# Modalities to Treat Venous Ulcers: Compression, Surgery, and Bioengineered Tissue

Lisa J. Gould, MD, PhD, FACS
Garima Dosi, MD, FACS
Kara Couch, MS, CRNP, CWS
Gary W. Gibbons, MD, FACS
Raelina S. Howell, MD
Harold Brem, MD, FACS
Marjana Tomic-Canic, PhD

*Warwick, RI; Boston and South Weymouth, Mass.; Washington, D.C.; Mineola, N.Y.; and Miami, Fla.*

**Background:** Venous leg ulcers (VLUs) represent the most common ulcers of the lower extremity. VLUs are notorious for delayed and prolonged healing with high rates of recurrence. Most patients with VLUs also have significant comorbidities that interfere with primary wound healing. Thus, caring for patients with VLUs requires an interdisciplinary approach that addresses the abnormal venous anatomy and the downstream effects that lead to inflammation, ulceration, and a hostile wound microenvironment.
**Methods:** The current literature regarding venous ulcer treatment with an emphasis on compression, surgical options, and use of bioengineered tissue was reviewed. A combination of society guidelines, Cochrane reviews, and over 80 primary articles with high-level evidence were utilized to develop this summary and algorithm for an integrated approach to treating patients with venous ulcers. Details regarding compression modalities and venous diagnostic imaging are presented to help the clinician understand the rationale for using these technologies.
**Results:** The comprehensive approach to the patient with chronic venous insufficiency (CVI) includes advances in compression, diagnostics, minimally invasive surgical treatment of venous disease, wound bed preparation, and bioengineered skin and soft tissue substitutes. An algorithm that incorporates early treatment of the ulcer and the venous disease leading to healing with prevention of recurrence is presented.
**Conclusions:** Utilizing guidelines that incorporate evidence-based modalities will lead to the highest quality outcomes with the most appropriate resource utilization. A proactive approach to treating venous disease will alleviate suffering and prevent the long-term sequelae of CVI. (*Plast. Reconstr. Surg.* 138: 199S, 2016.)

## EPIDEMIOLOGY

Chronic venous disease (CVD), noted by Hippocrates more than 2500 years ago, is a major cause of human disability. CVD describes a wide range of symptoms from spider veins, reticular veins, varicose veins, and edema to more advanced forms, referred to as chronic venous insufficiency (CVI), with hyperpigmentation and dermal sclerosis. Venous leg ulcers (VLUs), the most severe manifestation of CVI, are notoriously slow to heal with high recidivism rates. As a result, they pose significant physical, emotional, and socioeconomic costs to patients, families, and the healthcare system. With the global increase in age and obesity, the incidence of VLU is increasing.[1,2] It is estimated that of the 2.5 to 3 million Americans affected by venous insufficiency at least 600,000 suffer from chronic leg ulcers, resulting in an annual economic burden of up to $15 billion.[3,4] The negative impact of venous ulcers on patients' lives is underappreciated and rarely assessed. Recent qualitative and quantitative studies have identified numerous issues, including pain, social isolation, depression, and disability.[5–7] Although

*From the Kent Hospital Wound Recovery and Hyperbaric Medicine Center; Department of Vascular Surgery, Brigham and Women's Hospital; George Washington University Hospital, Wound Healing and Limb Preservation Center; South Shore Hospital, Center for Wound Healing; Boston University School of Medicine; Division of Wound Healing and Regenerative Medicine, Department of Surgery, Winthrop University Hospital/Stony Brook University School of Medicine; and Wound Healing and Regenerative Medicine Research Program, Department of Dermatology, University of Miami Miller School of Medicine.*
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not a mortal disease, the impact on quality of life (QoL), in terms of physical function, mental health, and bodily pain, is reported to be greater for patients with either healed or active ulcers than for patients with colorectal and breast cancer.[8]

Unfortunately, the current treatment of patients with VLUs is episodic, fragmented, and inconsistent across disciplines. A recent clinical trial demonstrated a startling lack of adherence to evidence-based VLU practice guidelines. Thirty-five percent of patients were not debrided in the 12 months before enrollment, only 60% were adequately compressed 30 days before enrollment and 48% were treated with advanced therapies without an adequate trial of compression.[8]

A proactive approach to treatment with institution of organized interdisciplinary treatment algorithms developed from evidence-based comprehensive guidelines such as those recently published by the Society for Vascular Surgery and American Venous Forum (SVS/AVF) in the early stages of venous disease could reduce cost and decrease the number of patients suffering from intractable ulcers (Fig. 1).

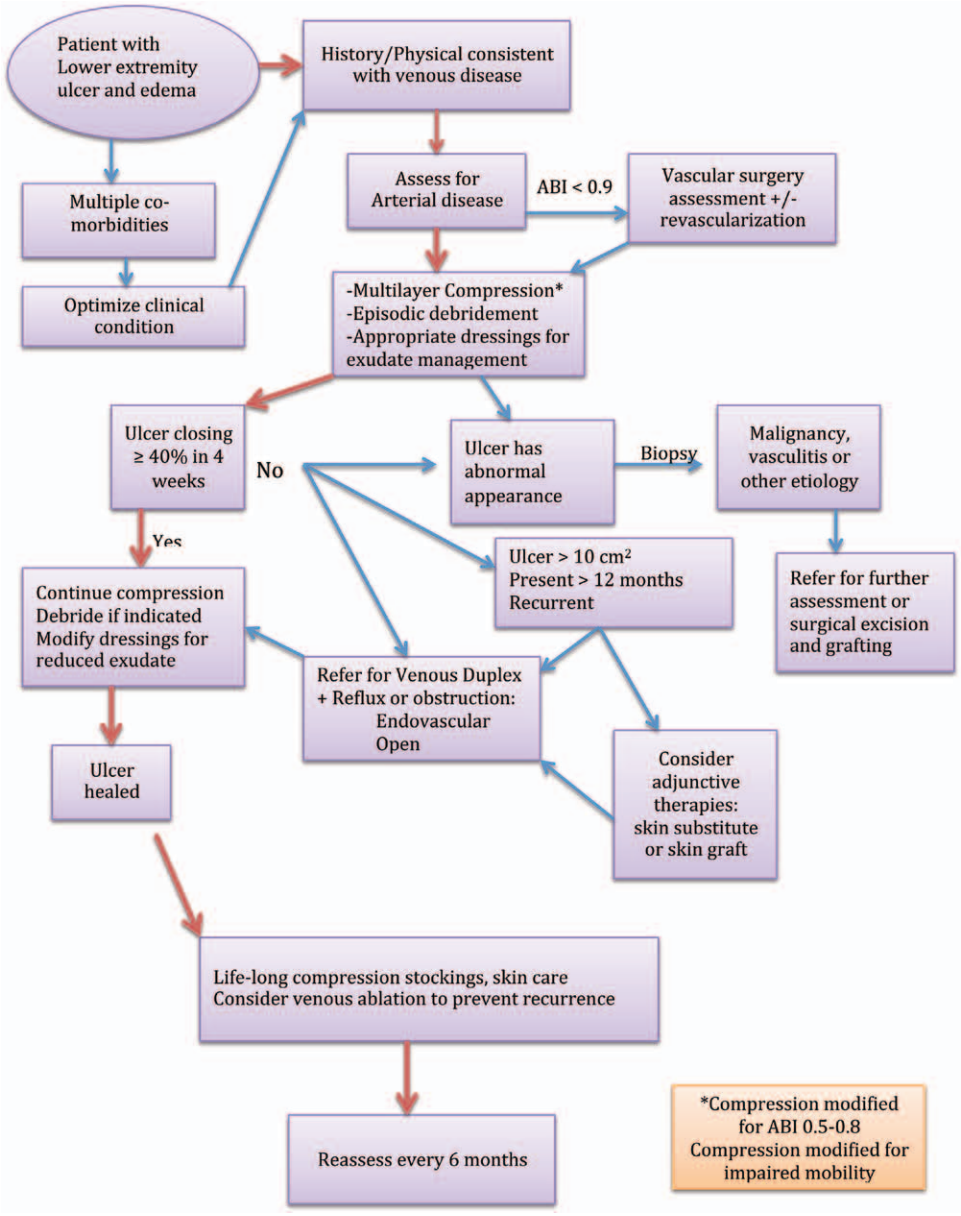


**Fig. 1.** Algorithm for interdisciplinary evidence-based treatment of patients with venous ulcers (CEAP 6). The red arrows outline the anticipated progression for a patient who demonstrates consistent healing with standard of care treatment. *ABI*, ankle brachial index.

## Anatomy and Pathophysiology

Understanding the anatomic and pathophysiologic basis for venous ulceration is critical for developing treatments that reduce recurrence. Risk factors for venous disease include obesity, advanced age, prolonged standing, physical inactivity, greater height, and genetic predisposition.[9] These factors lead to prolonged venous hypertension resulting in chronic inflammation in the veins and surrounding tissue. Although the majority of venous hypertension can be ascribed to reflux through incompetent valves, additional causes include venous outflow obstruction and failure of the calf-muscle pump owing to obesity or leg immobility.

The venous system consists of superficial and deep veins connected by perforating or communicating veins. Correct venous flow depends on healthy cardiac function combined with intact venous valves and a well-functioning calf muscle pump. Venous pressure is a balance between the weight of the column of blood from the right atrium to the foot (hydrostatic) and the pressure generated by contraction of the skeletal muscles of the leg (hydrodynamic). After prolonged standing, the venous pressure in the foot may reach 90 mm Hg, with and without competent valves.[10] When people with competent valves ambulate, venous blood flows to the heart, the deep and superficial systems are emptied, and the pressure is reduced to less than 30 mm Hg. In patients with venous insufficiency, regardless of etiology, this system is ineffective and pressure remains elevated. The combination of elevated venous pressure and a shift in fluid shear stress results in leukocyte adhesion, inflammation, and destruction of the protective endothelial glycocalyx in the walls of the venules and the valves.[11] Unrestrained matrix metalloproteinase and inflammatory cytokine activity results in destruction of the dermis with skin changes and eventual ulcer formation.[10,12,13]

Prolonged or untreated CVI with chronic accumulation of protein-rich interstitial fluid may damage the delicate lymphatic collectors resulting in secondary lymphedema or "phlebolymphedema." This progressive condition requires a multimodal approach employing massage, compression bandaging, and exercises for optimal management.[14] Treatment regimens can be intense and require hours of time daily, which is very difficult for most patients. Early intervention is the key to prevention. Although lymph node transfers may one day prove beneficial, studies to date have only been performed in patients with lymphedema secondary to cancer treatments.[15]

## Assessment of Patients with Venous Disease

The CEAP (Clinical, Etiologic, Anatomic, and Pathophysiologic) classification was first developed in 1994 and later revised into basic and advanced format in 2004.[16,17] The basic CEAP (Table 1) is recommended for clinical practice, whereas the advanced format, which subdivides the basic CEAP into 18 anatomic venous locations, is primarily intended for research.[17] Although the CEAP has standardized communication among clinicians and researchers regarding venous disease severity, it is descriptive and static, and is therefore not an ideal tool for evaluating the effectiveness of an intervention.

The Venous Severity Score (VSS), developed in 2000 by the AVF, was derived from the CEAP as a tool to evaluate the clinical condition over time. It consists of 3 components: Venous Clinical Severity Score (VCSS), Venous Segmental Disease Score (VSDS), and Venous Disability Score (VDS).[18] The VCSS, revised in 2010, is simple to apply in clinical practice, includes pain as a QoL measure and provides a universal, patient-centered outcome tool that can measure the response to treatment and compare treatment modalities over time (Table 2).[19] The SVS/AVF Joint Clinical Practice Guideline Committee on VLUs recommends classifying venous disease using CEAP, revised VCSS, and a disease-specific QoL assessment.[20]

**Table 1. CEAP Classification**

| |
|---|
| C-Clinical |
| C0: No visible or palpable signs |
| C1: Telangiectases and/or reticular veins |
| C2: Varicose veins |
| C3: Edema |
| C4: Skin and subcutaneous tissue changes |
| C4a: Pigmentation or eczema |
| C4b: Lipodermatosclerosis or atrophic blanche |
| C5: Healed ulcer |
| C6: Active ulcer |
| Descriptors A (asymptomatic) and S (symptomatic: pain, ache, tightness, skin irritation, heaviness, muscle cramps, etc.) are used after the C clinical classification |
| E-Etiologic |
| Ec: Congenital |
| Ep: Primary |
| Es: Secondary (postthrombotic) |
| En: No venous cause identified |
| A-Anatomic |
| As: Superficial |
| Ad: Deep |
| Ap: Perforator |
| An: No venous location identified |
| P-Pathophysiologic |
| Pr: Reflux |
| Po: Obstruction |
| Pr,o: Reflux and obstruction |
| Pn: No venous pathophysiology identified |

**Table 2. Modified VCSS**

| Descriptor | Absent (0) | Mild (1) | Moderate (2) | Severe (3) |
|---|---|---|---|---|
| Pain | None | Occasional | Daily | Daily limiting |
| Varicose veins | None | Few | Calf or thigh | Calf and thigh |
| Venous edema | None | Foot and ankle | Above ankle, below knee | To knee or above |
| Skin pigmentation | None | Perimalleolar | Diffuse, lower 1/3 calf | Wider, above lower 1/3 calf |
| Inflammation | None | Perimalleolar | Diffuse, lower 1/3 calf | Wider, above lower 1/3 calf |
| Induration | None | Perimalleolar | Diffuse, lower 1/3 calf | Wider, above lower 1/3 calf |
| No. active ulcers | None | 1 | 2 | ≥3 |
| Active ulcer size | None | <2 cm | 2–6 cm | > 6 cm |
| Ulcer duration | None | <3 mo | 3–12 mo | >1 yr |
| Compression therapy | None | Intermittent | Most days | Full compliance |

A detailed history and physical examination is imperative to establish the etiology of venous disease and rule out conditions that may present with similar signs and symptoms. Systemic conditions such as congestive heart failure, kidney failure, liver failure, or nephrotic syndrome commonly present with leg edema. Comorbid conditions including obesity, diabetes, rheumatoid disease, hypertension, and aging complicate healing. Evaluation for arterial insufficiency will identify the 15% to 20% of patients who have mixed arterial and venous disease [Grade 1B per Clinical Practice Guidelines (CPG)].[20–22] Doppler evaluation and measurement of ankle brachial index (ABI) is recommended for patients without palpable pulses. If the ABI ≤ 0.9, it is recommended that patients see a vascular specialist before compression or operative intervention for venous leg ulcer is undertaken.[23] Underlying thrombophilia should be considered in patients with VLUs, especially those with history of DVT.[24]

Noninvasive diagnostic modalities aid in establishing the diagnosis of CVI and can measure the severity and location of the abnormal venous anatomy. This may help guide the type of therapy and provide a basis for long-term follow-up. Venous Duplex ultrasound is the preferred noninvasive test for patients with VLU (Grade 1B per CPG).[20] It provides objective evidence of venous disease and gives information about the pathophysiology (reflux, obstruction) and anatomic location (superficial, deep, perforator). Valvular incompetence is present when reflux time (reversal of flow with provocative maneuvers like Valsalva) is ≥0.5 seconds for superficial, tibial, deep femoral, and perforator veins; ≥1.0 seconds for femoral and popliteal veins.[22] Other noninvasive tests may be used for patients with equivocal findings on Venous Duplex or in recurrent/recalcitrant ulcers (Grade 2B per CPG) to establish diagnosis and assess disease severity.[20] Venous refill time <18 to 20 seconds by photoplethysmography is indicative of CVI (normal = 18–20 s).[25] Venous filling index > 4 ml/s by air plethysmography correlates with reflux (normal < 2 ml/s).[26]

Newer modalities to assess the central and iliocaval system for intrinsic or extrinsic obstruction as a cause of VLUs include CT and MR venography, contrast venography, and intravascular ultrasound. They are increasingly used for operative planning before endovascular and open venous interventions. Contrast venography and intravascular ultrasound have both diagnostic and therapeutic uses, but have associated risks of contrast-induced allergy, contrast-induced renal insufficiency, and nephrogenic systemic fibrosis with use of Gadolinium in patients with chronic renal disease.

### Compression Modalities

Compression is the gold standard for managing edema caused by venous hypertension.[20,27] External compression forces fluid from the interstitial space into the vascular and lymphatic compartments and enhances the activity of the calf muscle pump.[20] Compression options range from single layer garments to multilayer bandaging systems with subbandage pressures ranging from 10 to 50 mm Hg. Patients may require various modalities of compression throughout their disease process as their symptoms change. In addition, several methods of compression are indicated for healing active ulcers versus preventing ulcer recurrence.[27–35]

There are 4 main types of compression: bandages, bandage-like systems, stockings/hosiery, and intermittent pneumatic compression (IPC) pumps.[31–33] Bandages can be either elastic, inelastic or a combination of the two. Elastic or long-stretch bandages are highly extensible, locking out at >140% extension. ACE bandages are one example. These bandages stretch with increasing edema and provide minimal resistance to the calf-muscle pump but will maintain pressure when

edema decreases. Inelastic or short-stretch bandages, for example, Unna's boot or Circ-Aid, lock out at <70% extension. They produce low resting pressure, but high pressure during walking due to resistance of the calf muscles against the stiff cylinder and are therefore most useful for patients who are able to exercise the calf-muscle pump during ambulation. Multilayer bandages combine attributes of elastic and inelastic compression. Using 2 to 4 layers, resulting in 70% to 140% extension, the short-stretch (inelastic) component provides high pressure during walking, while the long-stretch (elastic) element provides sustained compression. Elastic compression or combination systems are most appropriate for patients who are not very active and who cannot activate their calf-muscle pump when ambulating.

Stockings/hosiery that provide graduated compression are primarily used for prevention of recurrence but can be used for ulcer care in selected patients and can be customized to the patient's body habitus. IPC pumps are dynamic devices used to treat chronic venous hypertension and lymphedema. They are generally used for at least 2 hours daily as part of a multimodal approach.[32]

Although it is well established that compression improves healing of VLU compared with no compression, evidence regarding the most effective type of compression is limited because of small sample size, high degree of bias, and lack of blinding.[27–35] Current evidence suggests that multicomponent compression achieves better healing outcomes than single-component systems and that high compression (35–45 mm Hg ankle compression) is more effective than low (15–25 mm Hg).[27] Nonetheless, only 62% of patients treated with multilayer compression were healed by 24 weeks.[36] A recently developed algorithm for compression in patients with CVI illustrates how difficult it is to interpret the data. Multiple decision points lacked adequate supporting evidence; therefore, the final algorithm relied upon a 20-member consensus panel and is "evidence and consensus based."[35]

Compliance with compression therapy presents numerous challenges.[37] Compression bandages are bulky and must be kept dry, which limits shoewear and bathing options. For best results removable devices are donned before arising from bed and removed at bedtime. Most patients prefer to perform activities of daily living, including showering, before donning their devices. Minimal upright activity leads to lower extremity edema, resulting in discomfort or poor fit of the compression devices. Patients report that the bandages or devices are particularly uncomfortable on warm days. Obese and physically frail individuals find it physically challenging to don stockings over the ankle or edematous calves. To overcome these obstacles, manufacturers have modified their designs, providing more color and fabric choices, donning aids and closure options (e.g., Velcro or zippers) that may be appropriate for some patients. When compression is first initiated, patients may experience pain and remove their devices. Patient education and a personalized approach is the best way to achieve compliance with this lifelong therapy.[37]

Compression therapy is more challenging in the growing population of patients with mixed arterial and venous disease. Many bandage systems have a "lite" version for patients with an ABI between 0.5 and 0.8. There is some evidence that compression may actually increase arterial flow in these patients.[38] Nonetheless, assessment of both the arterial and venous system is needed before applying compression and patients with arterial insufficiency should be monitored closely. The central redistribution of blood increases preload and can affect cardiac output by about 5%. Thus, patients with concomitant congestive heart failure need careful monitoring of their fluid status and may require modified approaches to compression.

**Surgical Management**

Despite compliance with compression therapy, recurrence rates of greater than 50% have been noted in long-term follow up.[39,40] This has sparked growing interest in surgical correction of the underlying pathophysiology of CVD. Depending upon anatomic location and pathophysiology of venous leg ulcer, various open, endovascular, and minimally invasive surgical interventions are available.

The ESCHAR trial demonstrated a statistically significant reduction in ulcer recurrence (12% vs 28% at 12 mo, $P = 0.001$) in CVI patients with active (CEAP C6) or healed (CEAP C5) venous ulcers treated with ablative surgery for superficial reflux along with compression compared with medical management alone.[41] The rate of ulcer healing was unchanged in both arms.

Multiple RCTs have shown comparable efficacy and safety of endovenous radiofrequency or laser ablation versus open surgery for removal of the refluxing saphenous vein.[42–45] The endovenous technique carries the advantage of less postoperative pain and early return to work, with most of these procedures being performed in office/outpatient settings under local anesthesia

(Fig. 2). Thus, for C5/C6 VLUs with documented underlying incompetent superficial veins, operative ablation combined with compression therapy is recommended to promote healing and prevent recurrence (Grade 2C, 1B, and 1C, respectively).[20]

Perforator veins are pathological if present at the base of healed or active ulcers, have reflux of ≥0.5 second (flowing from deep to superficial) and size ≥3.5 mm.[46,47] Minimally invasive techniques such as endovenous radiofrequency ablation and sclerotherapy for pathologic perforator veins are preferred over open or endoscopic ligation.[48]

Infra-inguinal deep vein valve reconstruction for C5 or C6 disease with deep vein reflux or obstruction is undertaken only after superficial and perforator reflux has been evaluated and treated (Grade 2C). The goal of these procedures is to provide a competent valve in the deep system.[49] This can be done by internal valvuloplasty (open direct repair of the incompetent valve by tightening the valve cusps), external valvuloplasty (placement of transmural sutures along valve attachment lines without venotomy), external banding (reduction of vein diameter allowing apposition of valve cusps), valve transplantation (a short segment of vein containing a competent valve from the upper extremity replaces the incompetent deep vein), and valve transposition (the incompetent segment is transposed distal to the competent valve).

All of these techniques can be used primarily or in conjunction with each other and, in the hands of an experienced venous reconstruction specialist, have been shown to result in short- and long-term valve competence and prevention of ulcer recurrence.[50–53] Comparative RCTs are lacking and the current quality of evidence is low.

The majority of patients with iliocaval stenosis and/or obstruction can be treated with endovenous stenting, which improves venous outflow, reduces venous hypertension, and reduces ulcer recurrence. Endovenous stents have high patency rates, long duration (≥72 mo), and ulcer healing rates of 60% to 80%.[24,54–56] Open reconstruction/bypass procedures are reserved for those who fail endovascular stenting.

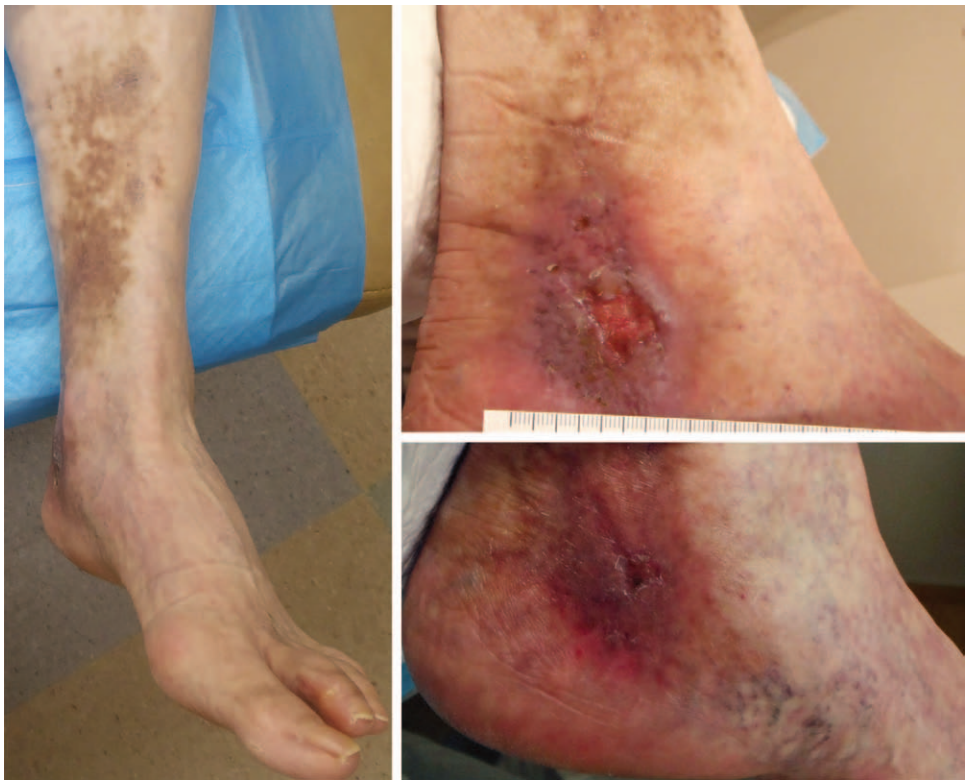

**Fig. 2.** Endovenous ablation of veins with incompetent valves and perforators can facilitate healing, reduce pain, and reduce recurrence when combined with continued compression therapy. (*Left*) Appearance of patient's leg with chronic hemosiderin deposits. (*Above, right*) Nonhealing medial malleolus ulceration recalcitrant to treatment with multi-layer compression therapy and requiring narcotic analgesics. (*Below, right*) Two months after endovenous ablation patient reports no pain and no drainage.

Randomized controlled trials for treating VLUs with valve reconstruction and management of iliocaval obstruction are needed. The availability of percutaneous prosthetic valves will change the face of deep valve reconstruction.

**Surgical Treatment of the Wound Bed**

Sustained limb compression with multilayer bandages providing ≥30 mm Hg of pressure reduces proinflammatory cytokine levels in the periwound tissue, yet over one quarter of patients with VLUs fail to heal with this evidence-based standard care.[57] Histologic analysis of refractory venous ulcers reveals hyperkeratotic epidermis, dermal fibrosis with increased procollagen synthesis at the wound edge, and loss of growth factor receptors in the wound bed (Fig. 3).[58–60] Nuclearization of β-catenin in cells at the wound margin leads to activation of the oncogene c-*myc* with loss of cell cycle control. Incompletely differentiated keratinocytes build up at the nonhealing wound edge, manifesting as a hyperkeratotic, parakeratotic rim.[58,61] Furthermore, the epidermis of the nonhealing edge demonstrates an absence of receptors for multiple growth factors, including epidermal growth factor (EGF) and transforming growth factor beta (TGFβ).[61,62] Lack of functional receptors on the keratinocyte membranes at the wound margin makes them unresponsive to endogenous or exogenously applied growth factor stimuli.[63] Further analysis of these tissues demonstrates aberrant microRNA expression leading to inhibition of the EGF and leptin signaling pathways, with deregulation of the molecular signals required for epithelization and granulation tissue formation.[64] Postdebridement tissues show reconstitution of the growth factor receptors that may facilitate efficacious signaling. This supports the critical role of surgical debridement before the application of advanced tissue therapies; however, the extent of debridement that is required for optimal response is not well defined. Technological developments facilitating a molecular approach to surgical excision of the chronic wound, similar to Mohs surgery for tumor excision, would preserve tissue while enhancing the efficacy of subsequent interventions.[57,62,65,66]

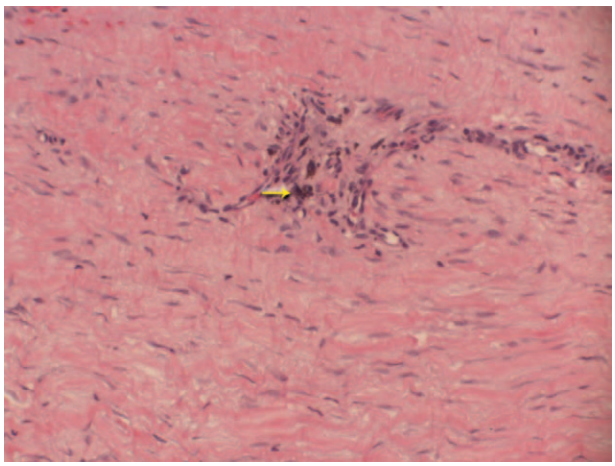

**Fig. 3.** Hematoxylin and eosin stain of debrided tissue from a venous ulcer depicting dense fibrous connective tissue with hemosiderin deposition (*arrow*). Courtesy of Dr. Virginia Donovan, Chairman, Department of Pathology, Winthrop University Hospital.

The role of regenerative therapy is to kick start cellular growth by stimulating the freshly debrided wound with powerful paracrine mechanisms. Patients with poor prognostic indicators including ulcer duration of >12 months, size >10 cm,[2] or ulcer recurrence are the most likely to require (and benefit from) adjunctive modalities to stimulate healing. The development of bioengineered skin and soft-tissue substitutes has created a paradigm shift from passive dressings that provide moisture balance and protection to active interventions that interact with the patient's ulcer, providing cytokines and growth factors, extracellular matrix and/or cells to promote healing. These products may be cellular or acellular, and may be derived from human or nonhuman tissue, synthetic, or a composite. Although the number of products has expanded greatly over the last several years, the evidence remains limited for use in VLUs (Table 3).[67–71]

Two therapies, Apligraf and EpiFix, have clinical data demonstrating a paracrine mechanism of action. Apligraf, a bilayered living construct of keratinocytes and fibroblasts, was FDA approved in 1998 for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers caused by venous insufficiency. The live cells in Apligraf produce most of the cytokines and growth factors present in normal skin.[72,73] EpiFix, a dehydrated human amnion/chorion membrane, is minimally processed and classified by the FDA as banked human tissue. The tissue has been shown to retain the cytokines, chemokines, growth factors, and extracellular matrix structure characteristic of native amniotic membrane and to contain intact but nonviable cells.[74] Both products have been shown to have efficacy for healing VLUs, although the clinical trial evidence for Epifix is quite preliminary.[67,68,74,75]

Whether the presence of live cells makes a difference remains a topic of much debate, but

**Table 3. Summary of RCTs for Bioengineered Skin Substitutes**

| Product/ Publication | Comparator | Final Timepoint | Patients/Ulcers Completely Healed | Days to Complete Healing |
|---|---|---|---|---|
| Apligraf (Living bilayered human skin equivalent)[67] | Unna boot | 6 mo | Apligraf: 92/146 (63%)<br>Control: 63/129 (49%)<br>$P = 0.02$ | 61<br>181<br>$P = 0.003$ |
| Epifix (dehydrated human amnion/chorion membrane)[68] | Multilayer compression | Interim analysis 4 wk | Epifix: 6/53 (11%)<br>Control: 2/31 (6%)<br>≥40% wound area reduction<br>Epifix: 33/53 (62%)<br>Control: 10/31 (32%)<br>$P = 0.005$ | NR |
| Dermagraft (Human fibroblast-derived dermal replacement)[69] | Multilayer compression | 12 wk | Dermagraft: 11/40 (27.5%)<br>Control: 2/13 (15%)<br>$P < 0.05$ | 34.7 (12 pieces)<br>52 (4 pieces)<br>43.3 (single application)<br>73.7 (control) |
| Dermagraft[70] | Multilayer compression | 12 wk | Dermagraft: 5/10 (50%)<br>Control: 1/8 (12.5%)<br>$P = 0.15$ | NR<br>Greater mean % reduction in ulcer area at 12 wk in Dermagraft group |
| Dermagraft Unpublished | Multilayer compression | 16 wk | Phase 3 International pivotal RCT, >500 patients abandoned due to inability to show greater complete healing at 16 wk | |
| Oasis (Porcine small intestine submucosa)[71] | Multilayer compression | 12 wk | Oasis: 34/62 (55%)<br>Control: 20/58 (34%)<br>$P = 0.0196$ | NR |

it is clear that both of these constructs deliver an appropriate balance of factors to stimulate healing when the wound bed is sufficiently prepared. Although likely to be beneficial, there is insufficient evidence to support the use of autografts for these "hard to heal" ulcers. Comparative trials that delineate the effectiveness and costs between these modalities are needed.

## CONCLUSIONS

As we move into the era of "real world" data collection to demonstrate interventional clinical effectiveness for VLUs, it is critical to adopt a universal treatment algorithm that is interdisciplinary, includes patients with comorbid conditions that impact wound healing, and incorporates patient-centered outcomes such as pain, function, QoL and disability while emphasizing prevention, and improved rates of healing with reduction of recurrence.

***Lisa Gould, MD, PhD***
Kent Hospital
455 Toll Gate Road
Warwick, RI 02886
lgould44@hotmail.com

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