

# Managing the Patient with Venous Ulcers

Tami de Araujo, MD; Isabel Valencia, MD; Daniel G. Federman, MD; and Robert S. Kirsner, MD

Venous disease is the most common cause of leg ulcers. The refractory nature of venous ulcers affects the quality of life and work productivity of those persons afflicted. This, in combination with the high costs of long-term therapy, makes venous ulcers a major health problem in developed countries. Management of venous leg ulcers is based on understanding pathophysiologic abnormalities. In recent years, identifying prognostic factors for

healing and developing novel therapeutic approaches for venous ulcers have offered valuable tools for the management of patients with this disorder.

*Ann Intern Med.* 2003;138:326-334.

www.annals.org

For author affiliations, see end of text.

**A** 75-year-old woman presents with a 2-month history of ulceration of her lower right leg. She has a history of congestive heart failure and has varicosities on the lower limbs. She does not drink or smoke. Despite the discomfort from the ulcer on her leg, she feels well overall. Her physical examination is unremarkable except for the presence of a 12-cm<sup>2</sup> ulcer over her right medial malleolus. The ulcer is shallow, with a yellowish base and scattered islands of granulation tissue. There is a scaly brown hyperpigmentation surrounding the ulcer's borders. There are no signs of infection. A neurologic examination regarding perception of pain, touch, and pressure was performed and yielded normal results. The patient's extremities are cool, and the presence of 2+ edema of the right extremity makes palpation of the dorsalis pedis pulses difficult.

Venous ulcers are a major health problem because of their high prevalence and associated high cost of care. The cost of venous leg ulcers is estimated to be \$1 billion per year in the United States, and the average cost for one patient over a lifetime exceeds \$40 000 (1). There is no racial predilection; however, women seem to develop venous ulcers more often than men (2). Venous ulcers are more common with increasing age, with peak prevalence between 60 and 80 years of age (3, 4). However, 22% of persons develop venous ulcers by 40 years of age and 13% do so before 30 years of age, which may represent a substantial effect on work productivity (5, 6). Therefore, proper diagnosis and adequate management are vital when caring for patients with venous leg ulcers to promote faster healing and prevent recurrences.

## WHAT ARE THE POTENTIAL CAUSES OF THIS PATIENT'S LEG ULCER?

The four most common causes of lower-extremity ulcers are venous insufficiency, arterial insufficiency, neuropathy (often due to diabetes), and ulcers caused by prolonged pressure and ischemia (Table 1). At times, several of these causes may overlap in one patient. Less common causes of lower-extremity ulcers include trauma, inflammatory or metabolic conditions, malignancy, and infections (7). When caring for a patient with lower-extremity ulcers,

a provider should identify the underlying cause to determine the management and prognosis.

Venous insufficiency is the most common cause of lower-leg ulcers, accounting for nearly 80% of all cases. Of the approximately 7 million people in the United States with venous insufficiency, approximately 1 million develop venous leg ulcers (1). Patients with venous ulcers suffer from ambulatory venous hypertension, which is an abnormally sustained elevation of the venous pressure upon ambulation. The mechanism by which venous hypertension results in ulceration remains unclear. Recently proposed theories, such as pericapillary fibrin cuff deposition, abnormalities of the fibrinolytic system, trapping of growth factors by macromolecules in the dermis, and leukocyte plugging in the vessels of the lower extremities, are some of the consequences of venous hypertension thought to be responsible for the development of venous leg ulcers (8–10).

*The patient reports occasional leg pain and swelling, especially at the end of the day. She notes that her mother had varicose veins.*

## WHAT CLINICAL CHARACTERISTICS SUGGEST THAT LEG ULCERS ARE DUE TO VENOUS DISEASE?

Patients with venous ulcers commonly report swelling and aching of the legs, often worse at the end of the day, which may be exacerbated by dependency and improved by leg elevation (1). A history of ulcer recurrence, particularly at the same location, is characteristic. Recent publications have challenged the assumption that venous ulcers are not painful; as many as three quarters of patients with venous ulcers report pain that adversely affects their quality of life (11, 12). Several risk factors for the development of venous ulcers have been identified. Up to 50% of patients with chronic venous insufficiency have a history of leg injury (13). Obesity, phlebitis, family history of varicose veins, type of employment and lifestyle (activities that require long hours of standing or sitting), deep venous thrombosis, and previous surgery for varicose veins have also been considered important risk factors for venous ulcerations (14, 15).

Venous ulcers are characteristically located over the

**Table 1. Clinical Aspects of the Most Common Types of Ulcers of the Lower Limbs\***

Wound Type	General Information	Pathophysiology	Clinical Features	Therapy
Venous ulcers	Most common type of leg ulcers; women affected more than men; often elderly	Venous hypertension	Presence of varicosities; ulcer located in the gaiter area; shallow, painful, granulation tissue and fibrin present. Associated findings include edema, venous dermatitis, and LDS	Leg elevation, compression therapy, aspirin, pentoxifylline, tissue-engineered skin, growth factors
Arterial ulcers	Elderly patients with history of cardiac or cerebrovascular disease; leg claudication, impotence, pain in distal foot. Concomitant with venous disease in up to 25% of cases	Tissue ischemia	Ulcers are commonly deep, located over bony prominences, round or punched out with sharply demarcated borders, yellow base, or necrosis; exposure of tendons. Associated findings include abnormal pedal pulses, cool limbs, femoral bruit, and prolonged venous filling time	Revascularization, antiplatelet and other rheologic agents, address risk factors
Neuropathic ulcers	Most common cause of foot ulcers, most commonly due to diabetes	Trauma, prolonged pressure	Usually plantar aspect of feet in patients with diabetes, neurologic disorders, or Hansen disease	Off loading; topically applied growth factors; tissue-engineered skin
Pressure ulcers	Usually bed-ridden patients; monoplegia	Tissue ischemia and necrosis secondary to prolonged pressure	Located over bony prominences in patients with limited mobility; risk factors include excessive moisture and altered mental status	Off loading; adequate nutrition, reduction of excessive moisture, shear, and friction

\* LDS = lipodermatosclerosis.

medial malleolus, also called the gaiter area. They may be single or multiple and can involve the entire circumference of the leg if untreated. Venous ulcers usually have irregular, flat, or only slightly steep borders. The ulcer bed tends to be shallow with granulation tissue, as well as some fibrinous material, and the wound surface rarely, if ever, shows necrosis or exposed tendons; their presence should lead a provider to consider another cause (16).

Commonly associated findings include dependent edema, varicose veins (ranging from a submalleolar venous flare to various degrees of vessel dilatation), a reddish-brown pigmentation and purpura due to extravasation of erythrocytes, and subsequent hemosiderin deposition. Eczematous changes with redness, scaling, and pruritus, often referred to as venous dermatitis, are also commonly present. This eczematous dermatitis is caused or aggravated by sensitization to applied topical medications, to which patients with venous disease are particularly susceptible (17, 18). Atrophie blanche—smooth, ivory-white atrophic plaques of sclerosis speckled with telangiectases—is described in up to one third of patients with chronic venous insufficiency and, when present in the gaiter area, may point to a venous cause of a lower-extremity ulcer (19).

In long-standing venous disease, the skin develops an induration and fibrosis of the dermis and subcutaneous tissue, usually restricted to the medial leg and sharply demarcated from proximal normal skin, resulting in the appearance of an inverted bottle. *Lipodermatosclerosis*, a term used to describe these clinical findings, suggests a greater impairment of the fibrinolytic system and is highly associated with and usually restricted to the legs of patients with venous insufficiency (17, 20).

Other possible causes of lower-extremity ulcers are arterial insufficiency and neuropathy (Table 1) (21–23). The ulcer presented by the patient in this case has a typical presentation of venous leg ulcer with associated venous dermatitis.

### WHAT DIAGNOSTIC PROCEDURES ARE USEFUL IN EVALUATING LEG ULCERS?

In up to three quarters of cases of venous ulcers, diagnosis may be made by clinical criteria alone (21–23). However, 25% of patients will have ulcers with mixed characteristics; therefore, noninvasive methods may aid in an accurate diagnosis, as may anatomic and functional evaluation of the venous system (24, 25).

The ankle–brachial index (ABI) may aid in detecting peripheral vascular disease. The systolic blood pressure is obtained by placing an appropriately sized cuff around the calf and inflating it so to occlude the pedal arteries. When the sounds are heard with Doppler ultrasonography after deflation of the cuff, the ankle systolic pressure is obtained. This is then compared with the brachial systolic pressure to determine the ABI (value > 1 is normal). Values less than 0.97 identify patients with peripheral arterial disease with a sensitivity of 96% to 97% and a specificity of 94% to 100% (23). Although false-normal results may be observed in patients who are elderly or diabetic, this simple, noninvasive method can be useful in detecting arterial disease. In the elderly and in diabetic patients, a transcutaneous oxygen measurement may be preferred to evaluate arterial flow. This is important since compression therapy, the

mainstay of therapy for venous ulcers, can lead to worsening of an arterial ulcer and, at times, gangrene (26).

Color duplex ultrasonography is the gold standard in evaluating venous disease. It is accurate, reproducible, and noninvasive and provides anatomic and functional information about both arterial and venous systems (27, 28). With the use of color duplex ultrasonography, veins can be identified and their dimensions measured, as can the velocity and direction of flow. Other examinations, such as photo and air plethysmography, allow the clinician to assess whole-limb venous hemodynamics at rest and after exercise and are adjuncts to duplex scanning. Invasive venography is usually reserved for investigation before surgery, if indicated.

If osteomyelitis is suspected, radiography, bone scanning, and bone biopsy should be considered. The incidence of osteomyelitis in chronic venous ulcers is unknown. For diabetic foot ulcers, a prospective trial found that probing of sinuses and deep ulcers was a highly sensitive method of detecting bone infection (29). Therefore, if bone is palpable at the base of an ulcer, with no intervening soft tissue, osteomyelitis is likely and further investigation is warranted.

Independent of the suspected cause, if a wound is present for more than 3 months, a biopsy is recommended to rule out malignancy. At that time, an atypical infection can be detected by microscopic examination, as well as tissue culture.

*Since palpation of the dorsalis pedis pulses on the affected limb is difficult to perform in this patient because of edema, further diagnostic evaluation to rule out an associated arterial insufficiency is warranted. You perform an ABI examination, which yielded a score of 1, and a transcutaneous oxygen measurement was normal. A leg ulcer secondary to venous insufficiency was diagnosed on clinical grounds, and no further venous studies were performed. The patient asks how you will treat her.*

The goals of treatment for patients with venous ulceration include reduction of edema, improvement of pain and lipodermatosclerosis, ulcer healing, and prevention of recurrence. The simplest method to reverse the effects of venous hypertension is bed rest with leg elevation. Elevation of the legs above the heart level for 30 minutes, three to four times daily, as well as leg elevation at night, allows swelling to subside and improves venous microcirculation (30). The ABI was performed to rule out concomitant arterial disease, which is seen in up to 25% of patients with venous ulcers. The presence of a reduced ABI suggesting arterial insufficiency would warrant further evaluation of the arterial circulation.

*You tell the patient you are prescribing compression therapy for her ulcer and recommend leg elevation for 30 minutes, three times daily.*

## WHAT IS THE ROLE OF COMPRESSION THERAPY IN TREATING VENOUS ULCERS?

As adherence with leg elevation is often difficult to achieve, graduated compression remains the cornerstone of therapy for patients with venous ulcers. Patients who adhere to compression therapy have improved ulcer healing rates, and continued compression after healing prevents recurrence (31–33). Most patients tolerate compression therapy without adverse effects. Care should be taken in patients with chronic heart failure because compression of the lower limbs can cause an increase in the preload volume and worsen their condition.

The optimal pressure necessary to overcome venous hypertension is not well defined, but an external pressure of 35 to 40 mm Hg at the ankle is necessary to prevent capillary exudation in legs affected by venous disease (34, 35). There are two types of compression bandages: inelastic and elastic bandages. Rigid, inelastic bandages provide limited pressure at rest but high pressure with muscle contraction (high working pressures). The prototype of this bandage is the traditional Unna boot, a moist zinc oxide-impregnated paste bandage that hardens to inelasticity (36, 37). The disadvantage of this compression method is that the Unna boot does not accommodate changes in the volume of the leg with edema reduction and has limited absorptive capacity for highly exudative wounds (leading to a foul smell). As a consequence, Unna boots require frequent reapplication. Because elastic bandages accommodate volume changes and provide both resting and working pressures, their use has become more common. The use of a rigid bandage, such as the Unna boot, may be helpful during the initial edema reduction phase (38, 39).

Elastic compression bandages provide sustained pressures and, when compared with Unna boots, conform to the leg better, are easy to use, and require less frequent dressing changes (40, 41). (Clinicians can find useful information on applying compression wraps in Wiersema-Bryant's article on management of edema [42]). Compression wraps provide both high working and resting pressures. The major disadvantage of elastic wraps is that they require a substantial degree of sophistication for adequate application (43). They can be divided into single- or multilayer bandage systems. A recent meta-analysis found that multilayer compression bandages seem to be superior to single-layer bandage systems (44). Several multilayer bandage systems have been developed and are currently the mainstay of therapy for venous ulcers. They comprise a wool or cotton layer (designed to absorb exudate and provide padding), one or two elastic wraps, and a self-adherent wrap that keeps the bandage in place (22). A multilayer system can be adapted to a wide range of ankle circumferences and leg sizes and provides sustained pressures of 40 to 45 mm Hg at the ankle, graduating to 17 mm Hg below the knee. Although three- or four-layer elastic bandages cost more than the single-layer elastic bandages, they seem

to be less expensive because they promote faster healing rates (32). Compression therapy should be used with caution in patients with concomitant cardiac insufficiency because it may worsen their condition. As previously mentioned, care must also be used in patients with arterial insufficiency because compression may cause limb ischemia.

### FOR HOW LONG SHOULD CLINICIANS PRESCRIBE COMPRESSION THERAPY FOR VENOUS ULCERS?

Compression therapy with dressings and inelastic or elastic bandages should continue until the ulcers are healed. After healing, patients should wear graded compression stockings to prevent ulcer recurrence (45). Assuming proper measurement and fitting of hose, specific instructions on how to put on compression stockings may enhance adherence. Patients who are arthritic, obese, or elderly often have difficulty putting on the stockings, and aids to assist with application have been introduced to increase adherence (38, 46). Repeated use and washing of the stockings reduce their level of compression; therefore, stockings should be replaced after 6 months of use.

Recurrence is a major issue when dealing with venous ulcers. In a large study by Nelzén and colleagues (47), venous ulcers healed without recurrence in only 44% of patients. Other authors have had similar results (48). Several studies, however, point out that adherence to compression therapy may reduce recurrence of venous ulcerations (49, 50). Samson and Showalter (50) reported recurrence rates of 79% in patients with venous ulcers who did not adhere to compression therapy versus only 4% recurrence in those who did. In addition, a prospective study demonstrated that patients who adhered to compression therapy had faster healing and fewer recurrences than did less-adherent patients (51). Another study showed that nonadherence to compression stockings statistically significantly decreased initial ulcer healing rate; all patients who did not adhere had recurrent ulceration by 36 months, whereas recurrence in adherent patients was only 15% (52). Therefore, when managing the patient with venous leg ulcers, stressing the importance of adherence with treatment regimens may be as important as the treatment itself.

*The patient is treated with multilayer compression therapy. She returns 1 month later, and her ulcer is unchanged. She becomes frustrated and wonders if her ulcer will ever heal. She asks if there are any medications she might take to help heal the ulcer.*

### WHAT MEDICATIONS HAVE A POTENTIAL ROLE IN TREATING VENOUS ULCERS?

Aspirin, whose anti-inflammatory action may have beneficial effects in venous ulcers, has been found to improve rates of healing. In a study of 20 patients treated

with compression therapy, patients who also received aspirin (300 mg/d) had improved healing compared with those who received compression plus a placebo pill (53). An increased rate of ulcer healing in patients treated with aspirin was found in a prospective, placebo-controlled study of 40 patients (54), but the small sample tempers enthusiasm.

The effects of pentoxifylline, a methylxanthine derivative, in treating venous ulcers may be due in part to its fibrinolytic properties, its ability to reduce leukocyte adhesion to the vascular endothelium, and its antithrombotic effects (55–58). A systematic review performed by the Cochrane Collaboration (59) on the use of pentoxifylline to treat venous leg ulcers analyzed nine trials involving 572 patients and concluded that pentoxifylline (800 mg three times daily) seems to be an effective adjuvant to compression bandages. Common side effects are indigestion, nausea, and diarrhea.

Other agents, such as Daflon (Les Laboratoires Servier, Neuilly-sur-Seine, France) (60) and Sulodexide (Giofil, Rome, Italy) (61), may be useful but are not available in the United States. Stanozolol (Sanofi-Winthrop Pharmaceuticals, Morrisville, Pennsylvania), an androgenic steroid with fibrinolytic properties, reduces pain and induration of venous ulcers and surrounding lipodermatosclerosis (62–64) but does not speed healing (65–67).

*The patient asks what else can be done to help her heal and heal faster.*

### WHAT SURGICAL INTERVENTIONS HAVE A POTENTIAL ROLE IN TREATING VENOUS ULCERS?

Skin grafting has been used for large or slow-healing venous ulcers (68). In addition to healing, graft placement may rapidly decrease pain (69). Grafts work by a combination of “take” (graft adherence) and provision of a pharmacologic stimulus to healing (69). Both pinch grafts (70) and split-thickness skin grafts (71–75) have been successfully used in a number of studies involving patients with venous ulcers. However, randomized trials have not been performed and grafts have been used primarily in refractory patients. Not all ulcers heal after skin grafting. Possible contributing factors include nonadherence to use of compression bandages and leg elevation, a local fibrin deficiency in the wound bed preventing the adhesion of the graft (76), or the presence of microthrombi in the dermal vessels leading to ischemia and impairment of graft take. In addition, recurrence after grafting is not uncommon.

Both cultured epidermal autografts and allografts have been used to treat venous ulcers and to reduce pain (77, 78). For cultured autografts, cells obtained from an initial biopsy specimen of the patient’s own skin are isolated and cultured and subsequently applied to the wound. Use of this therapeutic approach has been restricted, however, because it takes several weeks from harvesting to transplantation and manipulation and is often difficult. Also, some

studies suggest that dermal elements, such as collagen and fibroblasts, are necessary for wound healing (79).

Despite a lack of data proving that debridement is beneficial for venous ulcers, clinicians still use this method as a standard of care. Surgical debridement also allows the removal of necrotic tissue and may promote formulation of granulation tissue. In addition, enzyme-debriding agents (chemical debridement), such as proteolytic enzymes (papain and trypsin), may accelerate the removal of fibrin cuffs and trapping by other macromolecules (80–86). The advantages of other methods of debridement (such as wet-to-dry dressings, hydrotherapy, irrigation, dextranomers, and surgery) (85) are also unproven.

The role of superficial venous surgery in patients with venous ulcers and a combination of superficial and deep venous reflux is controversial. However, superficial venous surgery may have a role in treating venous ulcers associated with isolated superficial incompetence (87). Subfascial endoscopic perforator surgery is a promising, minimally invasive procedure for certain venous ulcers. In a recent review, Olivencia (87) reported that 79% of 428 ulcers treated by subfascial endoscopic perforator surgery healed in 2.3 months, on average. New perforators continue to develop over time. Radical excision of the ulcer bed, the fibrotic suprafascial tissues, and the pathologic superficial and perforating veins and coverage of the large soft-tissue defect with a free flap have been successfully used in a few cases. However, the magnitude of the surgical technique limits its application (88, 89).

Skin equivalents represent an exciting development in the treatment of venous ulcers. The tissue-engineered skin equivalent Graftskin (Organogenesis, Canton, Massachusetts) is approved by the U.S. Food and Drug Administration to treat venous ulcers and has been tested in a large randomized trial. Graftskin is an allogeneic cultured bilayer of human-skin origin containing both epidermal and dermal components. In a pivotal trial, 275 patients were assigned to receive compression therapy with or without Graftskin (90). More patients healed at 6 months when treated with Graftskin plus compression therapy than with compression alone (63% vs. 49%;  $P = 0.02$ ). In addition, the median time to complete wound closure was statistically significantly shorter with Graftskin (61 days vs. 181 days). Graftskin was particularly effective in ulcers that were difficult to heal (ulcers > 6 months' duration and larger ulcers). Graftskin was both safe and nonimmunogenic in this trial. Other bioengineered skin equivalents are currently under evaluation for the treatment of venous ulcers (91).

### IS THERE A ROLE FOR GROWTH FACTORS IN TREATING VENOUS ULCERS?

Several case series and pilot studies have demonstrated that topical and perilesional injection of granulocyte-macrophage colony-stimulating factor (GM-CSF) pro-

motes healing of leg ulcers and is safe (92–96). Two randomized, double-blind, placebo-controlled studies (92, 96) showed increased healing of chronic leg ulcers treated with GM-CSF compared with controls. Marques da Costa and colleagues (92) found that half of patients treated with a single intradermal injection of GM-CSF had complete healing of their ulcers at 8 weeks compared with 11% of patients in the placebo group. A randomized, dose-finding, double-blind trial of weekly dosages of GM-CSF in patients with chronic venous leg ulcers also showed a higher rate of healing in patients receiving perilesional injected GM-CSF. The number of healed wounds in the placebo and treated groups was statistically significantly different ( $P = 0.05$ ); 4 of 21 patients (19%) in the first group healed at week 13 compared with 12 of 21 patients (57%) and 11 of 18 patients (61%) in the 200- $\mu\text{g}$  and the 400- $\mu\text{g}$  groups, respectively (96). Case reports and case series have shown that GM-CSF is useful for treating leg ulcers due to various other causes as well (93–95). The GM-CSF promotes wound healing through many mechanisms, affecting one or all of the wound healing phases, such as homeostasis, inflammation, proliferation, and maturation (92–96).

Because of the pain associated with injections, Jaschke and colleagues (95) studied topical GM-CSF in a series of 52 venous ulcers. Ninety percent of ulcers healed, with an average healing time of 19 weeks. Further studies, however, are necessary to confirm the efficacy of this agent in healing venous ulcers and to define the optimal dose and dosing schedule.

Another growth factor that seems promising as therapy for venous ulcers is keratinocyte growth factor-2 (KGF-2), a member of the fibroblast growth factor family. In the skin, KGF-2 stimulates normal keratinocyte proliferation. Studies performed in animal models have shown that topically applied recombinant KGF-2 substantially promotes reepithelialization and enhances granulation tissue formation on chronic wounds (97). Phase IIb trials are currently under way to determine the safety and efficacy of KGF-2 in promoting wound healing in humans, and preliminary results from recently completed phase IIa trials have been encouraging (98). One randomized trial reported success with calcitonin gene-related peptide in combination with vasoactive intestinal peptide for venous ulcers (99).

### WHEN SHOULD PRIMARY CARE PHYSICIANS REFER A PATIENT WITH VENOUS ULCERS TO A SPECIALIST?

Adherence to compression therapy is still the key to healing a venous leg ulcer. Prognostic indicators for ulcer healing are important in identifying potentially slow or nonhealing ulcers that might benefit most from new treatment options, and a multidisciplinary team of specialists (dermatologists and vascular surgeons) is needed to provide a concise, cost-effective yet comprehensive assessment (100).

**Table 2. Adjunct Therapies (in Combination with Multilayer Compression) for Venous Ulcers\***

Type	Therapy (Reference)	General Information
Medical: topical	GM-CSF (92–96)	Several randomized trials support efficacy of perilesional injections. Topical application reported in case series. Phase IIa trial suggested improved healing. Phase IIb trial under way. Single trial showed greater healing when combined with vasoactive intestinal peptide.
	KGF-2† (97, 98)	
	Calcitonin gene-related peptid† (99)	
Medical: systemic	Aspirin (53, 54)	Two small trials demonstrated improved healing over compression alone. Nine trials performed, five in combination with compression. In those five trials, the relative risk for healing was 1.3 (95% CI, 1.1–1.54). One trial demonstrated that higher doses of 800 mg three times daily were superior to 400 mg three times daily or placebo. One trial showed improved healing in small venous ulcers. One trial reported improved healing.
	Pentoxifylline (55–59)	
	Daflon‡ (60)	
	Sulodexide‡ (61)	
Surgical	Skin grafting (pinch grafts, split-thickness grafts, cultured autografts) (69–79)	No randomized trials performed. Several series report healing of refractory venous ulcers. No conclusive data demonstrating efficacy. Despite this, the practice of removal of nonviable, necrotic tissue or senescent tissue and promotion of granulation tissue formation are considered standard of care. Surgical correction of incompetent valves; decrease of venous hypertension. Endoscopic procedure superior to open surgery. Randomized, controlled trials comparing endoscopic procedure not published. Several series report healing of refractory venous ulcers.
	Debridement (80–86)	
	Venous surgery (SEPS) (87–89)	
	Bioengineered skin (90)	Large randomized trial demonstrated improved amount and speed of healing, especially in refractory ulcers that were large and of long duration.

\* GM-CSF = granulocyte-macrophage colony-stimulating factor; KGF-2 = keratinocyte growth factor-2; SEPS = subfascial endoscopic perforator surgery.

† Investigational therapy.

‡ Daflon (Les Laboratoires Servier, Neuilly-sur-Seine, France) and Sulodexide (Giofil, Rome, Italy) are not available in the United States.

One way to potentially predict nonhealing is to examine certain baseline prognostic risk factors. Prognostic factors consistently found in a number of studies are a large wound area (>5 cm<sup>2</sup>) and a wound of long duration. Patients who possess either or both of these factors are at risk for not healing (101). A second method to predict healing is by measuring the healing rate through the first month of therapy (102). A decrease in wound size, determined by a variety of methods, is a favorable prognostic factor for healing, and patients whose ulcers do not decrease in size during the initial month of therapy are likely not to heal and would benefit most from alternative therapies (103). Thus, a follow-up evaluation after 1 month of therapy will indicate patients who are not likely to heal and should, therefore, be referred to a team of specialists. Approximately 50% to 70% of patients with venous ulcers will be healed after 6 months of treatment (34).

As our understanding of the pathophysiology of venous ulcers increases, we have used novel therapies as adjuncts to compression therapy in order to capitalize on scientific advances and accelerate healing. These novel agents act on a variety of abnormalities that have been postulated in the development and nonhealing of venous

ulcers: a local deficiency of growth factors, local fibrinolytic abnormalities, inadequate nutritional and oxygen supply caused by pericapillary fibrin cuffs, and leukocyte plugging on the lower extremities of patients with venous hypertension. While some agents have been well studied, others remain investigational and further studies are necessary to confirm their safety and efficacy (Table 2).

*You perform surgical debridement of the ulcer and start the patient on pentoxifylline, 800 mg three times per day, in association with compression therapy. You schedule a follow-up visit in 1 month. At the return visit, the patient reports gastrointestinal upset since she began taking pentoxifylline. Her ulcer size is unchanged. The patient is referred to a wound care center, where she undergoes grafting of the ulcer with bioengineered skin. She returns to your office 2 months later, and her ulcer is healed.*

## SUMMARY

Because of their high prevalence and associated high cost of treatment, venous ulcers are a major health problem. Early diagnosis and recognition of prognostic factors

will help the provider to optimize treatment for patients with venous leg ulcers and improve their quality of life. Future studies should aim to determine the optimal cost-effective approach to treatment of patients with venous ulcers.

From University of Miami School of Medicine, Veterans Administration Medical Center, Miami, Florida; and Yale University School of Medicine, Veterans Administration Medical Center, West Haven, Connecticut.

**Requests for Single Reprints:** Robert S. Kirsner, MD, Department of Dermatology, University of Miami, Veterans Administration Medical Center, 1201 NW 16th Street, Miami, FL 33125; e-mail, Rkirsner@med.miami.edu.

Current author addresses are available at [www.annals.org](http://www.annals.org).

## References

1. Valencia IC, Falabella A, Kirsner RS, Eaglstein WH. Chronic venous insufficiency and venous leg ulceration. *J Am Acad Dermatol*. 2001;44:401-21; quiz 422-4. [PMID: 11209109]
2. Nelzén O, Bergqvist D, Lindhagen A. Venous and non-venous leg ulcers: clinical history and appearance in a population study. *Br J Surg*. 1994;81:182-7. [PMID: 8156328]
3. Callam MJ, Harper DR, Dale JJ, Ruckley CV. Chronic ulcer of the leg: clinical history. *Br Med J (Clin Res Ed)*. 1987;294:1389-91. [PMID: 3109669]
4. Bergqvist D, Lindholm C, Nelzén O. Chronic leg ulcers: the impact of venous disease. *J Vasc Surg*. 1999;29:752-5. [PMID: 10194512]
5. Callam MJ, Ruckley CV, Harper DR, Dale JJ. Chronic ulceration of the leg: extent of the problem and provision of care. *Br Med J (Clin Res Ed)*. 1985;290:1855-6. [PMID: 3924283]
6. Ruckley CV. Socioeconomic impact of chronic venous insufficiency and leg ulcers. *Angiology*. 1997;48:67-9. [PMID: 8995346]
7. Falabella A, Falanga V. Uncommon causes of ulcers. *Clin Plast Surg*. 1998;25:467-79. [PMID: 9696906]
8. Falanga V, Eaglstein WH. The "trap" hypothesis of venous ulceration. *Lancet*. 1993;341:1006-8. [PMID: 7682272]
9. Browse NL, Burnand KG. The cause of venous ulceration. *Lancet*. 1982;2:243-5. [PMID: 6124673]
10. Thomas PR, Nash GB, Dormandy JA. White cell accumulation in dependent legs of patients with venous hypertension: a possible mechanism for trophic changes in the skin. *Br Med J (Clin Res Ed)*. 1988;296:1693-5. [PMID: 3135881]
11. Phillips T, Stanton B, Provan A, Lew R. A study of the impact of leg ulcers on quality of life: financial, social, and psychologic implications. *J Am Acad Dermatol*. 1994;31:49-53. [PMID: 8021371]
12. Friedman SA. The diagnosis and medical management of vascular ulcers. *Clin Dermatol*. 1990;8:30-9. [PMID: 2129948]
13. Scott TE, LaMorte WW, Gorin DR, Menzoian JO. Risk factors for chronic venous insufficiency: a dual case-control study. *J Vasc Surg*. 1995;22:622-8. [PMID: 7494366]
14. Nelzén O, Bergqvist D, Lindhagen A. Leg ulcer etiology—a cross sectional population study. *J Vasc Surg*. 1991;14:557-64. [PMID: 1920653]
15. Browse NL, Clemenson G, Thomas ML. Is the postphlebotic leg always postphlebotic? Relation between phlebographic appearances of deep-vein thrombosis and late sequelae. *Br Med J*. 1980;281:1167-70. [PMID: 7427621]
16. Sibbald RG. An approach to leg and foot ulcers: a brief overview. *Ostomy Wound Manage*. 1998;44:28-32, 34-5. [PMID: 9866603]
17. Falanga V. Venous ulceration. *J Dermatol Surg Oncol*. 1993;19:764-71. [PMID: 8349918]
18. Falanga V. Venous ulceration. *Wounds*. 1996;8:102-8.
19. Maessen-Visch MB, Koedam MI, Hamulyák K, Neumann HA. Atrophic blanche. *Int J Dermatol*. 1999;38:161-72. [PMID: 10208608]
20. Kirsner RS, Pardes JB, Eaglstein WH, Falanga V. The clinical spectrum of lipodermatosclerosis. *J Am Acad Dermatol*. 1993;28:623-7. [PMID: 8463465]
21. Phillips TJ, Dover JS. Leg ulcers. *J Am Acad Dermatol*. 1991;25:965-87. [PMID: 1810997]
22. Phillips TJ. Successful methods of treating leg ulcers. The tried and true, plus the novel and new. *Postgrad Med*. 1999;105:159-61, 165-6, 173-4 passim. [PMID: 10335328]
23. McGee SR, Boyko EJ. Physical examination and chronic lower-extremity ischemia: a critical review. *Arch Intern Med*. 1998;158:1357-64. [PMID: 9645831]
24. Scriven JM, Hartshorne T, Bell PR, Naylor AR, London NJ. Single-visit venous ulcer assessment clinic: the first year. *Br J Surg*. 1997;84:334-6. [PMID: 9117300]
25. Lopez A, Phillips TJ. Venous ulcers. *Wounds*. 1998;10:149-57.
26. McGuckin M, Stineman M, Goin J, Williams S. Draft guideline: diagnosis and treatment of venous leg ulcers. *Ostomy Wound Manage*. 1996;42:48, 50-2, 54 passim. [PMID: 8826138]
27. Labropoulos N, Leon M, Geroulakos G, Volteas N, Chan P, Nicolaides AN. Venous hemodynamic abnormalities in patients with leg ulceration. *Am J Surg*. 1995;169:572-4. [PMID: 7771618]
28. Thibault PK. Duplex examination. *Dermatol Surg*. 1995;21:77-82. [PMID: 7600024]
29. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. *JAMA*. 1995;273:721-3. [PMID: 7853630]
30. Abu-Own A, Scurr JH, Coleridge Smith PD. Effect of leg elevation on the skin microcirculation in chronic venous insufficiency. *J Vasc Surg*. 1994;20:705-10. [PMID: 7966805]
31. Erickson CA, Lanza DJ, Karp DL, Edwards JW, Seabrook GR, Cambria RA, et al. Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. *J Vasc Surg*. 1995;22:629-36. [PMID: 7494367]
32. Blair SD, Wright DD, Backhouse CM, Riddle E, McCollum CN. Sustained compression and healing of chronic venous ulcers. *BMJ*. 1988;297:1159-61. [PMID: 3144330]
33. Partsch H. Compression therapy of the legs. A review. *J Dermatol Surg Oncol*. 1991;17:799-805. [PMID: 1918586]
34. Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. *BMJ*. 1997;315:576-80. [PMID: 9302954]
35. Stemmer R, Marescaux J, Furderer C. [Compression therapy of the lower extremities particularly with compression stockings]. *Hautarzt*. 1980;31:355-65. [PMID: 7399921]
36. Margolis DJ, Cohen JH. Management of chronic venous leg ulcers: a literature-guided approach. *Clin Dermatol*. 1994;12:19-26. [PMID: 8180941]
37. Dickey JW Jr. Stasis ulcers: the role of compliance in healing. *South Med J*. 1991;84:557-61. [PMID: 2035072]
38. Kunimoto BT. Compression therapy: theory and practice. *Dermatologic Therapy*. 1999;9:63-8.
39. Falanga V. Overview of chronic wounds and recent advances. *Dermatologic Therapy*. 1999;9:7-17.
40. Simon DA, McCollum CN. Approaches to venous leg ulcer care within the community: compression, pinch skin grafts and simple venous surgery. *Ostomy Wound Manage*. 1996;42:34-8, 40. [PMID: 8703294]
41. Falanga V. Venous ulceration: assessment, classification and management. In: Krasner D, Kane D, eds. *Chronic Wound Care*. 2nd ed. Wayne, PA: Health Management Publications; 1997:165-71.
42. Wiersma-Bryant LA. Management of edema. In: Sussman C, Bates-Jensen BM, eds. *Wound Care: A Collaborative Practice Manual for Physical Therapists and Nurses*. Gaithersburg, MD: Aspen; 1998:179-200.
43. Hansson C, Swanbeck G. Regulating the pressure under compression bandages for venous leg ulcers. *Acta Derm Venereol*. 1988;68:245-9. [PMID: 2455419]
44. Fletcher A, Cullum N, Sheldon TA. A systematic review of compression treatment for venous leg ulcers. *BMJ*. 1997;315:576-80. [PMID: 9302954]
45. Weingarten MS. State-of-the-art treatment of chronic venous disease. *Clin*

- Infect Dis. 2001;32:949-54. [PMID: 11247717]
46. Cahall E, Spence R. Nursing management of venous ulceration. *J Vasc Nurs.* 1994;12:48-56. [PMID: 7748780]
  47. Nelzén O, Bergqvist D, Lindhagen A. Long-term prognosis for patients with chronic leg ulcers: a prospective cohort study. *Eur J Vasc Endovasc Surg.* 1997;13:500-8. [PMID: 9166274]
  48. Moffatt CJ, Franks PJ, Oldroyd M, Bosanquet N, Brown P, Greenhalgh RM, et al. Community clinics for leg ulcers and impact on healing. *BMJ.* 1992;305:1389-92. [PMID: 1486301]
  49. Phillips TJ, Machado F, Trout R, Porter J, Olin J, Falanga V. Prognostic indicators in venous ulcers. *J Am Acad Dermatol.* 2000;43:627-30. [PMID: 11004617]
  50. Samson RH, Showalter DP. Stockings and the prevention of recurrent venous ulcers. *Dermatol Surg.* 1996;22:373-6. [PMID: 8624664]
  51. Erickson CA, Lanza DJ, Karp DL, Edwards JW, Seabrook GR, Cambria RA, et al. Healing of venous ulcers in an ambulatory care program: the roles of chronic venous insufficiency and patient compliance. *J Vasc Surg.* 1995;22:629-36. [PMID: 7494367]
  52. Mayberry JC, Moneta GL, Taylor LM Jr, Porter JM. Fifteen-year results of ambulatory compression therapy for chronic venous ulcers. *Surgery.* 1991;109:575-81. [PMID: 2020902]
  53. Layton AM, Ibbotson SH, Davies JA, Goodfield MJ. Randomised trial of oral aspirin for chronic venous leg ulcers. *Lancet.* 1994;344:164-5. [PMID: 7912767]
  54. Ibbotson SH, Layton AM, Davies JA, Goodfield MJ. The effect of aspirin on haemostatic activity in the treatment of chronic venous leg ulceration. *Br J Dermatol.* 1995;132:422-6. [PMID: 7718459]
  55. Weithmann KU. The influence of pentoxifylline on interactions between blood vessel wall and platelets. *IRCS Medical Science [microform].* 1980;8:293-4.
  56. Colgan MP, Dormandy JA, Jones PW, Schraibman IG, Shanik DG, Young RA. Oxpentifylline treatment of venous ulcers of the leg. *BMJ.* 1990;300:972-5. [PMID: 2256974]
  57. Dale JJ, Ruckley CV, Harper DR, Gibson B, Nelson EA, Prescott RJ. Randomised, double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. *BMJ.* 1999;319:875-8. [PMID: 10506039]
  58. Falanga V, Fujitani RM, Diaz C, Hunter G, Jorizzo J, Lawrence PF, et al. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. *Wound Repair Regen.* 1999;7:208-13. [PMID: 10781212]
  59. Jull AB, Waters J, Arroll B. Pentoxifylline for treating venous leg ulcers. *Cochrane Database Syst Rev.* 2002;(1):CD001733. Review. [PMID: 11869606]
  60. Guilhou JJ, Dereure O, Marzin L, Ouvry P, Zuccarelli F, Debure C, et al. Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomized, controlled versus placebo trial in 107 patients. *Angiology.* 1997;48:77-85. [PMID: 8995348]
  61. Scondotto G, Aloisi D, Ferrari P, Martini L. Treatment of venous leg ulcers with sulodexide. *Angiology.* 1999;50:883-9. [PMID: 10580352]
  62. Lyon RT, Veith FJ, Bolton L, Machado F. Clinical benchmark for healing of chronic venous ulcers. Venous Ulcer Study Collaborators. *Am J Surg.* 1998;176:172-5. [PMID: 9737626]
  63. Falanga V, Kirsner RS, Eaglstein WH, Katz MH, Kerdel FA. Stanozolol in treatment of leg ulcers due to cryofibrinogenaemia. *Lancet.* 1991;338:347-8. [PMID: 1677702]
  64. Burnand K, Clemenson G, Morland M, Jarrett PE, Browse NL. Venous lipodermatosclerosis: treatment by fibrinolytic enhancement and elastic compression. *Br Med J.* 1980;280:7-11. [PMID: 6986945]
  65. Helfman T, Falanga V. Stanozolol as a novel therapeutic agent in dermatology. *J Am Acad Dermatol.* 1995;33:254-8. [PMID: 7622653]
  66. McMullin GM, Watkin GT, Coleridge Smith PD, Scurr JH. Efficacy of fibrinolytic enhancement with stanozolol in the treatment of venous insufficiency. *Aust N Z J Surg.* 1991;61:306-9. [PMID: 2018441]
  67. Davidson JF, Lochhead M, McDonald GA, McNicol GP. Fibrinolytic enhancement by stanozolol: a double blind trial. *Br J Haematol.* 1972;22:543-59. [PMID: 4555715]
  68. Douglas WS, Simpson NB. Guidelines for the management of chronic venous leg ulceration. Report of a multidisciplinary workshop. British Association of Dermatologists and the Research Unit of the Royal College of Physicians. *Br J Dermatol.* 1995;132:446-52. [PMID: 7718464]
  69. Kirsner RS, Falanga V. Techniques of split-thickness skin grafting for lower extremity ulcerations. *J Dermatol Surg Oncol.* 1993;19:779-83. [PMID: 7794287]
  70. Ahnlied I, Bjellerup M. Efficacy of pinch grafting in leg ulcers of different aetiologies. *Acta Derm Venereol.* 1997;77:144-5. [PMID: 9111828]
  71. Kirsner RS, Mata SM, Falanga V, Kerdel FA. Split-thickness skin grafting of leg ulcers. The University of Miami Department of Dermatology's experience (1990-1993). *Dermatol Surg.* 1995;21:701-3. [PMID: 7633815]
  72. Trier WC, Peacock EE Jr, Madden JW. Studies on the effectiveness of surgical management of chronic leg ulcers. *Plast Reconstr Surg.* 1970;45:20-3. [PMID: 4902838]
  73. Julien OC, Dye WS, Schneewind J. Surgical management of ulcerative stasis disease of the lower extremities. *Arch Surg.* 1954;68:757.
  74. Lofgren KA, Lauvstad WA, Bonnemaïson MF. Surgical treatment of large stasis ulcer: a review of 129 cases. *Mayo Clin Proc.* 1965;40:560-3.
  75. Harrison PV. Split-skin grafting of varicose leg ulcers—a survey and the importance of assessment of risk factors in predicting outcome from the procedure. *Clin Exp Dermatol.* 1988;13:4-6. [PMID: 3061688]
  76. Teh BT. Why do skin grafts fail? *Plast Reconstr Surg.* 1979;63:323-32. [PMID: 368835]
  77. Limova M, Mauro T. Treatment of leg ulcers with cultured epithelial autografts: treatment protocol and five year experience. *Wounds.* 1995;7:170-80.
  78. Phillips TJ, Kehinde O, Green H, Gilchrist BA. Treatment of skin ulcers with cultured epidermal allografts. *J Am Acad Dermatol.* 1989;21:191-9. [PMID: 2768568]
  79. Leigh IM, Purkis PE, Navsaria HA, Phillips TJ. Treatment of chronic venous ulcers with sheets of cultured allogenic keratinocytes. *Br J Dermatol.* 1987;117:591-7. [PMID: 2446651]
  80. Falanga V. Occlusive wound dressings. Why, when, which? *Arch Dermatol.* 1988;124:872-7. [PMID: 3288123]
  81. Sinclair RD, Ryan TJ. Proteolytic enzymes in wound healing: the role of enzymatic debridement. *Australas J Dermatol.* 1994;35:35-41. [PMID: 7998898]
  82. Eaglstein WH, Falanga V. Chronic wounds. *Surg Clin North Am.* 1997;77:689-700. [PMID: 9194887]
  83. Westerhof W. Future prospects of proteolytic enzymes and wound healing. In: Westerhof W, Vanscheidt W, eds. *Proteolytic Enzymes and Wound Healing.* New York: Springer-Verlag; 1994:99-102.
  84. Kennedy KL, Tritch DL. Debridement. In: Krasner D, Kane E, eds. *Chronic Wound Care.* 2nd ed. Wayne, PA: Health Management Publications; 1997:227-34.
  85. Zacur H, Kirsner RS. Debridement: rationale and therapeutic options. *Wounds.* 2002;14(7 Suppl F):2E-7E.
  86. Douglas WS, Simpson NB. Guidelines for the management of chronic venous leg ulceration. Report of a multidisciplinary workshop. British Association of Dermatologists and the Research Unit of the Royal College of Physicians. *Br J Dermatol.* 1995;132:446-52. [PMID: 7718464]
  87. Olivencia JA. Subfascial endoscopic ligation of perforator veins (SEPS) in the treatment of venous ulcers. *Int Surg.* 2000;85:266-9. [PMID: 11325008]
  88. Dunn RM, Fudem GM, Walton RL, Anderson FA Jr, Malhotra R. Free flap valvular transplantation for refractory venous ulceration. *J Vasc Surg.* 1994;19:525-31. [PMID: 8126867]
  89. Weinzwieg N, Schuler J. Free tissue transfer in treatment of the recalcitrant chronic venous ulcer. *Ann Plast Surg.* 1997;38:611-9. [PMID: 9188977]
  90. Falanga V, Margolis D, Alvarez O, Auletta M, Maggiamico F, Altman M, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol.* 1998;134:293-300. [PMID: 9521027]
  91. Lindgren C, Marcusson JA, Toftgård R. Treatment of venous leg ulcers with cryopreserved cultured allogeneic keratinocytes: a prospective open controlled study. *Br J Dermatol.* 1998;139:271-5. [PMID: 9767241]
  92. Marques da Costa R, Jesus FM, Aniceto C, Mendes M. Double-blind randomized placebo-controlled trial of the use of granulocyte-macrophage colony-stimulating factor in chronic leg ulcers. *Am J Surg.* 1997;173:165-8. [PMID: 9251027]

9124619]

93. Halabe A, Ingber A, Hodak E, David M. Granulocyte-macrophage colony-stimulating factor—a novel therapy in the healing of chronic ulcerative lesions. *Med Sci Res.* 1995;23:65-6.

94. Pojda Z, Struzyna J. Treatment of non-healing ulcers with rhGM-CSF and skin grafts [Letter]. *Lancet.* 1994;343:1100. [PMID: 7909116]

95. Jaschke E, Zabernigg A, Gattringer C. Recombinant human granulocyte-macrophage colony-stimulating factor applied locally in low doses enhances healing and prevents recurrence of chronic venous ulcers. *Int J Dermatol.* 1999;38:380-6. [PMID: 10369552]

96. Da Costa RM, Ribeiro Jesus FM, Aniceto C, Mendes M. Randomized, double-blind, placebo-controlled, dose-ranging study of granulocyte-macrophage colony stimulating factor in patients with chronic venous leg ulcers. *Wound Repair Regen.* 1999;7:17-25. [PMID: 10231502]

97. Xia YP, Zhao Y, Marcus J, Jimenez PA, Ruben SM, Moore PA, et al. Effects of keratinocyte growth factor-2 (KGF-2) on wound healing in an ischaemia-impaired rabbit ear model and on scar formation. *J Pathol.* 1999;188:431-8. [PMID: 10440755]

98. Robson MC, Phillips TJ, Falanga V, Odenheimer DJ, Parish LC, Jensen JL, et al. Randomized trial of topically applied repifermin (recombinant human keratinocyte growth factor-2) to accelerate wound healing in venous ulcers. *Wound Repair Regen.* 2001;9:347-52. [PMID: 11896977]

99. Gherardini G, Gürlek A, Evans GR, Milner SM, Matarasso A, Wassler M, et al. Venous ulcers: improved healing by iontophoretic administration of calcitonin gene-related peptide and vasoactive intestinal polypeptide. *Plast Reconstr Surg.* 1998;101:90-3. [PMID: 9427920]

100. Kunimoto B, Cooling M, Gulliver W, Houghton P, Orsted H, Sibbald RG. Best practices for the prevention and treatment of venous leg ulcers. *Ostomy Wound Manage.* 2001;47:34-46, 48-50. [PMID: 11235498]

101. Stewart AJ, Leaper DJ. Treatment of chronic ulcers in the community: a comparison of Scherinsorb and Iodosorb. *Phlebology.* 1987;2:115-21.

102. Margolis DJ, Gross EA, Wood CR, Lazarus GS. Planimetric rate of healing in venous ulcers of the leg treated with pressure bandage and hydrocolloid dressing. *J Am Acad Dermatol.* 1993;28:418-21. [PMID: 8445057]

103. Tallman P, Muscare E, Carson P, Eaglstein WH, Falanga V. Initial rate of healing predicts complete healing of venous ulcers. *Arch Dermatol.* 1997;133:1231-4. [PMID: 9382561]

#### Personae

In an effort to bring people to the pages and cover of *Annals*, the editors invite readers to submit photographs of people for publication. We are looking for photographs that catch people in the context of their lives and that capture personality. *Annals* will publish photographs in black and white, and black-and-white submissions are preferred. We will also accept color submissions, but the decision to publish a photograph will be made after the image is converted to black and white. Slides or prints are acceptable. Print sizes should be standard (3" × 5", 4" × 6", 5" × 7", 8" × 10"). Photographers should send two copies of each photograph. We cannot return photographs, regardless of publication. We must receive written permission to publish the photograph from the subject (or subjects) of the photograph or the subject's guardian if he or she is a child. A cover letter assuring no prior publication of the photograph and providing permission from the photographer for *Annals* to publish the image must accompany all submissions. The letter must also contain the photographer's name, academic degrees, institutional affiliation, mailing address, and telephone and fax numbers.

Selected Personae submissions will also appear on the cover of *Annals*. We look forward to receiving your photographs.

*Christine Laine, MD, MPH*  
Senior Deputy Editor

---

**Current Author Addresses:** Drs. de Araujo, Valencia, and Kirsner: University of Miami School of Medicine, 1201 NW 16th Street, Miami, FL 33125.

Dr. Federman: Yale University School of Medicine, Veterans Administration Connecticut Health Care System (11ACSL), 950 Campbell Avenue, West Haven, CT 06516.