, Téot, Dompmartin, Bachelet, Carsin, Matz, Richard, Rochet, Sales-Aussias, Zagnoli, Guillot, and Chosidow. Drafting of the manuscript: Chaby, Senet, Vaneau, and Guillaume. Critical revision of the manuscript for important intellectual content: Senet, Vaneau, Martel, Guillaume, Meaume, Téot, Debure, Dompmartin, Bachelet, Carsin, Matz, Rochet, Sales-Aussias, Zagnoli, Denis, Guillot, and Chosidow. Statistical analysis: Chaby. Obtained funding: Chaby and Vaneau. Administrative, technical, and material support: Vaneau, Martel, and Sales-Aussias. Study supervision: Chaby, Senet, Vaneau, Guillaume, Debure, Dompmartin, Rochet, Denis, Guillot, and Chosidow.

Financial Disclosure. Dr Meaume participates in educational programs on Profore multilayer bandaging manufactured by Smith & Nephew and is a co-organizer for an international study on the epidemiology of pain and wounds for Molnlycke Products. Dr Téot is involved in the following collaborations and partnerships: scientific collaboration of wound dressings with Braun (randomized trial on calgitrol vs alginate in infected wounds) and Kinetic Concepts Inc (KCI) (and the French Ministry of Health) on a medical-economic study of the effects of vacuum-assisted closure (KCI); editorial collaboration with Molnlycke Products (pain and dressing changes for acute wounds), KCI (on technical considerations of vacuum-assisted closure [World Union of Wound Healing Societies statement]), and Coloplast (on pain management of wounds); and educational partnerships with Smith & Nephew, Johnson & Johnson, and Urgo. Drs Senet and Chosidow are presently involved in building a protocol using Dermagen to treat diabetic foot ulcers; Dermagen is manufactured by Genevrier, a French company that also sells HA-associated dressings.

REFERENCES


Injection Drug Use

An Understudied Cause of Venous Disease

Barbara Pieper, PhD, APRN, BC, CWOCN; Robert S. Kirsner, MD, PhD; Thomas N. Templin, PhD; Thomas J. Birk, PhD, MPT

Injection drug use has devastating effects on the veins, skin, muscles, and joints of the lower extremities, thus increasing the risk of chronic venous disease (CVD). We examined the following risk factors for CVD in persons who injected drugs: health and drug use history, ankle mobility, pain, and skin and wound assessment. Because of deep venous thrombosis and injury and immobility to the calf muscle pump from injected drugs, CVD occurs at a young age. Decreased ankle joint movement, decreased walking, and increased pain are associated with worsening CVD clinical classification. Associated venous ulcers tend to be multiple and large by the time wound care is sought. Cellulitis and abscesses may also be present. Injection drug users serve as a model for the multifactorial nature of CVD including vein damage, diminished ankle range of motion, and decreased calf muscle strength. Persons who inject drugs need to have their lower extremities assessed for CVD on a routine basis.

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Injected drugs, heroin being the most common, account for 12% of all illicit drug use in the United States. The term injection drug use (IDU) encompasses the 3 routes of injecting (ie, intravenous, subcutaneous, and intramuscular). The intravenous route is preferred because of the rapid drug response. Intravenous injecting generally begins in the veins of the arms and upper part of the body, but as these sites become more difficult to find, the veins of the groin, legs, and feet are used. Because of such factors as substances mixed (“cut”) with the drug, injection technique, and frequency of injecting, IDU leads to venous scarring and collapse, abscess formation and other infections, nerve and muscle damage, and lymphatic blockage. While IDU is often considered in terms of acute complications, it has long-term, deleterious effects even after stopping. Among these long-term effects is the development of chronic venous disease (CVD). Previously, we reported CVD as a complication of IDU in a large sample of persons receiving methadone treatment, with a point prevalence of 87% and more than half (52%) being in the most advanced stages (classes 4 through 6 of the Clinical-Etiology-Anatomy-Pathophysiology [CEAP] classification). We discuss risk factors, health and drug use history, ankle mobility, pain, and wound assessment for persons who injected drugs in terms of CVD.

PATHOPHYSIOLOGIC FEATURES OF VENOUS DISEASE

Pathophysiologic features of CVD involve abnormalities of the venous system or other parts of the calf muscle pump of the lower extremities. Anatomically, the venous system of the legs consists of the deep, superficial, and communicating/perforator veins. The deep venous system is surrounded by muscle and fascia for support. In contrast, the superficial system is not well supported but is protected from the higher pressures in the deep system by 1-way valves in the perforating system. Valves throughout the venous system allow for unidirectional blood flow to the heart. The most common...
of DVT. McColl and colleagues re-
drugs have an increased prevalence.
As a result, persons who inject
tors affecting the general popula-
tensifies" the typical CVD risk fac-
Injection drug use "augments or in-
we found a high preva-
cases of DVT and increases to 52.4% 
reported that the association of IDU
cause of CVD by 2.4-fold. After injury, to
and muscle damage from injecting
drugs may impair function of the call
muscle and ankle joint. Whether
damage occurs directly from injec-
tions or from events related to the
stuporous state, serious leg injury
may occur, increasing the risk of
CVD by 2.4-fold. After injury, to
control pain in their legs and feet,
injection drug users often do not
move their feet or ankle joints while
walking, thus negatively affecting
the calf pumping mechanism.
Increasing age is a risk factor for
CVD. Injection drug use typically be-
gins around age 19.5 years; thus, ve-
nous damage begins at a young age.
At present, persons born between the
late 1940s and early 1960s have the
highest prevalence of IDU. Unlike
the general population that reports
problems with CVD in the sixth and
seventh decade of life, persons who
inject drugs have venous ulcers in
their 30s and 40s. As an example,
the mean age of participants in our
studies is 46 to 48 years.

HEALTH AND
DRUG USE HISTORY
As health and psychosocial histo-
ries may play a critical role in un-
derstanding CVD and wound care,
they need to be carefully exam-
ined. Injection drug users have com-
plex medical histories often reporting
2 to 3 health problems. Among
the most frequent health problems
reported are arthritis, hepatitis C, hy-
pertension, heart disease, mental ill-
ness, human immunodeficiency vi-
rus, stomach ulcer, and diabetes
mellitus. While substance abuse might
be thought to affect a specific demog-
raphy, in fact, it may occur at any
age, in either sex, in any race, or in
any socioeconomic group; there-
fore, its history should be assessed
for all patients. Substance use ques-
tions will provide information about

cigarette, alcohol, and illicit drug use.
Tobacco use, as a comorbidity, is
common and associated with arte-
rial disease and may negatively affect
wound healing. While arterial dis-
 ease commonly affects one-quarter
of patients with CVD, whether the
incidence of arterial disease is higher
in injection drug users with CVD is
not known. Alcohol should be ex-
amined in terms of amount and fre-
quency of use; it may be heavily con-
sumed by some. Although a person
often has a drug preference, most use
more than 1 substance. We found
that among our participants, inject-
ing heroin ranged from 83% to 99%
and cocaine, a vasoconstrictor that
is associated with cardiovascular
problems, by various routes ranged
from 62% to 81%. Besides the
type of substance, the route of use
(e.g., inhaled, smoked, injected), years
of use, and location of injecting are
critical. The mechanism of CVD de-
velopment may occur for a variety
of reasons in persons who use illicit
substances. We have hypothesized
that the site of injection is one such
critical factor, and for injected drugs,
we found that injecting in the groin,
legs, and feet was correlated with
CVD (P = 0.47, P < .001). Self-reported information of il-
licit drug users appears to be reli-
able. Although blood, urine, and
sputum analysis may document cur-
rent drug use, drug use of past years
does not have a chemical analysis and
is dependent on self-report. The re-
liability of self-report of health and
drug use histories is high (r = 0.71-
0.95). We also found similarly high
reliability of health and drug
history questions (i.e., interclass cor-
relations for youngest and oldest ages
of injecting, years not injecting, and
total injecting years ranged from
0.90-0.98).

ANKLE MOBILITY
Normal ankle mobility and pain-
less calf muscle action are required
for normal calf pump function. In
the absence of normal function, the
muscle vein pump of the leg can be
especially impaired by restriction
of ankle joint mobility. Weight bear-
ing and dorsiflexion of the upper
ankle joint have been suggested as
the key mechanisms for the calf

| Table. The Clinical-Etiology-
Anatomy-Pathophysiology Clinical
Classification |
<table>
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<tr>
<td>Class</td>
<td>Description</td>
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<tr>
<td>0</td>
<td>No visible or palpable signs of venous disease</td>
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<td>1</td>
<td>Telangiectases or reticular veins</td>
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<td>2</td>
<td>Varicose veins, distinguished from reticular veins by a diameter of ≥ 3 mm</td>
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<td>3</td>
<td>Edema</td>
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<td>4a</td>
<td>Pigmentation or eczema</td>
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<td>4b</td>
<td>Lipodermatosclerosis or atrophie blanche</td>
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<td>5</td>
<td>Healed venous ulcers</td>
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<td>6</td>
<td>Active venous ulcer</td>
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causes of CVD are superficial vein
regurgitation and deep vein obstruc-
tion. Superficial vein regurgitation
results from dysfunctional valves in
the superficial or communicating
veins that permit the high pressure
generated in the deep venous sys-
tem during calf pump contraction to
be transmitted to the superficial sys-
tem. Deep vein obstruction is pri-
marily caused by deep venous thrombosis (DVT).

Injection drug use "augments or in-
tensifies" the typical CVD risk fac-
tors affecting the general popula-
tion. As a result, persons who inject
drugs have an increased prevalence of DVT. McColl and colleagues reported that the association of IDU with DVT is as high as 21.4% for all cases of DVT and increases to 52.4% for women younger than 40 years. We have also found a high preva-
elence of DVT, with 27% of our par-
ticipants in one study reporting DVT. Thrombi, while extending centrally
within the vein lumen, may par-
tially or completely occlude it and are
often silent without a person ever
knowing they occurred. A history of
DVT increases the risk of CVD by
25.7-fold.

Immobility as a risk factor has implications for IDU. In a stuporous
drug state, the muscles of the lower extremities are inactive, and dimin-
ished venous return occurs. Nerve
and muscle damage from injecting
drugs may impair function of the call
muscle and ankle joint. Whether
damage occurs directly from injec-
tions or from events related to the
stuporous state, serious leg injury
may occur, increasing the risk of
CVD by 2.4-fold. After injury, to
tcontrol pain in their legs and feet,
injection drug users often do not
move their feet or ankle joints while
walking, thus negatively affecting
the calf pumping mechanism.

Increasing age is a risk factor for
CVD. Injection drug use typically be-
gins around age 19.5 years; thus, ve-
nous damage begins at a young age.
At present, persons born between the
late 1940s and early 1960s have the
highest prevalence of IDU. Unlike
the general population that reports
problems with CVD in the sixth and
seventh decade of life, persons who
inject drugs have venous ulcers in
their 30s and 40s. As an example,
the mean age of participants in our
studies is 46 to 48 years.

HEALTH AND
DRUG USE HISTORY
As health and psychosocial histo-
rices may play a critical role in un-
derstanding CVD and wound care,
they need to be carefully exam-
ined. Injection drug users have com-
plex medical histories often reporting
2 to 3 health problems. Among
the most frequent health problems
reported are arthritis, hepatitis C, hy-
pertension, heart disease, mental ill-
ness, human immunodeficiency vi-
rus, stomach ulcer, and diabetes
mellitus. While substance abuse might
be thought to affect a specific demog-
raphy, in fact, it may occur at any
age, in either sex, in any race, or in
any socioeconomic group; there-
fore, its history should be assessed
for all patients. Substance use ques-
tions will provide information about

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A simple way to measure calf muscle function is the standing heel rise test. This is a noninvasive measure of strength and endurance of the calf muscle pump and consists of eccentric-concentric muscle action of planar flexion. Ankle planar flexion strength has an important role in standing balance, walking, and most activities of daily living. The heel rise test is the ability to lift the heel 5 cm off the ground while holding the opposite foot off the floor and only lightly touching a surface with a hand. Participants with venous disease classes 5 and 6 performed rises (mean±SD, 14.6±7.34) than the healthy controls (23.5±6.54). We are also currently examining psychometric properties and use of the heel rise test with injection drug users.

Another simple method to measure calf muscle function indirectly is by measuring ankle range of motion. Using goniometry, one can measure joint angles including dorsiflexion (upward foot movement), plantar flexion (downward foot movement), inversion (inward foot movement), and eversion (outward foot movement). Goniometry uses a hinged tool designed to measure such joint angles. As an example, in persons positive for human immunodeficiency virus with (n=46) and without (n=27) a history of IDU, CVD in each leg correlated significantly (P<.001) with goniometric measurements of dorsiflexion-plantar flexion (right and left, r=-0.43 and -0.43, respectively) and inversion-eversion (right and left, r=-0.45 and -0.45, respectively). Thus, severity of CVD was associated with reduced ankle joint motion. Others have reported that ankle range of motion and calf pump function worsened with worsening CVD.

PAIN

Pain is associated with CVD, and while it may be present before leg ulcers develop, it is worse with more advanced CVD. Pain appears to be common in injection drug users with CVD. Using an 11-point scale (0, no pain, to 10, worst pain), persons who injected drugs rated their CVD-related leg pain. Interestingly, the more severe the CVD, the more severe the leg pain. The most painful activities identified by persons who injected drugs were working, walking outside, standing, and stair climbing. In those who had ulcers, ulcer size was a predictor of pain, and larger venous ulcer area was significantly related to greater current pain (r=0.44, P=.02), worst pain in 24 hours (r=0.41, P=.02), and higher pain intensity (r=0.44, P=.02) for persons who injected drugs.

ONGOING RESEARCH ABOUT IDU AND CVD

Our present study is designed to examine the causal relations among the variables of IDU, CVD, mobility, and leg pain. The initial reliability phase has been completed using the first 104 participants (the sample is described elsewhere). Preliminary findings support the proposed association between CVD, mobility, and pain are shown in the Figure. Figure, A, shows that as the venous disease advances (using the venous disease CEAP clinical classification), the amount of time spent sitting during work increased (r=0.33, P=.001) and the distance walked per day decreased (r=-0.25, P=.009). From this and the evidence reviewed in this article, we concluded that CVD affected mobility. Figure, B, shows leg pain and difficulty in using the legs as a consequence of CVD. In Figure, B, the difficulty score was a composite computed by taking the mean rating for difficulty walking, standing, stair climbing, and working, as rated on a scale from 0 (no difficulty) to 10 (great difficulty). As the CVD worsened, leg pain (r=0.27, P=.006) increased and difficulty using the legs increased (r=0.23, P=.02).

While these associations exist, whether the relationship among mobility, pain, and CVD is unidirectional or bidirectional is not known. Nor is it known whether pain is only
a consequence of CVD or causally involved. A larger, ongoing study is designed to address these types of etiological questions. We hypothesize that mobility and leg pain will mediate the relationship between injection in lower extremities and CVD.

**SKIN AND WOUND ASSESSMENT**

Skin and soft tissue infections, which may occur along with venous ulcers, are common reasons for hospitalization of persons who inject drugs. The mechanism for the development of infection usually includes tissue trauma, direct effect of the drugs, tissue ischemia, and bacteria. The most frequent presenting symptoms of an abscess for persons who inject drugs are pain and tenderness (100%), erythema (93%), wound fluctuance (74%), leukocytosis (54%), lymphadenopathy (48%), and fever (42%). Infections that are deep may not present with the typical manifestations. Microorganisms tend to be flora from the skin and oropharynx because of injecting practices. With incision and drainage, these areas should be cultured and the appropriate antibiotic selected.

Injection drug use does not change the need for careful wound assessment—location, size, depth, color, drainage, odor, pain, infection, causative factors, and self-care. Unfortunately, persons who inject drugs frequently have multiple, large leg ulcers when they present for care. We previously examined medical records of 172 injection drug users who had venous ulcers. These patients had leg ulcers for a mean ± SD of 5.4 ± 4.7 years. Venous ulcers were present on both legs in 42% and on 1 leg in 58%. Patients often had multiple ulcers, up to 6 per leg. The total area of ulceration was often large, up to 485 cm². Persons who healed tended to have a shorter duration of leg ulcer history (P = .06) and had significantly smaller ulcers (P = .01) than those unavailable for follow-up or those continuing treatment. A larger wound area was associated with greater illness-induced difficulties in the home, greater psychological distress, and poor quality of life. These persons should be encouraged to seek medical care early for the treatment of venous ulcers.

**IMPLICATIONS FOR WOUND CARE**

Considerations when providing wound care to a patient who has a history of drug use are summarized below.

- Substance use history is critical and must include cigarette use, alcohol, and illicit drugs. For illicit drugs, the drug, route of use, and location of injecting are important.
- Clinicians need to be aware of the increased risk for CVD in persons who have injected drugs, assess for it, and encourage these persons to seek professional wound care when leg ulcers are small.
- Persons who inject drugs often have additional chronic illness that may affect skin and wounds on the lower extremities.
- Pain assessment and pain treatment need to be done for persons with IDU. Pain is associated with CVD and wound area. Patients need to be educated in the use of analgesic medications.
- Prevention or delayed advanced stages of CVD is important. Discourage injecting in the groin, legs, and feet. Encourage leg elevation and the use of compression hose.
- Ankle mobility is affected by IDU and CVD. Encourage ankle mobility and staying active. Discourage shuffling gait or walking on the side of the foot. This may necessitate a detailed physical therapy assessment and management plan.
- Living arrangements affect wound care. Odor is a great problem in group living. Dressings that are associated with odor need to be avoided.
- Lack of transportation, drug treatment, legal issues, and mental health problems affect psychological functioning and the person’s ability to follow long-term wound care treatment.

Even at a young age, CVD needs to be considered in persons who have injected drugs, especially when injecting occurs in the lower extremities. The health and surgical histories provide information about health conditions that affect wound healing. The psychosocial history helps focus the impact of factors such as housing, transportation, and mental health on receiving care. Homelessness has a high association with drug dependency. Depression and anxiety are commonly reported disorders among substance abusers. Living arrangements, economics, mental status, and dental status affect nutrition. Drug treatment programs, court mandated programs, employment, and family commitments affect when a person can receive wound care. Because venous ulcer care is often administered weekly, transportation difficulties affect the person’s return visits to the clinic. We found that the education level of our participants tended to be between the 11th and 12th grade. Since reading ability, on average, is 3 to 5 grade levels below the number of grades of school completed, education and literacy levels have an impact on the patient teaching of CVD.

All patients should be asked questions about substance use. Tobacco use is assessed for current use and years of use. The National Institute on Alcohol Abuse and Alcoholism provides recommendations for the assessment of alcohol use and helping patients. Asking about street drug use in terms of type, route, body sites of use, and years of use will give information about the risk of CVD. The skin and wounds need to be carefully assessed and a treatment plan developed. Because CVD is a chronic condition, patient teaching is critical, and they should be encouraged to adhere to the treatment plan. These patients need to understand their role of self-care in terms of nutrition, protecting their legs such as with leg elevation, leg and ankle exercises, compression therapy, and pain management. Leg pain and decreased functioning occur with worsening CVD state. Leg ulcers are frequently hidden under clothing and may be large when the person seeks care; thus, both legs must be examined on each clinic visit. Large wounds require special consideration in terms of the amount of wound drainage, odor, time to heal, and pain. These persons are able to learn dressing protocols. Patients must feel comfortable with the
clinician and be encouraged to actively participate in wound care. Clinicians must understand that substance abuse can be long-term, with periods of abstinence and periods of active use.

CONCLUSIONS

Chronic venous disease has a high point prevalence in persons who have injected drugs. Vein, nerve, and muscle-joint damage to the lower extremities affects the physiologic characteristics of normal venous function. This damage continues to evolve even after drug use has ceased. These persons are also at high risk for DVT. Lower extremity changes may occur at a young age; thus, these persons may exhibit advanced CVD in early adulthood. Substance abuse history is critical to obtain when evaluating for the risk of CVD. Chronic venous disease increases pain in the legs and decreases mobility, affecting one’s quality of life and activity involvement. Recognition of CVD as a complication of IDU is crucial.

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Author Contributions: Dr Pieper had full access to all data in studies she conducted and takes responsibility for the integrity of the data and the accuracy of data analyses. Dr Tempkin was the statistician and coinvestigator with Dr Pieper; Dr Kirsner was the medical advisor and coinvestigator; and Dr Birk was the physical medicine advisor and coinvestigator.

Study concept and design: Pieper, Kirsner, Tempkin, and Birk. Acquisition of data: Pieper and Birk. Analysis and interpretation of data: Pieper, Kirsner, Tempkin, and Birk. Drafting of the manuscript: Pieper, Kirsner, and Tempkin. Critical revision of the manuscript for important intellectual content: Pieper, Kirsner, Tempkin, and Birk. Statistical analysis: Pieper and Tempkin. Obtained funding: Pieper, Kirsner, Tempkin, and Birk. Administrative, technical, and material support: Pieper, Kirsner, Tempkin, and Birk. Study supervision: Pieper.

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Additional Contributions: Joyce Peck, BSN, RN, Terri Gibbons, and Cynthia Birk, BA, CET, assisted in research, and Edwin Frank Thompson performed data entry.

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Hydroxyurea-Induced Leg Ulcers Treated With a Protease-Modulating Matrix

Marco Romanelli, MD, PhD; Valentina Dini, MD; Paolo Romanelli, MD

**Background:** The development of painful leg ulcers in the ankle area is a rare and only partially described complication in patients receiving high-dose, long-term hydroxyurea treatment for myeloproliferative diseases. Several reports have described treatments for chronic wound management with this type of lesion.

**Observations:** We describe 2 patients who were diagnosed as having hydroxyurea-induced leg ulcers that were successfully treated with a freeze-dried sponge containing oxidized regenerated cellulose and bovine purified collagen. This dressing is able to modulate the activity of proteases such as plasmin, neutrophil-derived elastase, and matrix metalloproteinase by physically entrapping them and thus inhibiting their activity.

**Conclusion:** This case demonstrates that topical application of a matrix metalloproteinase modulator can be a successful and safe treatment option for patients with hydroxyurea-induced recalcitrant leg ulcers.

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**HYDROXYUREA IS A HYDROXYLATED DERIVATIVE OF UREA THAT HAS BEEN RECOGNIZED SINCE 1960 AS AN EFFECTIVE AGENT FOR TREATING CANCER.** It is an inhibitor of cellular DNA synthesis and promotes cell death in the S phase of the cell cycle through its inhibition of the enzyme ribonucleotide reductase. The most common indications for hydroxyurea therapy are chronic myeloid leukemia and gastrointestinal malignant melanoma. It has also been used in the management of other myeloproliferative disorders, sickle-cell disease, polycythemia vera, psoriasis, and to inhibit viral replication in human immunodeficiency virus disease. While the drug’s mode of action on bone marrow elements is well established, its effects on actively proliferating epithelial cells remain less well described.

Most adverse effects of hydroxyurea are mild and include fatigue, headache, nausea, vomiting, diarrhea, or fever. Rare and severe adverse effects appear to be linked to long-term administration and may be systemic (eg, leukopenia and anemia) or restricted to skin and mucous membranes (eg, stomatitis and diarrhea). Other dermatologic adverse effects are commonly reported with long-term daily therapy and include alopecia, hyperpigmentation, scaling, poikiloderma, atrophy of the skin and subcutaneous tissues, nail changes with multiple pigmented nail bands or brittleness, erythema and scaling of the face and acral sites stimulating chronic dermatomyositis, and lichen planus-like lesions or skin tumors on UV light-exposed areas.

Another rare and incompletely characterized complication, painful leg ulcers, has been described in patients with myeloproliferative diseases receiving high-dose, long-term hydroxyurea treatment. Poor response to traditional local and systemic therapy is a typical feature of hydroxyurea-induced leg ulcers, and discontinuation of treatment with the drug is often required to achieve complete wound healing.

Herein, we describe 2 cases of a pronounced association between hydroxyurea therapy and the development of painful leg ulcers unresponsive to standard treatment, as well as their successful treatment with local application of a sponge prepared from bovine collagen and oxidized regenerated cellulose (Promogran; Johnson & Johnson Wound Management, Piscataway, New Jersey).

**REPORT OF CASES**

**CASE 1**

In 1993, a 70-year-old woman was diagnosed as having thrombocytopenia. In 1994, she began treatment with oral hy-
droxyurea (500 mg, twice a day) after failure of an anticoagulant therapy. In June 1999, painful ulcers developed in both lateral malleolar regions. Examination revealed 2 shallow, painful, well-defined ulcers with an adherent, yellow, fibrinous necrotic base and a livid border. The ulcers showed no signs of healing when treated with several local therapies such as gauzes impregnated with hydrogel, local hyperbaric oxygen, fibrinolytic ointment, and silver sulfadiazine cream. A full workup for venous and arterial assessment produced no abnormal results. In February 2000, because of high platelet values, hydroxyurea treatment was discontinued and oral busulfan therapy was started; this was maintained for 1 month. The size and severity of the ulcers partially reduced in 8 weeks with a topical hydrofiber dressing therapy.

In December 2001, the patient restarted therapy with oral hydroxyurea (500 mg, twice a day) because of high platelet values, and in April 2002, painful leg ulcers recurred in both lateral malleolar regions (Figure 1A). We successfully treated the ulcers by local application of Promogran dressing, which was applied on a wound bed moistened with isotonic sodium chloride solution and then covered with a nonadherent secondary dressing. Initially, we treated the ulcers with an application of the dressing every other day, and then twice weekly (Figure 1B). The treatment resulted in complete healing in 8 weeks, and the ulcers had not recurred at 1-year follow-up (Figure 1C).

**CASE 2**

An 82-year-old woman was diagnosed as having a polycythemia vera of 6 years’ duration. After 2 years of continuous treatment with oral hydroxyurea (1000-1500 mg/d), she developed a small painful ulcer on her right heel, distal to the medial malleolus. No preceding trauma was reported. Clinical examination and color Doppler evaluation showed venous dysfunction, but the patient could not tolerate any type of compression therapy. Treatment with hydroxyurea was stopped, and subcutaneous interferon alfa therapy was begun (5 × 10⁶ IU every other day). The ulcer healed in 4 weeks under treatment with Promogran dressing twice a week.

Because interferon was not well tolerated, oral hydroxyurea was reinstated a few weeks later. Within 3 months, 2 painful ulcers had appeared on her right lateral malleolus. Both ulcers were circular and well demarcated at her first visit and became confluent in a single large lesion with a fibrinoid-necrotic base 48 hours later (Figure 2A). Topical application of Promogran dressing twice a week was restarted. The ulcers showed a progressive increase in the formation of granulation tissue after 2 weeks (Figure 2B) and were 85% healed in 6 weeks (Figure 2C).

**COMMENT**

Hydroxyurea is usually well tolerated and has a low toxic effect profile. However, cutaneous adverse effects such as diffuse hyperpigmentation, brown discoloration of nails, acral erythema, photosensitization, fixed drug eruption, alopecia, and oral ulceration have been described. Painful, difficult-to-heal leg ulcers associated with hydroxyurea therapy have been rarely reported. Montefusco and colleagues describe 17 patients who had hydroxyurea-related leg ulcers and achieved complete resolution or significant improvement after hydroxyurea therapy was discontinued. Another study described 4 patients with hydroxyurea-induced skin ulcers that eventually healed with appropriate wound care. Other authors describe the effectiveness of pentoxifylline and prostaglandin E₃ in the treatment of leg ulcers in patients continuing systemic therapy with hydroxyurea. There is also a case report concerning the suc-
Successful treatment of these kind of lesions with the local application of Apligraf (Novartis, East Hanover, New Jersey), a tissue-engineered human skin equivalent.15

Herein we describe 2 patients who developed cutaneous leg ulcers while receiving long-term treatment with hydroxyurea. Our clinical experience confirms and clarifies the association between hydroxyurea therapy and the development of chronic leg ulcers, while our observations show that the patients who had hydroxyurea-induced leg ulcers developed hard-to-heal ulcers again when hydroxyurea treatment was resumed. We successfully treated the ulcers with local therapy by using Promogran dressing during the concomitant hydroxyurea treatment. In the beginning, we treated the ulcers with an application of the dressing every other day, and then twice weekly. The treatment resulted in complete healing in the first case and 85% healing in the second after 8 and 6 weeks of dressing application, respectively.

Other common features of these wounds include round shape and well-defined aspect at an early stage, high level of pain, and occurrence at the malleolar region. This localization may be caused by mechanical injury and trauma, but chronic and progressive cytologic damage is also involved due to the antimetabolic activity of the drug. The exact mechanisms by which hydroxyurea may lead to the formation of leg ulcers is still unclear, but long periods of exposure to the drug, latency in ulcer formation, chronic and slow ulcer enlargement, and healing after discontinuation of hydroxyurea therapy all suggest a chronic cumulative cytologic toxic effect of the medication.

Hydroxyurea selectively kills cells such as basal keratinocytes and inhibits collagen synthesis, so the drug itself could be considered a possible etiologic factor. However, platelet-derived inflammatory mediators related to the myeloproliferative disorders may play a part in the pathogenetic process. Usually cutaneous wounds develop spontaneously or after local previous trauma, and healing is possible only through discontinuation of the hydroxyurea treatment.16

Our study describes the successful treatment of hydroxyurea-induced leg ulcers with a novel material that modified the wound environment by significantly reducing the activity of proteases present in human chronic wound fluids. The treatment produced excellent pain relief in both patients, which was unexpected, and the mechanism of this benefit is unclear.

Promogran is a freeze-dried sponge containing oxidized regenerated cellulose and bovine purified collagen. This dressing lowers the activity of proteases such as plasmin, neutrophil-derived elastase, and matrix metalloproteinase by physically entrapping them and thus inhibiting their activity in diabetic foot ulcers.17 An alteration in the amount of these proteases plays a role in the occurrence of chronic wounds. This dressing inhibits the degradation of growth factors and the destruction of tissue, limiting the damage to collagen synthesis due to hydroxyurea. We believe that this rebalancing of the wound environment should hasten the wound repair process, diminish local pain, and consequently provide an efficacious treatment for hard-to-heal leg ulcers associated with hydroxyurea treatment. Local treatment was well tolerated compared with standard therapy and showed no adverse events.

In conclusion, we describe 2 patients with hydroxyurea-induced leg ulcers that responded to a protease-modulating matrix treatment. However, the use of this advanced dressing in the treatment of this atypical ulcer requires more evaluation in future studies.

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Author Contributions: Dr M. Romanelli had full access to all the data in the study and takes responsibility for

Figure 2. A, Large chronic wound with fibrinoid and necrotic tissue at baseline; B, after 2 weeks of treatment with Promogran dressing (Johnson & Johnson Wound Management, Piscataway, New Jersey); and C, after 6 weeks of treatment with Promogran.
the integrity of the data and the accuracy of the data analysis. Study concept and design: M. Romanelli. Acquisition of data: M. Romanelli and Dini. Drafting of the manuscript: M. Romanelli and Dini. Critical revision of the manuscript: P. Romanelli. Administrative, technical, and material support: Dini. Study supervision: P. Romanelli. Financial Disclosure: None reported.

REFERENCES


Announcement

Manuscript Submission

• Before preparing a manuscript authors should review the Instructions for Authors available at http://www.archdermatol.com.
• Manuscripts are submitted to all sections of the Archives by Web access at http://manuscripts.archdermatol.com.
• Authors may check the status of their manuscript as it proceeds through the review and decision process by logging into http://manuscripts.archdermatol.com.
• It is important for authors to update their contact information, especially their e-mail addresses, by logging into http://manuscripts.archdermatol.com. Publication of accepted manuscripts may be delayed by our inability to locate authors, who need to approve copyedited manuscript proofs.
Phenylephrine-Induced Microvascular Occlusion Syndrome in a Patient With a Heterozygous Factor V Leiden Mutation

Andrew H. Kalajian, MD; Klark B. Turpen, MD; Kristin O. Donovan, MD; Janine C. Malone, MD; Jeffrey P. Callen, MD

Background: Cutaneous microvascular occlusion syndromes (MOS) present with noninflammatory retiform purpura with variable outcomes that are dependent on the severity, duration, and specific underlying cause. Transient cases are often associated with few sequelae, while severe forms such as symmetrical peripheral gangrene may be associated with amputation and death.

Observations: A middle-aged man developed MOS after exposure to phenylephrine hydrochloride and experienced complete resolution when treatment with the vasopressor was discontinued. Further evaluation detected a previously subclinical heterozygous factor V Leiden mutation.

Conclusions: We propose that phenylephrine-mediated vasoconstriction superimposed on an underlying thrombotic predisposition precipitated the transient MOS. The role of vasopressors in the development of cutaneous MOS is well documented in the critical care literature; however, it is underrepresented in the dermatologic literature, and, to our knowledge, there are no reports of phenylephrine use inducing MOS. We hope to raise awareness of the potential role of vasopressor medications in causing MOS.

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REPORT OF A CASE

A 45-year-old man with diabetes mellitus and hypertension was admitted to the neurosurgical intensive care unit after undergoing a C5-C6 vertebrectomy with postsurgical spinal degeneration and infectious complications that required prolonged hospitalization, numerous neurosurgical procedures, and ventilatory and vasopressor support over a 4-month period. His family history included a pulmonary embolism that had occurred in his mother at the age of 35 years. We were asked to evaluate a purple discoloration of his hands and feet that had begun 4 days before the consultation. His medications included intravenous levofloxacin, quinupristin-dalfopristin (Synercid), hydrocortisone succinate, propofol, and midazolam hydrochloride as well as electrolyte supplementation, furosemide, hydroxyzine hydrochloride, and metoprolol tartrate (Lopressor) as needed. He had received heparin sodium via flushes of his intravenous access lines and had not received warfarin sodium.

Physical examination revealed an intubated and sedated patient with symmetrical, well-demarcated purpura accompanied by several tense hemorrhagic bullae on his hands and feet in a “stocking-glove” distribution (Figure 1A). Retiform purpura involved his thighs and antecubital fossae (Figure 1B and 1C). His distal pulses were normal and his extremities were warm. He had previously been treated with norepinephrine bitartrate for vasomotor instability resulting from neurosurgical procedures. However, in the past month, his only vasopressor exposure had consisted of a 2-day course of phenylephrine hydrochloride (at a dosage titrated to maintain target mean arterial pressure), which had been discontinued 1 day before the onset of his rash. It was his first

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and only exposure to phenylephrine. He had been afebrile and hemodynamically stable since the phenylephrine therapy had been discontinued.

His platelet count had decreased from 220 to 105 x 10^3/µL over 2 days, and his D-dimer level was elevated at 1.9 mg/L (normal range, 0-1.5 mg/L). The fibrinogen level, prothrombin time, activated partial thromboplastin time, fibrin split product levels, and results of urinalysis were within normal limits. The leukocyte count was normal, and blood cultures were sterile. A skin biopsy specimen revealed fibrin microthrombi in the superficial and middle dermal vessels, with minimal inflammation and no vasculitis (Figure 2). A diagnosis of microvascular occlusion syndrome (MOS) was made.

Spontaneous improvement began on the second day after the evaluation and was hastened by the addition of lepirudin (a direct thrombin inhibitor used as an alternative to heparin) to the patient’s therapy, resulting in a dramatic resolution of the purpura and superficial sloughing and yielding mildly erythematous erosions. He experienced no further thrombotic complications, and his condition had almost completely resolved 2 weeks later (Figure 3), with no long-term sequelae.

Further evaluation revealed negative results or normal levels for the following laboratory investigations: heparin-induced thrombocytopenia antibodies, protein C, homocysteine, prothrombin 20210a mutation, antithrombin III, cryofibrinogens, cryoglobulins, anticardiolipin antibody, lupus anticoagulant, β2-glycoprotein 1 antibody, serum protein electrophoresis, antinuclear antibody, rheumatoid factor, hepatitis panel, perinuclear and cytoplasmic antineutrophil cytoplasmic antibodies, parvovirus titers, echocardiography, and lower-extremity Doppler ultrasonography. A heterozygous factor V Leiden (FVL) mutation was found; the erythrocyte sedimentation rate was 53 mm/h (reference range, 0-10 mm/h); the C-reactive protein level was 27 mg/L (reference range, 0-9.0 mg/L); and the functional protein S value (during acute event) was 36% of the normal level. Subsequent functional protein S testing 2 weeks after resolution revealed a normal level.
The FVL mutation is one of the most common causes of inherited thrombophilia, with 4% to 6% of the US population manifesting heterozygous replacement of arginine by glutamine at position 506 of factor V. This mutated gene product, FVL, is resistant to normal physiologic degradation by activated protein C, yielding a hypercoagulable state. The abnormality is transmitted in an autosomal dominant manner, and the risk of thromboembolism is increased 7- and 80-fold, respectively, in individuals who are heterozygous and homozygous for FVL.  

This baseline-increased susceptibility to thrombotic events is perpetuated by the coexistence of additional genetic or environmental risk factors, including protein C and S deficiencies, antithrombin deficiency, prothrombin gene mutation, elevated levels of factor VIII, hyperhomocystinemia, other coagulation disorders, advanced age, smoking, surgery, immobilization, obesity, pregnancy/postpartum period, or use of oral contraceptives.  

Cutaneous MOS presents clinically with noninflammatory retiform purpura, which has a broad differential diagnosis that includes disorders of platelet plugging, cold-related agglutination, vessel-invasive organisms, embolization, local or systemic coagulopathies, or miscellaneous conditions (eg, calciphylaxis, Degos disease, and sickle cell anemia). Factors that affect the disease course include the severity and duration of the specific underlying cause. Transient precipitants can result in reversible MOS, without a significant event; however, considerable morbidity and mortality are associated with symmetrical peripheral gangrene (SPG). In 1891, Hutchinson described the first case of SPG, which was characterized by acral gangrene occurring in a symmetrical distribution with no evidence of large vessel occlusion or vasculitis. Symmetrical peripheral gangrene, which has been described by some authors as a form of purpura fulminans, is considered a severe form of MOS and is most commonly associated with septic shock and disseminated intravascular coagulation (DIC). Patients with preexisting vascular disorders, such as peripheral vascular disease, diabetes mellitus, Raynaud phenomenon, and prior cold injury, as well as patients who have been exposed to vasoactive medications, are further predisposed to develop SPG. Molos and Hall’s review of 71 cases of SPG revealed that 48% of the patients required intermittent vasopressor support and 35% cases proved fatal.  

Our patient’s heterozygous FVL mutation remained subclinical before this event. At the age of 35 years, his mother had experienced a deep venous thrombosis with pulmonary embolism, which was not further investigated. There was no other known family history of thrombotic events. While there was no evidence of sepsis or DIC, his risk factors for MOS included heterozygous FVL, diabetes mellitus, postsurgical status, immobilization, and obesity. An FVL mutation is highly associated with venous thrombosis; however, it rarely manifests with MOS. Our patient’s underlying neurosurgical issues had required numerous operations and prolonged immobilization over the past 4 months; however, he had only recently developed transient microvascular occlusion. He required intermittent vasopressor support, and treatment with phenylephrine, a pure α-adrenergic agonist that causes intense vasoconstriction and decreased perfusion to the acral vascular beds, had been discontinued just 1 day before the onset of his MOS.  

Considering the physiologic effects and temporal relationship of phenylephrine therapy to the onset of our patient’s microvascular occlusion, we propose that phenylephrine-mediated vasoconstriction superimposed on his thrombotic predisposition precipitated a transient MOS. Dünser et al reported ischemic skin lesions in only one-third of patients receiving vasoactive medications, suggesting that a combination of predisposing factors must surpass a critical threshold, above which MOS occurs, with the subsequent clinical course depending on the severity and duration of the threshold breach. This model would account for the transient and reversible nature of our patient’s MOS: the short-term intense vasoconstriction mediated by phenylephrine therapy resulted in a low-level microvascular occlusion, which spontaneously remitted once the vasoconstrictive effects of phenylephrine resolved and his cumulative thrombotic tendency returned to below the critical threshold value. It is noteworthy that the patient did not develop MOS from his numerous prior exposures to norepinephrine. Perhaps the β-adrenergic properties of norepinephrine (augmenting cardiac output and thus peripheral perfusion) counteracted the vasoconstrictive effects, with the cumulative thrombotic tendency remaining below the critical threshold value.  

Few cases of cutaneous MOS have been reported in patients who are heterozygous for FVL. Patel et al described an 81-year-old woman with heterozygous FVL who developed extensive acral cutaneous necrosis with no clear precipitant, resulting in septicemia and death. Jackson and Luplow reported 2 cases of heterozygous FVL that were complicated by sepsis and DIC, both of which resulted in digital amputations. To our knowledge, this is the first report of transient MOS precipitated by phenylephrine use in a patient with a heterozygous FVL mutation.  

While phenylephrine-induced vasoconstriction is the only identifiable temporally related transient factor associated with our patient’s transient MOS, it is possible that additional causative factors were involved. Antiphospholipid antibody syndrome manifests arterial or venous thrombosis of small or large vessels, and while our patient tested negative for anticardiolipin antibodies, lupus anticoagulant, and β2-glycoprotein 1 antibodies, these tests are technically difficult and false-negative results are not rare. Cryoproteins, including cryofibrinogen and cryoglobulins, are other potential contributors in the present case. Again, our patient tested negative for cryofibrinogen and cryoglobulins; however, the sensitivity of these tests is highly dependent on the method of collection. In the presence of protein S, activated protein C inhibits thrombin generation; therefore, a transient deficiency of protein C or S could trigger a thrombotic event. Proteins C and S are acute-phase reactants and are difficult to interpret during acute events; therefore, only an abnormally low level of either protein before the throm-
The role of vasopressors in the development of transient cutaneous MOS is well documented in the critical care literature. However, it is underrepresented in the dermatologic literature. Published reports have associated cutaneous microvascular occlusion with administration of dopamine, epinephrine, norepinephrine, and vasopressin. We have presented a case of transient MOS in a patient with a heterozygous FVL mutation, without active infection, shock, or DIC, and postulate that the transient nature of his MOS was precipitated by phenylephrine-mediated intense vasoconstriction. We hope that this report will raise awareness of the potential role of vasopressor medications in causing MOS. Cutaneous MOS should prompt a search to identify the potentially multiple causative factors, with dermatologists paying special attention to current or prior vasopressor medication use when consulting in the intensive care setting.

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Critical revision of the manuscript for important intellectual content: Kalajian, Donovan, Malone, and Callen. Administrative, technical, and material support: Kalajian. Study supervision: Kalajian, Donovan, Malone, and Callen.

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Wound Healing

It is a pleasure to serve as the guest editor for this special issue of the Archives dedicated to wound healing. This issue provides the opportunity to appreciate the special relationship dermatologists have with wound healing and to highlight dermatologists' role in advancing the science of wound healing and wound care. In addition, on the 50th anniversary of the Department of Dermatology and Cutaneous Surgery at the University of Miami, Miami, Florida, it provides an opportunity to recognize the outstanding contributions of the department's chairman emeritus, William H. Eaglstein, MD, to the field of wound healing.

Wounds and wound healing intersect medical, surgical, and cosmetic dermatology. Medical conditions as diverse as pemphigus vulgaris, primary syphilis, lupus erythematosus, and sarcoidosis all either have or can have wounds as part of their initial presentation. Dermatologists create more wounds through surgical procedures and biopsies than any other specialty. Often, wounds are treated with surgical procedures such as debridement or grafting. Finally, with regard to cosmetic dermatology, its goals and the goals of wound healing are often the same: to fill a defect or contour, to provide dermal support, and to normalize epithelialization.

See also pages 1267, 1275, 1283, 1305, 1331, and 1333

In 2006, the American Academy of Dermatology, in collaboration with the Society of Investigative Dermatology, published the results of a joint effort evaluating the burden of skin disease in the United States. The results are that skin care is costly, with the 5 conditions most expensive to treat combined costing Americans over $16 billion annually. Second, the conditions that are by far the most expensive to treat are wounds and ulcers. Therefore, wounds are common, extremely costly to the American health care system, and created to a greater extent by dermatologists than by any other specialty; therefore, they should be of interest to all dermatologists.

This issue allows the Archives to celebrate dermatology's role in advancing the science of wound care. This issue also coincides with the 50th anniversary of the Department of Dermatology and Cutaneous Surgery at the University of Miami. In March of this year, the department held a 3½-day academic and social event commemorating scientific and academic advances of the department and its alumni, faculty, and residents. Among the activities was a full day to honor the accomplishments of Dr Eaglstein in the field of wound healing. He was the second of only 3 chairmen that the department, founded by Harvey Blank, MD, has had in its illustrious 50-year history. Having trained under Dr Blank, as a resident and faculty member, Dr Eaglstein returned to Miami in 1986 to assume the chairmanship after serving as chairman of the Department of Dermatology at the University of Pittsburgh, Pittsburgh, Pennsylvania, for 6 years. He led the department at the University of Miami for 17 years, through 2003.

A founding member of the Wound Healing Society who was recently awarded the prestigious John Boswick Award for Lifetime Achievement in Wound Care, Dr Eaglstein has made seminal contributions to wound care. Working with colleagues, he has made many contributions, some of which include the development of the porcine model for wound healing, and the use of this model to study the effect of steroids on healing, to study the effect of occlusion on healing, and to study the effect of antimicrobial agents on healing. He, with others, developed the growth factor trap hypothesis to explain venous ulcer pathophysiologic characteristics, put forth the idea that skin grafts do not act solely as a tissue replacement but as pharmacologic agents in healing, and influenced his department's faculty to develop the concept that biofilms play a role in chronic wound healing. This and other work has led to or popularized the use of occlusive dressings, tissue-engineered skin, and cyanoacrylate dressings. Equally important to his scientific contributions has been Dr Eaglstein's mentorship of members of his departments and of the field. His mentees, like wound healing itself, cross interests and include dermatologic surgeons, scientists interested in wounds, and medical and cosmetic dermatologists. Dr Eaglstein is currently chairman emeritus in the department headed by Lawrence Schachner, MD. This issue of the Archives celebrates Dr Eaglstein's influence on the entire field of wound healing.

Also in this special issue of the Archives, we provide a wide variety of articles, both in terms of types of wounds addressed and the aspects of wound healing discussed. Two articles in the issue explore wound assessment techniques. Pressley et al present data from a recent randomized control trial demonstrating the benefit from a digital analysis system, and Romanelli et al provide rationale for an easy-to-use 3-dimensional laser system for wound assessment. Skin biopsy still remains an important diagnostic and assessment tool. Wahle and Lawrence studied patients undergoing diagnostic biopsies in the inpatient setting and found a high complication rate (29%), most commonly from infection.
Their data suggest that a biopsy site located below the waist, a biopsy performed bedside (vs in a operating suite), comorbid conditions (eg, diabetes mellitus), and lack of subcutaneous sutures were associated risk factors for wound infection.

Also in this issue, 2 articles are presented that discuss the pathophysiologic characteristics of nonhealing venous ulcers. Heinen et al,20 from the Netherlands, studied cases of patients with venous leg ulcers from 12 dermatology department–run wound clinics. The standard of care is multilayered compression dressing, but Heinen et al20 found that only slightly more than one-third of patients used the compression dressings. Interestingly, exercise levels were low in patients with venous leg ulcers. Thirty-five percent of patients with venous leg ulcers walked less than 10 minutes per day. These data are especially interesting in light of an article by Pieper et al,30 who describe a distinct group of patients who have venous disease: those who inject drugs into their legs. Pieper et al30 review the literature and present data from their ongoing study, funded by the National Institutes of Health, evaluating venous disease, mobility, gait, and balance among this subset of injection drug users compared with drug users who do not inject and those who inject into locations other than the legs. It becomes apparent that these patients with venous disease, perhaps representative of all patients with venous disease, have changes in gait, mobility, ankle range of motion, and balance. These 2 articles, taken together, suggest the importance of mobility and the ongoing role of physical therapy for patients with venous disease.

A third article in this issue related to venous ulcers presents new epidemiologic information. Margolis et al27 study the relationship between β-adrenergic receptor agonists and antagonist use and the likelihood of developing venous ulcers. Using a general practice database from the United Kingdom, they demonstrate that patients taking β-adrenergic receptor agonists were less likely to develop venous ulcers. Interestingly, using complex analysis called propensity analysis, they also demonstrate that some subsets of those taking β-adrenergic receptor antagonists were also less like to develop venous ulcers. Taking into account laboratory studies that suggest a role of β-adrenergic receptors in wound repair, this provides a rationale for considering these types of agents in clinical trials for the treatment of venous leg ulcers.

It has been a great privilege to serve as the guest editor for this issue. It has been a pleasure to have worked with June K. Robinson, MD, and the editorial staff of the Archives. Finally, it is an exceptional and singular honor to pay tribute to William H. Eaglstein, MD, who has had a profound influence on my career.

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The Archives of Dermatology Web Site

Adding New Dimensions to the Literature

ONE OF THE GREATEST MODERN-DAY EXTENSIONS of the power of the printed word has been the World Wide Web. Over the past several years, the Archives has stepped up and implemented many Web-based features to enrich readers’ experience and help them use the Archives Web site to the fullest. The latest, most indispensable, easy-to-use features, and the people who make them possible, are highlighted herein.

ADDING YET ANOTHER DIMENSION WITH VIDEO

Dermatology has always been an ideal application for good clinical photography. Essential for establishing diagnosis and monitoring treatment efficacy, accurate photographic reproduction has been indispensable for not only general dermatology but also pediatric dermatology, dermatopathology, procedural dermatology, and other subfields.

See also page 1352

Still photography, however, seems a needlessly limited medium that does not encompass all the expressive needs of dermatology research and education. In recent years, advances in technology have expanded the horizon by bringing high-quality videography within the reach of every dermatologist. Although video cannot be accommodated in the print version of the Archives, we are now at a point where Web-based video can be used to supplement articles appearing in the pages of the journal. This is accomplished superbly for the first time in this issue of the Archives with the “dancing Langerhans cells” video complementing the article by Mohr and Takashima, “Visualization of Epidermal Langerhans Cell Movement in Situ: A Model for Understanding Immunologic Function in the Skin.” We thank James M. Grichnik, MD, PhD, section editor for skINsights, for recruiting this most excellent submission.

The groundwork has been laid. Detailed guidelines have been developed and posted online to assist authors who wish to submit video with their manuscripts (http://archderm.ama-assn.org/misc/sfora.dtl#Videos). These guidelines explain the mechanics of the process, including steps required to maintain quality, uniformity, and usability. We hope that authors and future contributors take a look at these very specific instructions for authors and consider enhancing the Archives experience for our readers by providing videos for installation on the journal Web site.

To be most effective, videos should be brief and designed to enhance understanding of an article. Some article types that are particularly likely to benefit from selective use of video include Studies, Observations, Off-Center Fold, the online Continuing Medical Education (CME) articles, and skINsights. In appropriate cases, a dynamic process that may require hundreds of words to describe, or a series of still images to illustrate, may be best conveyed as a moving picture. For instance, articles that address biological processes or dermatologic procedures may be especially improved by an appended video clip. All video submissions will be evaluated by our video review committee (Ashish C. Bhatia, MD, James M. Grichnik, MD, PhD, and Murad Alam, MD) and the appropriate section editor. Furthermore, submissions involving surgical procedures will have the video reviewed by the surgical advisory board (Murad Alam, MD, Chairman; Daniel Berg, MD; Jeffrey S. Dover, MD, FRCP; Hayes B. Gladstone, MD; Dee Anna Glasser, MD; Ken K. Lee, MD).

When a video is found to enhance a submission, it will be posted on the Web site, and a link will be listed in the print version of the article. If authors are unsure of whether a video is right for a given article, we encourage them to contact the Archives editorial staff for advice. That being said, we rely on your good judgment and creativity to best utilize this modality and to pioneer its use in the peer-reviewed dermatology literature. Because this is an evolving technology with growing applications, we expect to periodically revise our instructions for authors to ensure that they remain most useful.

WEB SITE FEATURES THAT ENRICH THE ARCHIVES EXPERIENCE

In addition to providing a display medium for videography, the Archives Web site offers many useful features to readers to assist with exploring the content of the journal, assist with research, provide education and CME, as well as to stay connected to the journal through automated information delivery to one’s e-mail. Accessing the Online Features is easy: simply go to the Archives homepage (http://www.archderm.com/), click on any article, and then click on “Online Features” in the upper right-hand corner of the page.

Every month, the journal features the Archives Clinical Challenge: You Make the Diagnosis. This is one of
the most popular interactive sections of the Web site, where readers are presented with a challenging clinical case from an upcoming Off-Center Fold and are asked to provide a diagnosis. Readers from all over the world participate in this challenge, and the first to respond with the correct answer wins a prize and is recognized in the print version of the journal. Look for a new Clinical Challenge on the third Monday of every month.

To continue to promote learning and interacting, we also invite readers to peruse a free CME article and answer questions to earn CME credit online. Future CME articles will likely be an excellent proving ground for the benefit of rich media such as videography, adding a new dimension to the traditional learning pattern. The online CME section is edited by Andrew D. Samel, MD.

Staying connected with the latest content in the print journal is made easy by the features available on the Web site in the Stay Connected section. Here, readers can sign up for e-mail alerts containing the table of contents from the latest issue, including the titles, author listings, and links to the full-text articles in each new issue. Readers can also be the first to browse the latest articles online, even ahead of the print version, by using the Early Release alerts section of the Web site, complete with links to full-text articles published online ahead of print. One can even customize the types of articles delivered through e-mail by specifying the topics using the Topic Collections alerts section of the Web site.

Another feature available only through the Web site is the Citation Alert to provide notification via e-mail when
a particular article is cited by another article. Readers can also set up Search Alert notifications. These provide e-mail notification when an article matching one’s search criteria is published. This is a very handy way to stay on top of the literature in a particular subject without manually searching on a regular basis.

In the Research section of the Web site, there are tools to assist with the most daunting research tasks, making them much easier to manage. The My Folder feature allows readers to store and organize articles of interest in their personal storage space. The Citation Manager complements the My Folder section by helping readers store the proper citations from published articles of interest and by exporting these lists in a format that is readable by many popular citation management software packages.

Other resources available on the Web site include a searchable Dermatology Calendar of Events listing relevant meetings and events, an Evidence-Based Dermatology (EBD) page that provides access to the latest EBD articles and features, and a PowerPoint Downloads feature, which allows readers to download all of the figures and tables from an article directly onto their computers in PowerPoint format. This last feature can be invaluable to any reader wishing to rapidly compose a PowerPoint presentation that includes data from an article.

We are proud to be leading the way for innovations and standardizations in multimedia enrichment of the dermatology literature as well as to be taking full advantage of the interactive, customizable power of the Internet. As these processes and the benefits that they provide our readers around the world evolve, we hope to continue to lead the way and make available new ways to enrich the literature and expand the methods by which readers interact with it.

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Subcutaneous Nodule and Diffuse Lymphadenopathy in a 6-Month-Old Boy From Africa

Peter C. Friedman, MD, PhD; Samantha Hansen, MD; David N. Silver, MD; Maria C. Garcia, MD; Columbia University, New York, New York

REPORT OF A CASE

A 6-month-old boy from Guinea presented with a 4-month history of a left shoulder nodule at the site of a previous vaccination of unknown type. The child also had recurrent rashes and upper respiratory tract symptoms. On examination, the patient had a 3.5- by 3.0-cm, rubbery, freely movable subcutaneous nodule on his left shoulder, which extended into a 6-mm, round, red papule (Figure 1). A 1.0-cm rubbery subcutaneous nodule was present on the right back. He also had lymphadenopathy in the postauricular, cervical, inguinal, and axillary regions. The left edge was palpable 1 cm below the costal margin.

For many years he had been a rubber worker in the Amazon region. Hypohidrosis was noted in involved areas. Hair, nails, and teeth were normal. A biopsy of involved skin was performed, and the specimen was stained with hematoxylin–eosin and cosin methenamine–silver (GMS) (Figure 2 and Figure 3). What is your diagnosis?

Goosefleshlike Lesions and Hypohidrosis

Naomi Sorosh Dimon, MD; Douglas R. Pullin, MD; Yelanda Roe-Hollick, MD; University of Michigan, Ann Arbor

REPORT OF A CASE

A 15-year-old otherwise healthy boy presented with a 10-year history of tiny bumps on his trunk and extremities that appeared during exercise and resolved within 60 minutes. He also noted decreased sweating in affected areas and increased sweating in uninvolved areas. He felt hot and occasionally light-headed during episodes. Physical examination initially revealed normal skin. After he had jogged in place, his skin had a gooseflesh appearance, with tiny, semifluid, flesh-colored papules covering the trunk and upper extremities (Figure 1). Hypohidrosis was noted in involved areas. Hair, nails, and teeth were normal. A biopsy of involved skin was performed, and the specimens were stained with hematoxylin–eosin and cosin methenamine–silver (GMS) (Figure 2 and Figure 3). What is your diagnosis?

Nodular Lesions on the Arm

Anette Chrusciak-Talhari, MD; Caroline Talhari, MD; Mônica Nunes de Souza Santos, MD; Luís Carlos Fernandes, PhD; Sinésio Talhari, PhD; University of Amazonas (Dr C. Talhari and Ms de Souza Santos), Manaus, Brazil

REPORT OF A CASE

A healthy 66-year-old Brazilian man presented with a 4-month history of an asymptomatic mass of nodules affecting his left arm. The lesion had initially appeared as a papule and had been slowly enlarging since then. The patient reported pulling a tick out of the initial lesion.

For many years he had been a rubber worker in the Amazon region. Physical examination revealed 4 ill-defined, smooth, shiny, elastic nodules on the medial aspect of the right knee, with a 2-cm beefy red plaque with creamy exudate in the right popliteal fossa (Figure 1). What is your diagnosis?

Beefy Red Plaque in the Popliteal Fossa

Sarah Jane Grekin, MD; Nicole M. Annest, MD; Beth C. Madison, MD; University of Iowa Hospitals and Clinics, Iowa City (Drs Grekin and Madison), and Scripps Clinic and Research Institute, La Jolla, California (Dr Annest)

REPORT OF A CASE

A 27-year-old woman was evaluated for painful skin lesions present on her right leg for 2 months. They initially appeared as small papules, then progressively increased in size and developed a purulent surface exudate. One day prior to presentation she underwent incisional drainage of a 2-cm beefy red plaque with creamy exudate in the right popliteal fossa (Figures 1 and 2) and a 5-mm erythromasosus indurated papule on the right lateral thigh. There was no lymphadenopathy. A potassium hydroxide touch preparation of the specimen was performed, and a shave biopsy from the right popliteal lesion was stained with hematoxylin–eosin (Figure 2 and Figure 3). What is your diagnosis?
Gooseflesh Lesions and Hyphidrosis

Diagnosis: Lobomyces profunda

**MICROSCOPIC FINDINGS AND CLINICAL COURSE**

The lesion biopsy specimen revealed numerous and diffuse inflammatory granulomas in the dermis. The granulomas were composed of histiocytes and giant cell components. A single or multiple asteroid body was also seen. The GMS stain showed the typical lobomyces in chains of uniform oval cells. The nodules were completely excised, and the patient was treated with oral itraconazole for 6 months as an attempt to prevent disease relapse.

Diagnosis: Lobomyces profunda, also called Lebo disease, is a chronic fungal infection that affects the skin. It is caused by *Lobomycosis conglutinans*, a dimorphic fungus that can exist in either yeast-like or filamentous form.

**REFERENCES**


Nodule Lesions on the Arm

Diagnosis: Lobomyces profunda

**MICROSCOPIC FINDINGS AND CLINICAL COURSE**

Lobomyces profunda is a rare fungal infection that primarily affects the skin. It is caused by *Lobomyces conglutinans*, a dimorphic fungus that can exist in either yeast-like or filamentous form.

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RESEARCH LETTERS

Digital Image Analysis: A Reliable Tool in the Quantitative Evaluation of Cutaneous Lesions and Beyond

Quantitative evaluation of cutaneous lesions in clinical trials can be problematic for diseases such as lower extremity ulcers, vitiligo, and alopecia. Because of the irregular shapes of these lesions, calculation of their circumference, diameter, and area can be cumbersome using traditional manual tracings. As a result, most trials using manual tracings will measure the longest diameter or approximate circumference of a target lesion. To compound the problem, in some diseases, access to the lesions is difficult. These lesions include erosions of the oral or genital mucosa. New software is now readily available that incorporates digital technologies and allows for digital image analysis (DIA) to circumvent these traditional problems. Digital image analysis provides a means to calculate desired target diameter and area with ease.

Our objective was to compare the interrater reliability and application feasibility of Image Pro Express (Media Cybernetics, Silver Spring, Maryland) DIA software with traditional manual tracings to determine the area of lower extremity ulcers.

Methods. Our study was imbedded in a larger randomized, double-blind, placebo-controlled trial, and inclusion and exclusion criteria was previously described by Sumpio et al. After approval from the respective institutional review boards, participants were recruited from vascular surgery and podiatry clinics from a total of 16 sites in the United States.

Each site provided both digital images and tracings of the target ulcers (Figure 1). Of the 3 possible readers, 2 readers outlined the target ulcers from both the digital images and the tracings. At all sites, digital images were obtained using a Nikon (Melville, New York) Coolpix 8800 camera. Furthermore, all images were obtained using standardized procedures; notably, the target ulcers were positioned 6 inches away from the camera and facing the light, to avoid any shadows. A metric ruler was placed on both the digital images and tracings to allow for measurement calibration. Once the digital images were obtained, they were uploaded into an IBM (Chicago, Illinois) desktop computer, and the perimeter of each ulcer was outlined electronically by the 2 readers using a wireless mouse (Figure 2). Concurrently, the respective tracings were scanned and the 2 readers were scanned into the computer using a standard IBM flatbed scanner. We then used the Image Pro Express DIA software to determine the diameter and subse-
quent area of the target ulcers for both the digital images and the manual tracings.

Continuous variables were calculated as means±SDs and were compared by t test or analysis of variance where appropriate. Categorical variables were compared by χ² analysis. Finally, agreement between raters was determined by intraclass correlation coefficient. Reliability of DIA was determined by comparing the area obtained from DIA to the area obtained from manual tracings. P < .05 was considered statistically significant.

Results. A total of 99 patients with lower extremity ulcers were recruited into the study. The mean±SD patient age was 66±13 years; 65% were men (n=65), and 64% were white (n=64). In addition, 77% of the lower extremity ulcers were from participants who were diagnosed as having diabetes mellitus (n=76).

Of the 99 patients in the study, 91 patients had manual tracings and 91 had digital images; 87 had both. The mean±SD lower extremity ulcer area measured by reader 1 was 3.27±3.53 cm² in the manual tracings and 3.08±3.15 cm² in the digital images. Similarly, the lower extremity ulcer mean±SD area measured by reader 2 was 3.28±3.50 cm² in the manual tracings and 3.11±3.18 cm² in the digital images. The intraclass correlation coefficient between the 2 readers for manual tracing and digital images was 0.9994 and 0.9978, respectively. There was no statistically significant differences in areas between manual tracings and digital images (paired t test P=.12; 95% confidence interval, −0.51 to 0.06 cm²).

Comment. In our study, we demonstrated that area can be reliably measured across raters using DIA in targeted lower extremity ulcers. Also, we have shown that the results from the DIA approach are not significantly different from those of traditional manual tracings.

While traditional manual tracings have been the gold standard method by which to evaluate lower extremity ulcer circumference, diameter, and area, manual tracings can be cumbersome given the irregular shapes of these lesions. However, DIA can provide quantitative evaluation of target lower extremity ulcers with greater ease and efficiency. Therefore, we propose that if DIA is as reliable as traditional manual tracings, DIA may be used to estimate the size of lower extremity ulcers when the investigator sees fit.

The use of DIA is not limited to lower extremity ulcers but also potentially extends to other difficult-to-measure lesions. Specifically, DIA may serve a vital role in the quantitative evaluation of other diseases involving irregular-border cutaneous lesions, such as vitiligo and alopecia, as well as difficult to access lesions, such as erosions of the oral or genital mucosa. In fact, DIA may prove to be not only useful and reliable but also more precise than traditional manual tracings.
The greatest limitation of the DIA technology is for use on lesions that cannot be accurately represented in 2 dimensions, such as large ulcers that wrap around the curvature of the limb. In this circumstance, several standardized images of the ulcer and complex reconstruction may be necessary. However, in general, patient positioning, body curvature, or tapering of the limbs, as well as compromised accessibility can be

Figure 1. Three digital images with electronic manual tracings (left) and corresponding traditional manual tracings (right). All scales are given in millimeters.
Wound Assessment by 3-Dimensional Laser Scanning

Recent advances in our understanding of the biology of cutaneous tissue repair have influenced current therapeutic strategies for chronic wound management and will continue to influence chronic wound management strategies into the future.1

An effective and accurate monitoring of skin lesions should be performed by measuring in an objective, precise, and reproducible way the complete status and evolution of the wound.2 The main goal of current research projects is to design an easy-to-use technological system that can monitor the qualitative and quantitative evolution of a skin lesion.

This level of monitoring can be achieved by using 3-dimensional scanners: in particular, systems based on active optical approaches.3 There are 2 different areas of potential applications of such types of devices: in medical treatment (to improve the efficacy of therapeutic regimens)4 and pharmacologic scientific research (to assess the quality and effectiveness of new chemicals or clinical procedures).3

Methods. We prospectively examined 15 patients with venous leg ulcers. The patients who underwent sequential imaging of chronic wounds for this study all attended the leg ulcer clinic of the Wound Healing Research Unit at the University of Pisa, Pisa, Italy.

Our sequential imaging system is equipped with a Vivid 900 laser scanner (Minolta, Osaka, Japan), which is used for digitizing or scanning the wound shape. With regard to the calculation of the "external" surface and volume of a wound, it is necessary to assess its original shape to determine the missing volume virtually. At the time of patient presentation, information on the shape of the skin before the wound occurred is missing, and the technique for virtual reconstruction of the original wound surface must be as easy and user-friendly as possible. The system, relying on an analysis of the shape of the surface immediately outside the wound perimeter, creates an interpolating virtual surface that is continuously connected to the existing surface outside the wound and to that covering it.

The parameters we studied were the mean wound area (measured in square centimeters) and mean volume (cubic centimeters). To assess interrater reproducibility, scans were evaluated by 2 independent investigators. For assessment of intrarater reproducibility, a single investigator performed 2 consecutive measurements 5 minutes apart. Immediately after the first wound assessment of the first observer, a second observer, blinded to the findings of the first analysis, measured the same wound.

The means and standard deviations of duplicate determinations for each wound were used for analysis. The reproducibility of measurements was evaluated by means of an intraclass correlation coefficient (ICC) and its 95% confidence interval (CI).

Results. The measured total areas and volumes for independent raters and for subsequent measures of 1 rater are

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The Diagnostic Yield of Histopathologic Sampling Techniques in PAN-Associated Cutaneous Ulcers

Polymyalgia nodosa (PAN), a medium-sized vessel (MSV) vasculitis, may result in cutaneous ulcers.\(^1\) There is no specific serologic abnormality associated with PAN; therefore, the mainstay diagnosis consists of histologic evidence of MSV vasculitis in the context of pertinent clinical findings.\(^2\) Several factors may contribute to the potential low diagnostic yield of tissue biopsy specimens from MSV-vasculitic ulcers. The present study evaluates the role of tissue sampling in the histologic evaluation of PAN-associated cutaneous ulcers.

Methods. Retrospective analysis of de-identified archival biopsy specimens taken from skin ulcers and sural nerves of 29 patients with histologically proven PAN-associated MSV vasculitis. Patients met the classification.

Comment. The laser scanner system used in this study enables users to accurately acquire 3-dimensional digital models of various types of skin wounds. Since the final users will be physicians and not computer experts, a user-friendly system is believed to be a fundamental parameter for its success. The accuracy of scanning systems has improved in the past few years, and prices have also decreased, making these devices affordable for a wider community of potential users.\(^3\) The integration into a single system of capabilities that can capture the shape and surface reflection characteristics makes 3-dimensional scanning an invaluable resource in all those applications where it is necessary to sample both surface attributes.

### Table 1. The Total Areas and Volumes of the Different Wounds Measured by the 2 Independent Raters and the 2 Measurements Made by the Single Rater\(^a\)

<table>
<thead>
<tr>
<th>Wound Parameter</th>
<th>Measurement 1</th>
<th>Measurement 2</th>
<th>Rater 1</th>
<th>Rater 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area, cm(^2)</td>
<td>52.36 ± 8.5</td>
<td>51.26 ± 3.6</td>
<td>53.6 ± 8.4</td>
<td></td>
</tr>
<tr>
<td>Volume, cm(^3)</td>
<td>18.3 ± 2.6</td>
<td>18.6 ± 3.7</td>
<td>19.4 ± 4.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wound Parameter</th>
<th>Intrarater ICC</th>
<th>Interrater ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area, cm(^2)</td>
<td>0.9976</td>
<td>0.54 ± 0.39</td>
</tr>
<tr>
<td>Volume, cm(^3)</td>
<td>0.9832</td>
<td>1.44 ± 0.91</td>
</tr>
</tbody>
</table>

All data are reported as mean ± SD percentage relative error.

### Table 2. Percentage Relative Error in the Measurements of Total Areas and Volumes and ICC of the Different Scans Between 2 Independent Raters and Within a Single Rater\(^a\)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intrarater ICC</th>
<th>Interrater ICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area, cm(^2)</td>
<td>0.9976</td>
<td>0.54 ± 0.39</td>
</tr>
<tr>
<td>Volume, cm(^3)</td>
<td>0.9832</td>
<td>1.44 ± 0.91</td>
</tr>
</tbody>
</table>

Abbreviation: ICC, intraclass correlation coefficient.

\(^a\) Unless otherwise indicated, data are reported as mean ± SD percentage relative error.

Reported in Table 1. No statistically significant differences were found between scans evaluated by the 2 investigators about wound area and volume. The relative errors and the intraclass correlation coefficients are reported in Table 2. The ICC values were excellent for both intrarater and interrater reproducibility with a very low relative error value. The mean ± SD time for a full scan acquisition on the wound area and volume was 3.6 ± 1.4 minutes.

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tion and definitional criteria of the American College of Rheumatology and Chapel Hill Consensus Conference. Specimens were obtained from Johns Hopkins University, University of Pennsylvania, and Ameripath Inc. Biopsy technique, depth and site within the ulcer, and histologic findings were evaluated by the same dermatopathologist (C.H.N). Peripheral ulcer areas were defined to include the ulcer edge and surrounding nonulcerated skin, whereas nearby central ulcer areas included the areas near the ulcer center. Both areas were determined by the referring physician and histopathologically.

Results. Of the 29 biopsy-proven cases of PAN-associated cutaneous ulcers, 26 were confirmed with skin specimens that included subcutaneous tissue and peripheral and nearby central areas of the ulcer (Figure 1). Sampling techniques ranged from incisional to deep punch biopsies and included the double trephine method. Peripheral and nearby central biopsy specimens were ac-
quired by either a single elliptical incision or by multiple, separate, deep punch biopsies, both techniques performed along a radial trajectory (perpendicular to the ulcer edge).

Of the 26 patients with skin biopsy confirmation, 9 had to undergo repeated biopsies for diagnosis to be rendered. For 3 of the 29 patients, dermatopathologic confirmation could not be obtained despite repeated biopsy specimen evaluation, and histologic confirmation through sural nerve biopsies was required. Repeated skin biopsy specimens from only 1 of these 3 patients contained subcutis and were obtained from peripheral and nearby central areas. Specimens from the other 2 patients who underwent repeated skin biopsies contained subcutis but lacked nearby central ulcer tissue.

Owing to small sample size, Fisher exact and $\chi^2$ tests were performed on 2 variables: (1) specimens containing subcutis and peripheral and nearby central areas (n=27) vs (2) specimens with neither subcutis nor nearby central areas (n=14), both variables yielding a histologic diagnosis of PAN. The $\chi^2$ value (38.07), exceeded the critical threshold for .05 probability level (3.84); therefore, the difference in diagnostic yield between the 2 variables was significant. The Fisher exact test also yielded a nondirectional 2-tailed probability of $P<.001$.

Comment. Histologic evidence of MSV vasculitis in conjunction with pertinent clinical and ancillary study correlation are the gold standard diagnostic pillars for PAN. The present study shows that subcutis-containing specimens that include not only peripheral ulcer areas but also nearby central areas offer the best histologic yield for the diagnosis of PAN-associated ulcers (Figure 2). On the other hand, all initial and the vast majority of repeated nondiagnostic biopsy specimens were lacking subcutis and/or were obtained from only the ulcer periphery. Cutaneous MSVs are located in the dermal-subcutaneous junction, deep dermis, or subcutis. When MSVs are affected by a vasoocclusive process, ulcers can result in the wedge-shaped area of skin above the affected MSV that normally provides that skin’s blood supply. This finding supports the notion that obtaining subcutis-containing specimens from nearby central areas of PAN-associated ulcers would increase diagnostic yield.

Polyarteritis nodosa–associated cutaneous ulcers carry a worse prognosis that other cutaneous presentations. Early diagnosis and prompt and effective therapy would reduce the high PAN-associated morbidity and mortality. The present study underscores the importance of adequate sampling as a factor in the early diagnosis of PAN-associated cutaneous ulcers.

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Financial Disclosure: None reported.
lesions were healed. After 8 weeks, we stopped sodium thiosulfate therapy, and the patient has been without relapse for 4 months (Figure 2).

Comment. Calciphylaxis treatment is controversial. In the setting of end-stage renal disease, a major aim is to decrease the calcium-phosphate product under the saturation threshold (55 mg^2/dL^2). This is usually done by controlling an underlying secondary hyperparathyroidism, either by parathyroidectomy^3 or alternatively using calcimimetic agents. Sodium thiosulfate therapy can also be very helpful, especially in the absence of hyperparathyroidism. This inorganic salt enhances the solubility of calcium deposits and may restore endothelial cell dysfunction through its antioxidant effect.

For our patient, low serum parathyroid hormone levels and worsening with calcimimetic therapy and normocalcemic dialysate hemodialysis led us to suspect a low bone turnover or an adynamic bone syndrome. We cannot ascertain the relative contribution of each of the 2 interventions (sodium thiosulfate and a low-calcium dialysate hemodialysis) in the healing of the calciphylaxis lesions. However, it has been claimed that the benefit of hemodialysis with low-calcium dialysate was limited by the serum calcium plasma level rebound following the session, reinforcing our impression of sodium thiosulfate effectiveness.

This report illustrates the potential deleterious effect of excessive serum parathyroid hormone reduction on calciphylaxis lesions related to adynamic bone syndrome and supports the use of sodium thiosulfate as a first-line agent in this rare but life-threatening disease.

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Financial Disclosure: None reported.
We thank Ackermann et al for their comments regarding our case report of a patient with calciphylaxis and secondary hyperparathyroidism treated with cinacalcet. Cinacalcet treatment is indicated for dialysis patients with secondary hyperparathyroidism whose parathyroid hormone level is greater than 300 pg/mL. Our patient developed severe secondary hyperparathyroidism associated with parathyroid hormone levels as high as 1080 pg/mL (reference range, 7-53 pg/mL) and with varying calcium and phosphorous levels. Although not receiving dialysis, he was considered a good candidate for cinacalcet therapy with close monitoring of his parathyroid hormone, calcium, and phosphorous levels. Throughout therapy, his lowest measured parathyroid hormone level was 147 pg/mL, near the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI)3 recommended range for patients with stage 5 chronic kidney disease (150-300 pg/mL).

Adynamic bone disease is a common form of osteodystrophy in patients receiving dialysis, and excessive suppression of parathyroid hormone level is a principal risk factor in its development. Adynamic bone disease is a well-known risk associated with cinacalcet therapy. Parathyroid hormone level should be measured before the initiation of cinacalcet therapy and regularly monitored throughout therapy; if levels decrease below the recommended range of 150 to 300 pg/mL, the dose of cinacalcet and/or any vitamin D–related drug should be reduced or treatment discontinued.

Calciphylaxis is a poorly understood multifactorial disease, and treatment often aims to minimize suspected risk factors. Two additional cases of the successful use of cinacalcet in patients with calciphylaxis and secondary hyperparathyroidism have been described in the literature; in both cases, the parathyroid hormone level was significantly elevated (>190 and 244 pmol/L [>1727 and 2218 pg/mL]) before the initiation of cinacalcet therapy.3,4 Our case report along with these 2 reports suggest that with careful monitoring, cinacalcet could be an efficacious therapy in certain patients with calciphylaxis and secondary hyperparathyroidism.

However, the case described by Ackermann et al demonstrates that cinacalcet may not be effective in all patients with calciphylaxis. To our knowledge, all reports of the successful treatment of patients with calciphylaxis are anecdotal, including the use of 0 calcium dialysate (without sodium thiosulfate)5 and other reports of sodium thiosulfate treatment.6,7 Randomized controlled studies, not anecdotal cases, are necessary to ascertain the appropriate standard of care for patients with calciphylaxis. Only then will the potential therapeutic role of both cinacalcet and sodium thiosulfate be determined.

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VIGNETTES

Skin Cancer Presenting as a Nonhealing Wound: The Association of Polio and Skin Cancer

Survivors of polio epidemics from the 1940s and 1950s make up a significant proportion of the US patient population. In addition to morbidity secondary to paralytic polio and postpolio syndrome, an association with malignant neoplasm has been proposed.1 We present a case of skin cancers arising in a patient with polio to further strengthen this possible association.

Report of a Case. A 54-year-old white woman with paralytic polio since age 2 years was referred to our department with a 2-year-old wound on her right anterior shin. A 2.5 × 3.5-cm ulcer surrounded by thin and friable skin was noted (Figure 1). Owing to the nonhealing nature of the ulcer, a 4-mm punch biopsy was performed, the findings of which showed sclerosing basal cell carcinoma (Figure 2). The patient subsequently had an amputation of the right lower extremity after discussion of therapeutic options, including Mohs micrographic surgery.

Figure 1. A 2.5 × 3.5-cm ulcer on the right anterior shin.
The patient was referred again 6 months later with a several-month history of a chronic ulcer on her left anterior shin. A 10 × 11-cm annular, scaly, red patch with no central clearing was present, with a superficial denuded area measuring 1 × 1 cm. A 4-mm punch biopsy specimen showed squamous cell carcinoma (SCC) in situ with involved superficial margin and stasis changes. Two years after surgical resection of the SCC with Mohs surgery, the patient died due to complications of metastatic SCC.

Comment. The poliovirus is a single-stranded RNA enterovirus that shows preference for the anterior horn cells of the spinal cord. The resulting cell injury may produce paralytic polio. Although poliovirus is extremely infectious, clinical manifestations of infection are rare, with 1% to 2% of cases developing paralysis.

Paralysis is a predisposing factor for chronic ulcer formation and possibly malignant neoplasm. Factors including pressure-induced ischemia, maceration, and local trauma lead to skin breakdown, which becomes chronic as denervation plays an important role in wound healing. Malignant neoplasms, particularly SCC, arise in up to 1.7% of chronic wounds, although the mechanism for this transformation is unclear. While the ulcerations in our patient were a predisposing factor to the development of malignant neoplasms, it is possible that her polio represents a second, important causative agent.

A recent cohort study assessed cancer risk in 5883 patients with poliomyelitis and found that affected women may be at an increased risk for multiple malignant neoplasms, particularly breast and skin cancer. There was a 66% increased risk of skin cancer, primarily nonmelanoma. Significantly, both paralyzed and nonparalyzed patients were affected equally, and the lesion distribution in both groups reflected that of the general public, de-emphasizing the role of paralysis and associated morbidity such as chronic ulcers as causative factors. To our knowledge, no other study has evaluated the skin cancer risk among patients with polio.

Our patient's bilateral skin cancer may be a manifestation of the link between polio and malignant neoplasm suggested in the Danish cohort study. This may be owing to denervation and chronic wound formation or to another factor such as chronic infection with the poliovirus. Further studies are needed to support this association and to ascertain the mechanism of the cutaneous malignant neoplasms and poliomyelitis.

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She developed left calf edema without additional improvement in wound healing (Figure 1). Doppler sonography of the lower limbs was normal. Interferon treatment was discontinued, and wound healing progressed again with complete closure 2 months later (Figure 2).

Comment. Although low-dose regimens are used to minimize the toxic effect profile of high-dose interferon alfa-2b, there are still many adverse effects. Mucocutaneous adverse reactions to low-dose interferon alfa include hair loss, hair discoloration, eczematous reactions at injection or remote sites, pruritus, xerostomia, Raynaud phenomenon, or livedo reticularis. Other reactions include erythema or induration at injection sites progressing in rare instances to panniculitis and skin necrosis, atrophic Blanche, and Meyerson phenomenon. Some rare adverse effects have been observed: urticaria or angioedema, worsening seborrheic dermatitis, herpetic recurrence, pityriasis versicolor, recurrent buccal aphthous ulcer, and vitiligo.

The present report suggests that interferon alfa-2b treatment might jeopardize wound healing despite its use at low doses. Wound contraction is an essential component of wound healing. Interferon treatment for fibroproliferative disorders has been suggested because of its antifibrotic properties. The fibroblast-populated collagen lattice (FPCL) is an in vitro assay that simulates wound contraction. Treatment of fibroblasts with interferon has been shown to reduce the rate and extent of contraction using the in vitro FPCL model. Interferon alfa-2b inhibits wound contraction in vivo, not through an appreciable alteration in myofibroblast number or cytoskeletal protein expression, but possibly through a reduction in fibroblast cellularity by the induction of apoptosis.

After surgical management of cutaneous melanoma, the physician should delay interferon treatment until complete wound healing. Otherwise, it might jeopardize wound closure.

Intractable Wounds From a Herpes Simplex Infection in an Immunosuppressed Patient With Rheumatoid Arthritis

Herpes simplex virus (HSV) infections, characterized by painful grouped vesicles with erythema occurring on perioral and/or pubic areas, affect over 40 million people in the United States, where 1.6 million people are infected annually with HSV-2. The diagnosis of HSV is generally easy, but it becomes difficult in immunosuppressed populations.

Report of a Case. Our patient was a 76-year-old Japanese woman without human immunodeficiency virus but with rheumatoid arthritis (RA). She had been treated with prednisolone (5 mg/d) and methotrexate (4 mg/wk) for more than 20 years and had also been treated for multiple recurrent ulcers on her lower legs caused by RA-related leukocytoclastic vasculitis. Multiple bullae on her legs were successfully treated with a prednisolone dose increase to 20 mg/d. However, multiple painful ulcers appeared on her buttocks and gradually increased in both
number and size (Figure 1) prompting her admission to our hospital.

Differential diagnoses included autoimmune bullous disease, rheumatoid vasculitis, necrolytic migratory erythema (glucagonoma), zinc deficiency, erythema multiforme, allergic reactions, pyoderma gangrenosum, traumatic ulcerations, Behçet disease, and Crohn disease, all of which were ruled out clinically and pathologically.

We began administering levofloxacin (300 mg/d) for the bacterial infections, tapered the dose of prednisolone, and performed local wound care with difluprednate, a steroidal antedrug, and occlusive dressings. Within a week after her admission, she experienced respiratory failure caused by Pneumocystis carinii pneumonia due to hypogammaglobulinemia, which was treated with sulfamethoxazole (10 g/d) and immunoglobulin (5 g/d). She also had an intractable duodenal ulcer, which was treated with endoscopic hemostasis and frequent transfusions.

Her ulcers increased in size and fused with each other (Figure 2A). Although we did not detect HSV directly from a swab or biopsy specimen, we diagnosed her ulcers as HSV infections because (1) findings of polymerase chain reaction analysis for HSV DNA were positive in a swab obtained from the edge of the ulcers far from her pubic area; (2) the HSV-IgG titer increased from 41 to 476 in her serum, while a normal HSV-IgM titer was maintained; (3) treatment with intravenous acyclovir (750 mg/d) for 7 days without changing the local wound care regimen was effective in treating the ulcers and severe pain (Figure 2B); and (4) her immunosuppressed status was remarkable enough to indicate P. carinii pneumonia. She was ambulatory at the time of discharge, and at a follow-up visit, her ulcers were notably improved (Figure 3).

Comment. Immunosuppressed populations, including (1) patients undergoing long-term steroid treatment and/or immunosuppressant therapy, (2) organ transplant recipients, (3) patients with human immunodeficiency virus, and (4) those with other diseases, including leukemia, manifest varying characteristics HSV infection eruptions. We could not immediately diagnose our patient’s ulcers as being caused by HSV infection because our patient presented with lower leg ulcers caused by rheumatoid vasculitis, and her biopsy specimens did not show any sign of HSV. Treatment with acyclovir was sufficient to heal the wounds, but prophylactic therapy could be considered in the future. When intractable painful erosions and/or ulcers appear on the
buttocks of an immunosuppressed patient, an HSV infection should be considered. The fact that HSV-1 infection can occur in a genital area should also be remembered.

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Additional Contributions: Hiroyuki Murota, MD, PhD, Isao Ishida, MD, PhD, Yukari Nishimura, MD, and Noriko Umegaki, MD, PhD, provided critical review of this work.

Additional Information: All work for this case report was done at the Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, Japan, where Drs Hanafusa, Kitaba, and Katayama still practice.

cycle of iloprost treatment could begin, the general conditions quickly worsened, and the patient died.

Comment. Paraneoplastic Raynaud phenomenon with digital necrosis is a rare condition that may represent an unusual manifestation of internal malignant neoplasms such as neoplasm of the gastrointestinal tract, lung, and breast; ovarian and uterine carcinomas; renal adenocarcinoma; multiple myeloma; leukemia; and Hodgkin lymphoma.1-4 To our knowledge, the association with squamous cell carcinoma of the penis has never been reported.

The paraneoplastic digital necrosis is considered a vasculitis, even if the pathogenesis is still unclear.2-4 It may represent the only manifestation of an underlying malignant neoplasm; therefore, malignant disorders should be carefully searched for in patients with an abrupt onset of Raynaud phenomenon and digital necrosis, even in the absence of abnormal laboratory findings and negative medical history of thromboembolic disease or connective tissue disorders.

We report herein for the first time to our knowledge an alteration of the thrombophilic status that may be implicated in the pathogenesis of digital necrosis. Particularly, the presence of ACA and β2GPI may be an undiagnosed condition or the consequence of malignant neoplasm; in fact, the occurrence of ACA, lupus anticoagulant, and ANA in neoplasms is common.3-4

Our patient was heterozygous for both of the common MTHFR mutations with consequent hyperhomocysteinemia. This condition, usually silent, showed up because of the folate deficiency that might have been caused by the impaired dietary intake, the chemotherapy, or the neoplasm itself.

Hyperhomocysteinemia, known to cause vascular accident, and presence of ACA and β2GPI are important factors implicated in an altered coagulative status inducing an increased risk of the thrombotic fact.3 In the present case, these 3 factors may be responsible for the Raynaud phenomenon, the digital necrosis, and the persistence of the digital necrosis after chemotherapy, which differs from the usual course of the disease in previously reported cases.4

Resolution of Chronic Pain and Fingertip Ulceration Due to Hand-Arm Vibration Syndrome Following Combination Pharmacotherapy

Hand-arm vibration syndrome (HAVS) is a well-recognized cause of secondary Raynaud phenomenon. We report a percussionist with vibration-induced peripheral vasospasm and nonhealing fingertip ulceration that responded to combination therapy with pentoxifylline, extended-release nifedipine, and low-dose aspirin.

Report of Case. A 49-year-old white homeless man presented with an 8-month history of severe bilateral fingertip pain. He regularly awoke at night with cold fingers and pins-and-needles pain radiating up his left arm. The patient played conga drums for 4 years, averaging 1 to 2 hours, occasionally up to 5 hours daily. He had a 10 pack-year smoking history. Various treatment failures at outside facilities included cephalexin and trimethoprim/sulfamethoxazole double strength, acetaminophen/hydrocodone, topical 2% nitroglycerin ointment, and naproxen. Hand radiographs revealed preserved bone min-
eralization, no evidence of fracture or dislocation, and no significant soft tissue swelling.

Physical examination revealed thickened skin and tenderness to palpation at the pads of his second and third digits bilaterally (Figure 1). Ulcerations were present at the right middle and left index fingers. His chief complaint was severe and constant fingertip pain. A diagnosis of percussion- or vibration-induced vasospasm was made and he was prescribed pentoxifylline, 400 mg twice daily, extended-release nifedipine, 30 mg/d, and aspirin, 81 mg/d, and he was advised to stop smoking and drumming.

One month later, the patient reported dramatic pain relief. He noted improvement within 1 to 2 weeks of initiating therapy. By his own initiative, he had decreased the pentoxifylline dose from 400 mg twice daily to 400 mg/d for 1 week owing to transient nausea. He stopped smoking for the first week and then restarted. He was only “occasionally” drumming. Shallow, calloused fissures remained in the right third and left second fingertips (Figure 2).

Comment. The pathogenesis of HAVS is a complex interplay of vascular, neural, and intravascular effects. Vascular pathologic characteristics include fibrosis and vasoconstriction. Neuroendocrine factors include decreased calcitonin gene–related peptide (a vasodilator) and stimulation of α2-adrenergic receptors (vasoconstrictors). Intra-vascular factors include platelet and white cell activation. Symptoms typically appear after 2000 hours of vibration exposure. The diagnosis of HAVS was favored over thromboangiitis obliterans owing to the improvement despite continued smoking. Raynaud disease was excluded owing to lack of exacerbation by cold temperature or skin color change.

The goal of treatment was to improve microcirculation and decrease inflammation, platelet activation, and vasospasm. Pentoxifylline decreases leukocyte deformability and chemotaxis via decreased interleukin-1 and tumor necrosis factor (TNF) responsiveness; decreases TNF-α production in monocytes and macrophages; decreases platelet aggregation and adhesion; decreases fibroblast response to TNF-α; and improves red blood cell deformability. Nifedipine, a calcium channel blocker, increases vasodilation and decreases vasospasm. Low-dose aspirin has an antiplatelet effect. More study of the relative efficacy of this combination therapy vs monotherapy is warranted.

Hand-arm vibration syndrome is an important industrial occupational disorder that can present with unremitting pain and nonhealing fingertip ulcers. The combination therapy of pentoxifylline, nifedipine, and aspirin described herein to resolve vibration injury might be useful for other disorders of vasospasm and inflammation such as thromboangiitis obliterans, scleroderma, and vasculitis.

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Additional Contributions: The Venice Family Clinic performed much-appreciated hard work in patient care.

Epidermal Langerhans Cell Movement In Situ
A Model for Understanding Immunologic Function in the Skin
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Epidermal Langerhans cells (LCs) represent an immature dendritic cell subset at the environmental interface. They undergo maturational changes and migrate to draining lymph nodes in response to danger signals, eg, the presence of proinflammatory cytokines and microbial products (Figure 1). Our research group has recently developed a system to visualize dynamic behaviors of epidermal LCs by combining time-lapse, intravital, confocal imaging technology and I-Aβ–enhanced green fluorescent protein (EGFP) knock-in mice in which LCs can be identified by EGFP-associated fluorescence.1 Under the steady state, some LCs exhibited a unique motion, called the dendrite surveillance extension and retraction cycling habitus (dSEARCH), characterized by rhythmic extension and retraction of dendritic processes through intercellular spaces (Figure 2) (supplemental video S1). Topical application of dinitrofluorobenzene (DNFB) not only provoked dSEARCH motion but also triggered direct cell-to-cell contact formation among adjacent LCs (Figure 3) (supplemental video S2). Although functional outcomes of such motile behaviors remain unclear, it is tempting to speculate that dSEARCH motion may facilitate more efficient and broader antigen sampling by epidermal LCs and that adjacent LCs may exchange the antigens under pathologic conditions.

Additional Information: Supplemental videos are reproduced from the article by Nishibu et al1 with permission from the Journal of Investigative Dermatology.

REFERENCE