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Protocol for the successful treatment of venous ulcers

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Abstract

Venous ulcers affect up to 2.5 million patients per year in the United States. Although not usually fatal, these chronic wounds severely affect patients' quality of life because of impaired mobility and substantial loss of productivity. Although venous ulcers are typically small initially, they are often undertreated, progressing to larger ulcers that are associated with more serious complications requiring more complex treatments. In this report we detail the pathogenesis of venous ulcers together with potential complications, including exudate, erythema, cellulitis, dermatitis, pain, and possible malignancy. The clinician's regimen should always include a wide range of treatment modalities to ensure comprehensive care and effective wound closure. The treatment modalities and specific protocol for venous ulcers are discussed, and include topical dressings, antibiotics, debridement, compression therapy, and cellular therapy. These treatment modalities, in combination with early recognition and regular monitoring using digital photography and planimetry measurements, will ensure rapid healing and minimize complications and cost.

Venous ulcers are chronic wounds by definition and consequently have underlying physiologic impairments [1]. From the most extensive survey in the United States, it was estimated that approximately 400,000 to 600,000 venous ulcers affect the population [2]. Even though these ulcers are rarely fatal and hardly ever progress to osteomyelitis or amputation, they frequently result in repeated hospitalizations, which result in substantial costs and morbidity. For instance, the incidence rate of recurrent ulceration after wound healing with nonoperative methods has been reported at 37% and 48% at years 3 and 5 [3,4].

Venous ulcers also significantly reduce patients' quality of life: 81% of patients with venous stasis ulcers experience decreased mobility, and 57% report that their mobility is severely limited. As a result, 68% of patients with impaired mobility experience fear, anger, depression, and social isolation. In addition, venous ulcers account for annual losses of >2 million workdays in the United States. Moreover, leg ulcers have a major impact on quality of life. In 1 study, a significant number of patients had moderate to severe symptoms, principally pain, related to a leg ulcer; 81% believed that their mobility was adversely affected by the ulcer, and 68% of patients reported that the ulcer had a negative emotional impact on their lives [5].

Considering the levels of suffering associated with venous ulcers, the investigation and treatment of these wounds has not received adequate attention. Venous ulcers are often initially undertreated and mistakenly attributed to trauma. They can therefore progress to larger ulcers that may ultimately require complex plastic surgery procedures for successful treatment. Several studies have shown that ulcers of longer duration and larger size have a worse prognosis with regard to healing [6]. Unsuccessful treatment of these wounds is associated with increased rates of morbidity, which in turn increase costs and negatively impact the patient's quality of life. Comprehensive treatment of these ulcers is required to ensure prolonged success. The protocol outlined here should serve to provide early treatment in order to prevent progression of venous ulcers and eventually to keep any venous ulcer from taking >1 year to heal (Fig. 1).

Pathogenesis

The exact mechanism underlying the formation of venous ulceration is unknown. However, ulcers of this type have been attributed to venous hypertension caused by ve-

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nous reflux and obstruction. Reports indicate that prevalence of venous reflux in venous ulcerations is high.

In the venous system of the lower limbs, blood normally flows from the superficial system to the deep system. This process lowers the superficial venous pressure. Venous valvular competency is essential to prevent regurgitation during relaxation of the lower limb muscles, protecting the superficial veins and capillaries from elevations in venous pressure [7]. Valvular incompetency causes an increase in superficial venous pressure (venous hypertension), resulting in the development of tissue trauma and eventual ulceration [8]. This increased venous pressure causes dilation and elongation of the veins and venules, disrupting normal microcirculation by increasing the permeability and the leakage of plasma and erythrocytes into the surrounding tissue [9–12].

Several studies investigated the microcirculation of the tissue surrounding venous ulcers. An important observation is increased levels of leukocytes in the dependent limbs of patients with chronic venous insufficiency [13]. The "white cell trapping" hypothesis suggests that localized hypertension leads to leukocyte trapping and activation, releasing free radicals and other toxic substances that promote cell death and tissue damage [14]. This trap hypothesis also suggests that hypertension in the capillary bed causes the macromolecules leaking into the dermis to trap the growth factors and cytokines necessary for tissue repair [14]. Another observation concerns deficiencies in the fibrinolytic system in patients with venous ulcers [15], where fibrin is normally cleared rapidly by this system. A hypothesis suggests that this deficiency results from pericapillary fibrin cuffs that develop as a result of venous hypertension and extravasation of fibrinogen. It is hypothesized that these cuffs act as barriers to the diffusion of oxygen and nutrients, leading to tissue hypoxia, cell death, and ulceration [16]. Nevertheless, because the pericapillary fibrin cuffs around dermal capillaries are discontinuous, and ulcers can heal despite the persistence of these cuffs, their role as a purely physical barrier seems doubtful.

Regardless of which mechanism causes venous ulcers, these ulcers—like other chronic wounds—do not contract or epithelialize either at the rate that an acute wound does or in a patient who does not have venous reflux. They simply stop healing at some point and must therefore be actively treated in order to continue healing.

Diagnosis

Proper diagnosis of these ulcers is extremely important because misdiagnosis can lead to ulcer progression and other complications. Clinical features of venous ulceration include leg swelling, pain, scaling, discharge, edema, and lipodermatosclerosis [17,18]. The diagnosis of venous insufficiency is a reasonable consideration in any patient who has a leg (not a plantar) ulcer. Physical examination, although helpful, is imperfect, and venous studies such as ultrasound testing for venous reflux can avoid misdiagnosis and delay in treatment. Duplex ultrasonography is useful for determining the presence of venous insufficiency and is accurate, noninvasive, and reproducible [19]. Ultrasonography is also useful in diagnosing deep vein thrombosis (DVT) [20–23].

A common error is sending a patient with a venous ulcer and swelling for an ultrasound to "rule out DVT." A more appropriate order is to "evaluate for venous reflux." All vascular laboratories will examine the deep system by protocol and determine whether a clot is present so that information on reflux as well as DVT is obtained. By sending the patient for venous reflux testing, reflux, DVT, and perforators can be visualized.

Additionally, identification of arterial disease is mandatory in patients with lower-extremity ulcers, because it will determine available treatment options. The ankle–brachial index (ABI) can be obtained using Doppler ultrasonography. An ABI <0.9 indicates significant arterial insufficiency. This must be taken into account when formulating treatment for the venous ulcer in order to avoid complications resulting from inappropriate compression therapy. Consideration of consultation with a vascular surgeon should occur in the presence of an ABI <0.9 regardless of symptoms. Debridement in the face of arterial insufficiency may result in additional complications and, to avoid this, objective measure of arterial inflow is recommended.

Complications

Complications associated with venous ulcers include gait changes, pain, infection, cellulitis, malignant wound changes, and dermatitis.

Gait changes and pain

Among the common consequences of venous hypertension are musculoskeletal changes. These changes negatively affect the dynamics of the calf muscle pump. As the large muscles of the calf contract, venous blood is forced out of the legs [24]. When a change in gait is related to a painful ulcer, calf muscle atrophy may ensue because of disuse. Mild exercises (walking, bicycle peddling, ankle pumping, and swimming) causing contraction of the calf muscles (and increased heart rate) should be encouraged unless contraindicated. Notably, 72% of patients with venous ulcers stated that they had difficulty walking [25]. The importance of monitoring for gait changes is often underrecognized. Every patient should be observed for gait changes, and those who have them should be referred to a physiatrist and or a physical therapist for supervised rehabilitation while the ulcer is being treated.

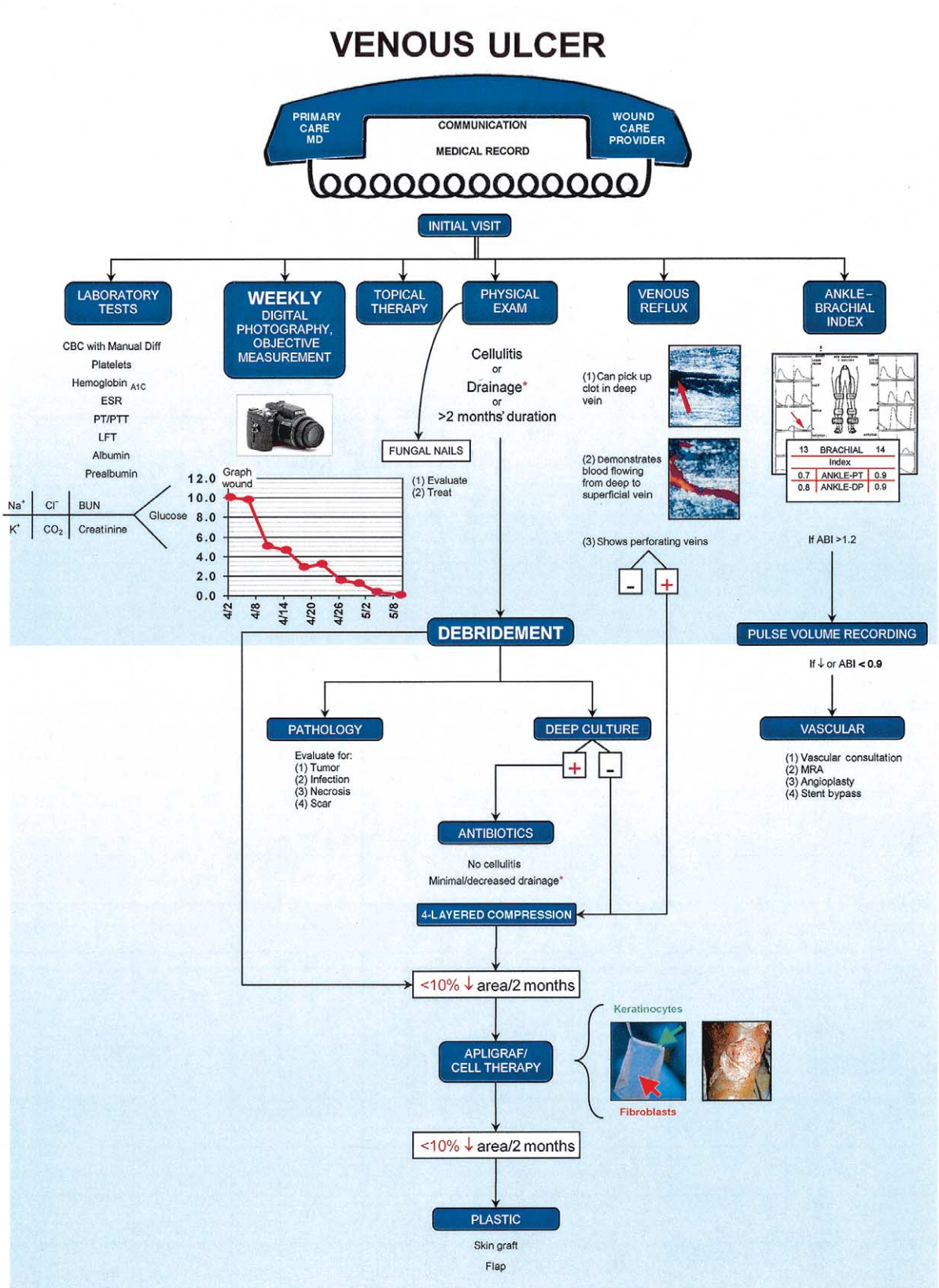

Fig. 1. Venous ulcer. Venous ulcers commonly occur on the ankle but include any area below the knee that has + reflux (eg, the foot). * Drainage is often a sign of infection in which case compression is not advisable. ABI = ankle–brachial index; ANKLE-DP = ankle–dorsalis pedis; ANKLE-PT = ankle–posterior tibia; BUN = serum urea nitrogen; CBC = complete blood cell count; Diff = differential; ESR = erythrocyte sedimentation rate; LFTs = liver function tests; MRA = magnetic resonance angiography; PT = prothrombin time; PTT = partial thromboplastin time.

Infection and cellulitis

Cellulitis, drainage, and tenderness are signs of infection in a venous ulcer. If such signs are present and an ulcer is increasing in size or does not have well-vascularized granulation tissue, a tissue specimen must be obtained for culture. The tissue specimen should be collected by punch biopsy and curette of the ulcer base, preferably of the deepest layer during debridement. Infections in venous ulcers most commonly include gram-positive organisms, such as *Staphylococcus* and *Streptococcus* and gram-negative organisms such as *Pseudomonas*. In addition, *Enterobacter cloacae* (74%), *Peptococcus magnus* (29%), and fungi (11%) commonly infect venous ulcers [26]. Oral or intravenous antibiotics should be selected depending on the patient's medical condition and the specific pathogen(s). Should surrounding tissue be involved, broad-spectrum oral antibiotics, such as levofloxacin and amoxicillin-clavulanate are excellent first choices for patients presenting with drainage or infection. If the infection does not resolve rapidly, however, and drainage continues, a deep culture must be taken and the appropriate parenteral antibiotics considered. Antibiotic coverage for presumptive anaerobic bacteria should be considered.

When a wound begins contracting and epithelializing (ie, healing), and yet exudate continues, this exudate is of less concern because healing of the wound is more important than the finding of exudate. However, in the absence of significant contraction, drainage should be addressed, and antibiotics are often effective. If a wound is not healing or the patient is not compliant and fails to return every week for compression therapy, prolonged use of antibiotics may promote resistance.

Colonized venous ulcers tend to heal more slowly than noncolonized ulcers and are larger on initial presentation [27]. Local wound care and antimicrobial agents are essential during the healing process. We emphasize the importance of wound-bed preparation, which translates into an attempt to eliminate local bacteria while stimulating well-vascularized granulation tissue [27].

Malignancy

Any venous ulcer present >3 months and unresponsive to therapy [28] should undergo biopsy to rule out malignancy. Although malignant transformation is rare, it does occur with chronic leg ulcers [29,30]. Squamous cell carcinoma in a leg ulcer is easily overlooked and most often is thought to be a deterioration of the ulcer until an exophytic tumor appears. Squamous cell carcinoma can be fatal, especially if poorly differentiated. The etiology of malignant transformation is unknown. A biopsy can be performed efficiently with minimal risk of complication.

The majority of ulcerated basal cell carcinomas occur at sites atypical for venous ulcers, and it is possible for a basal cell carcinoma to arise from a preexisting ulcer. Like all tumors, basal cell carcinoma may have the appearance of healthy granulation tissue [31,32], that is, of a wound.

In 1 report, 43 of 981 patients (2,448 ulcers) had either squamous cell or basal cell carcinoma malignant lesions within the ulcer, with a frequency of 2.2 malignancies per 100 leg ulcers [33]. Rare malignancies, that is, malignant fibrous histiocytoma [34], have also been documented in leg ulcers.

Dermatitis

Dermatitis is a common complication of venous stasis ulcers [35]. The periwound skin is often eczematous, presenting with erythema, scaling, weeping, and crusting, causing intense pruritus. We emphasize that it is very important to treat this dermatitis because it may lead to further ulceration. No patient with a leg ulcer should have associated dermatitis or cobblestone-type skin adjacent to a wound.

The initial visit

Physical examination

A venous leg or foot ulcer can occur anywhere there is reflux between the deep and superficial venous systems. Although the ankle is the most common site, these ulcers can occur anywhere below the knee, including the foot. The initial examination should include objective measurements of all manifestations of the wound, including cellulitis and drainage.

Pain

Pain is most often undertreated in venous ulcers. It should be immediately addressed and treated, and it may require the assistance of persons with additional expertise, such as an anesthesiologist. Although management of pain during debridement is essential, some have recognized that pain may be relieved after debridement, theoretically because the bacterial burden is removed.

ABI and pulse volume recordings

After initial presentation of a patient with a venous ulcer, arterial pulse volume recordings and ABIs should be obtained to determine whether the patient has mixed arterial and venous disease. Pulse volume recordings should always be obtained when an ABI is >1.2 or <0.9. Cautious use of compression is advisable in situations with compromised arterial flow, and therefore this knowledge is critical to appropriate therapy. In most cases, if the patient has a strong palpable pulse of +2, dorsalis pedis or posterior tibial pulses, and does not have diabetes, further arterial testing is unnecessary.

Laboratory values

A complete blood count with a manual differential should be performed. Manual differential and platelet counts help detect any underlying hematologic disease or undetected infection. A mechanical differential may reveal a shift to the left in the white blood cell (WBC) count, indicative of an infection. For reasons that are not well understood, patients with infected venous ulcers often have normal WBC counts and normal WBC count differentials. Thus, this laboratory value has significance only when it is abnormal.

Prothrombin time and activated partial thromboplastin time must be assessed to detect a bleeding diathesis. Analyses of routine chemistry laboratory values, including a sequential multichannel analysis–7 (sodium, potassium, chloride, CO_2, serum urea nitrogen, creatinine, glucose), glycosylated hemoglobin, basic nutritional markers (prealbumin and albumin), and liver function tests (including γ–glutamyl transpeptidase, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) should be performed. If the patient is $<$50 years old, a hypercoagulation profile, including protein C, protein S, antithrombin III, factor V Leiden, and homocysteine levels [36], are recommended.

Topical therapy

Topical dressings may decrease the rate of infection and promote a moist environment that enhances autolytic debridement and facilitates growth of granulation tissue. Cadexomer iodine [37–40] (Iodosorb or Iodoflex; Healthpoint, Fort Worth, TX, and Smith & Nephew, Hull, United Kingdom) has been shown in a number of well-conducted studies to promote healing of venous ulcers when used in combination with compression therapy. Although a rationale exists for the use of other antimicrobial agents, such as silver products [41–44]—which are efficacious antimicrobial topical treatments that do not require daily application and are excellent for ideal wound-bed preparation—data are limited regarding their ability to speed healing of venous ulcers [45].

Antibiotics

After obtaining a deep culture, antibiotic treatment is started if infection is present. Cephalosporin may be useful if gram-positive organisms are suspected. However, when multiple organisms are suspected or there is no response to the first treatment, levofloxacin (250 mg once a day or 500 mg once a day) with amoxicillin-clavulanate (875 mg twice daily) may be useful; 2 g of the extended-release form, that is, XL of amoxicillin-clavulanate twice a day, may also be used. Intravenous antibiotics may be necessary if cellulitis or other signs of infection are not improved after a week of oral antibiotics. Levofloxacin or ciprofloxacin and amoxicillin-clavulanate in combination may maximize oral antibiotics. When such aggressive regimens are required, however, objective criteria for improvement must be followed (ie, elimination of drainage and cellulitis) in evaluating the success of that treatment.

Wound assessment: photography and planimetry

On initial assessment and subsequently, once-weekly assessment of the wound should be performed. Several methods exist to carry this out. A digital photograph should be taken of the wound, and wound size should be measured objectively using planimetry (Fig. 2). The photograph and these measurements can be entered into a database (or the measurements can be entered into a spreadsheet) and a graph created demonstrating the rate of wound healing. Assessment is critical because wounds that fail to contract or epithelialize over a 2- to 4-week period require a change in treatment regimen. It is easier to note an unsatisfactory rate of healing by following the trend of these wound measurements graphically; this permits the requisite treatment changes to proceed in a more timely fashion.

Surgical debridement in venous ulcers

The rationale for surgical debridement is focused on removing nonviable tissue, decreasing bacterial burden, and stimulating contraction and epithelialization. Surgical debridement removes necrotic tissue, thereby promoting granulation tissue formation. Regardless of how the wound is debrided, the end result must be the same: a contracting and/or epithelializing edge and the removal of scar and infection.

Therefore, it may be appropriate to perform debridement if a venous ulcer shows signs of infection as manifested by $\geq$1 of the following symptoms: cellulitis, persistent or increased exudates, elevated WBC count, fever, persistent or increased drainage, and nonhealing wound (suboptimal healing rates occur when the wound area decreases $<$10% over a 2-week period).

Removing devitalized tissue promotes the formation of granulation tissue and epithelialization, and it may decrease the risk of infection. Empirically, the wound may be debrided to a depth where there is no fibrotic tissue or suggestion of excess bioburden. This is typically evaluated clinically and ideally is confirmed by pathologic analysis. Samples should be taken at different levels, with the last sample being taken from the tissue remaining in the wound bed after debridement. This will assist in determining if fibrotic tissue is absent and supply a deep tissue culture. Swab cultures are not adequate; a piece of tissue is necessary.

Although bleeding may occur with minimal debridement, often more extensive debridement is needed if removal of fibrotic tissue is the goal.

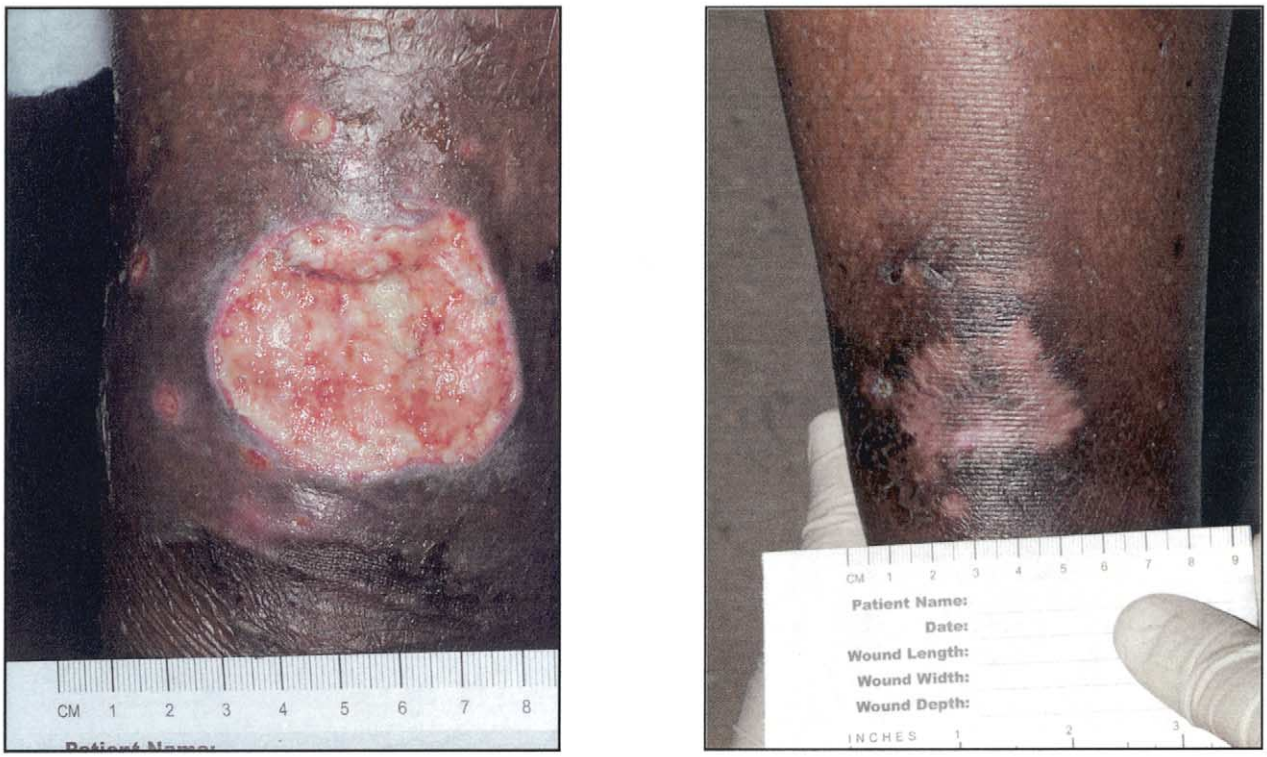

Fig. 2. (*Left*) This patient, an obese woman, presented with a cellulitic infected venous ulcer. (*Right*) This figure demonstrates healing after a combination of antibiotics, human skin equivalent (Apligraf; Organogenesis, Canton, MA), and compression therapy. Strict adherence to the protocols presented in this report will result in the healing of the majority of venous ulcers.

Depending on the planned debridement, the need for adequate hemostasis and pain management may require a setting other than the office. All debridement should have topical or intralesional anesthesia in the absence of general or regional anesthesia. Regional anesthetic (eg, femoral, popliteal, or sciatic nerve) and sometimes general anesthesia is often necessary for adequate debridement.

Initial debridement must always be combined with pathologic analysis of the discarded tissue and the remaining deep tissue. Deep cultures of tissue should be sent for microbiologic testing in sterile urine specimen bottles or moist air containers with only a few drops of sterile saline.

Compression therapy

Compression reduces distention of superficial veins, thereby reducing the vessel cross-sectional area, making previously incompetent valves competent. Compression also assists the calf muscle pump by reducing the venous pressure, increasing blood flow in the right direction, and reducing edema.

The Unna boot, traditionally the standard of care for venous ulcers, has significant utility but has been largely replaced by multilayered elastic bandages. In the absence of arterial insufficiency, the optimal amount of compression for venous insufficiency is 30 to 40 mm Hg. These bandages should be applied while the patient is supine, with the leg elevated and the foot dorsiflexed.

Cellular therapy

Treatment with cultured keratinocytes and fibroblasts (eg, Apligraf; Organogenesis, Canton, MA) is the only US Food and Drug Administration (FDA)–approved therapy to accelerate healing for venous ulcers [46–51]. Many drugs have failed randomized clinical trials for treatment of these wounds, including triboxony-2 inhibitors and transforming growth factor–β. No other biological therapies have passed randomized, controlled, clinical trials for efficacy in healing venous ulcers. Multiple growth factors (eg, platelet-derived growth factor–BB, granulocyte/macrophage colony-stimulating factor, and keratinocyte growth factor–2) are being investigated for potential use in venous ulcers.

Apligraf is approved by the FDA based on efficacy and safety to accelerate closure of venous ulcers and diabetic foot ulcers. Apligraf is a bilayered living skin construct containing an outer layer of live allogeneic human keratinocytes and a second layer of live allogeneic fibroblasts on type 1 bovine collagen dispersed in a dermal layer matrix. Both cell layers are grown from infant foreskin. Apligraf looks and feels like human skin; however, its biologic ac-

tivity is distinct from that of an autologous skin graft and is a potent stimulator of wound healing.

In a multicenter clinical trial for patients (n = 120) who had venous ulcers present for >1 year, Apligraf plus compression therapy by week 24 proved almost 2.5 times more effective than treatment without Apligraf (47% vs 19%, $P < 0.005$). This study demonstrated that the healing rate in wounds present for >1 year without the aid of any biologic therapy was only 19% [51]. Thus, we began treating nonhealing venous ulcers present for >1 year with Apligraf [52] and found a healing rate of 74% within 6 months when combined with the protocol described in this report.

Plastic surgery

When immediate healing is medically necessary, or at the patient's request, plastic surgery incorporating autologous skin grafts or muscle flaps should be considered for those who can tolerate either procedure. The healing rate outcome for autologous skin grafting is as high as 65% at 1 year [53]. Like all plastic surgery procedures, these are part of the physician's wound-healing regimen. Split thickness grafts should be considered for larger or nonhealing wounds. More conservative therapies, including debridement, cell therapy (Apligraf), and compression therapy, are not replacements but rather alternatives to plastic surgery.

Conclusion

Once properly diagnosed, the majority of venous ulcers are expected to heal. However, these wounds are often a source of significant pain and suffering if they are not rapidly diagnosed and treated. Initial diagnosis of venous ulceration should be confirmed using Doppler testing. Once diagnosed, compression therapy (if ischemia is ruled out), debridement, and antibiotic, topical, and cellular therapies should be used appropriately following the above protocol. Restoration of normal integument is the goal, and all these therapies must be available as part of the clinician's wound-healing regimen.

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