
What's new: Management of venous leg ulcers

Treating venous leg ulcers

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Learning objectives

After completing this learning activity, participants should be able to identify appropriate therapeutic strategies linked to venous and other leg ulcer diagnoses based on the evidence, highlight the role of compression therapy as the key component of venous leg ulcer management, assess educational methods to improve patient adherence to compression and other health promotion measures posthealing, and evaluate venous ulcer patients for referral to specialized centers and when to use adjunctive therapy.

Disclosures

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Venous leg ulcers account for approximately 70% of all leg ulcers and affect 2.2 million Americans annually. After a comprehensive patient and wound assessment, compression therapy remains the cornerstone of standard care. Adjuvant care with topical or systemic agents is used for wounds that do not heal within 4 weeks. Once healed, long-term compression therapy with stockings or surgical intervention will reduce the incidence of recurrence. This continuing medical education article aims to outline optimal management for patients with venous leg ulcers, highlighting the role of a multidisciplinary team in delivering high quality care. (J Am Acad Dermatol 2016;74:643-64.)

Key words: management; medical therapy; surgical intervention; varicose veins; venous leg ulcers.

INTRODUCTION

Venous leg ulcers (VLUs) are an important medical problem. The chronic and recurrent nature of VLUs causes morbidity, severely reduces quality of life, and increases the cost of health care. Standard

evidence-based care includes compression therapy and the use of adjunctive agents, which have been shown to accelerate healing, improve quality of life, and likely reduce cost.¹ Emerging therapies, including venous surgical interventions, hold

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Abbreviations used:

ABPI:	ankle brachial pressure index
BSE:	bilayered skin equivalent
CVI:	chronic venous insufficiency
EST:	electrostimulation therapy
FDA:	US Food and Drug Administration
IPC:	intermittent pneumatic compression
LDS:	lipodermatosclerosis
MPPF:	micronized purified flavonoid fraction
MTS:	May–Thurner syndrome
NPWT:	negative pressure wound therapy
RCT:	randomized controlled trials
SEPS:	subfascial endoscopic perforator surgery
VLU:	venous leg ulcer

promise, particularly in the prevention of ulcer recurrence. Before initiating treatment, a comprehensive patient and wound assessment should be performed to evaluate coexisting conditions that may impair healing. This includes addressing anemia, hypoproteinemia, malnutrition, thrombophilia, and patient behaviors, such as smoking (Fig 1).¹⁻⁴ In an effort to better understand the basis of treatment, a brief review of underlying pathophysiology is warranted. In healthy patients in the upright position, the venous system must overcome the force of gravity to facilitate the return of blood to the heart. The 2 main forces that make this return possible are active calf muscle contraction (augmented by ankle movement) and the reactive closing of the venous valves. These 2 forces work in concert to propel venous return and prevent retrograde blood flow.² A defect in any component of these 2 pathways can lead to venous insufficiency. These defects can include outflow problems, such as venous obstruction, or calf muscle impairment caused by deep venous thrombosis and reflux problems related to dilated veins or incompetent venous valves. In a compromised venous system, venous pressure is not reduced but rather sustained (as opposed to being reduced, which normally occurs) during leg exercise, such as walking, and this is referred to as sustained ambulatory venous pressure or venous hypertension. Sustained ambulatory venous pressure increases hydrostatic pressure within the venous system. The increased hydrostatic pressure forces fluid containing proinflammatory molecules to leak into interstitial tissue. This triggers a cascade of physiologic changes and edema formation, leading to ulcer formation (detailed in part I of this continuing medical education article).

COMPRESSION THERAPY**Key points**

- **Compression therapy is critical for the care of venous leg ulcers because it corrects impaired venous return**



Fig 1. Common clinical pictures of venous leg ulcers, which present as shallow ulcers over the medial malleolus surrounded by pigmentary changes.

- **Compression therapy is the mainstay of treatment for patients with venous leg ulcers and can be provided by 3 different techniques: (1) bandage systems, (2) stockings/hosiery, or (3) intermittent compression devices**

The physiologic effects of compression include accelerating venous flow, reducing venous reflux and edema, promoting oxygenation in the surrounding dermal skin tissue, and eventually stimulating fibrinolysis.³

Compression therapy can be provided through 3 techniques or types of compression systems. The first is sustained wear bandage systems, typically comprised of ≥ 2 components. The second is through removable stockings or hosiery. The third is through intermittent compression devices, which are pumps used periodically throughout the day. These compression techniques or systems have several different methods to deliver external pressure to the venous system.

Compression bandages

Compression bandages are classified as either elastic (long stretch) or inelastic (short stretch). Elastic bandages have an extensibility of 100% to 200%; inelastic bandages have an extensibility of 40% to 99%. Elastic bandages contain elastomeric fibers that provide easy stretchability and a sustained “squeeze” as the bandages recoil to their original length (Fig 2, A). Optimal use of elastic bandages occurs when the bandage is stretched from the relaxed state to the stopping distance (ie, maximum stretch), then relaxed and applied at 50% stretch to exert elastic energy in both directions of the bandage (Fig 2, B). By contrast, inelastic bandages are rigid and resist lateral expansion of the calf muscle during active contractions, such as when walking.

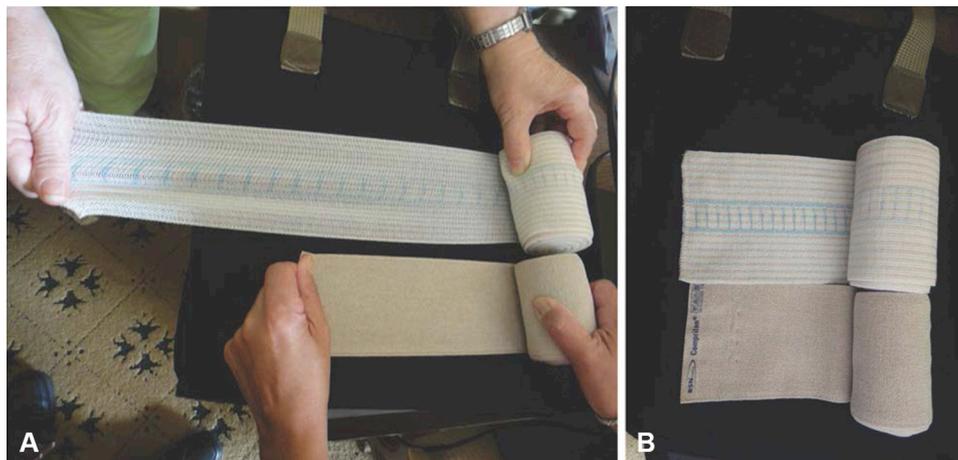


Fig 2. Compression bandages. **A**, Elastic or long stretch bandages with extensibility of 100% to 200%. **B**, Inelastic or short stretch bandages with extensibility of 40% to 90%.

With walking, calf muscle contraction is supported externally by the rigid bandage, thereby improving venous return. Inelastic bandages therefore provide compression during activity and also when fluids pool (ie, edema formation) with standing; however, they do not compress the limb at rest in a supine position. An Unna boot is a classic example of an inelastic bandage.

Compression bandages may be comprised of a single component or multiple components. Multicomponent bandages often have an initial protective layer of orthopedic wool padding, and may also include a crepe retention layer, an elastic compression bandage, and an outer elastic cohesive bandage to prevent slippage. When used correctly, both elastic (long stretch) and inelastic (short stretch) bandages are effective. A recent metaanalysis found both types of bandages to be equally efficacious in promoting healing of VLU in both ambulatory and nonambulatory patients.⁴ Nonetheless, inelastic bandages may have added benefit in some clinical situations through exertion of lower resting pressure compared to the higher resting pressure of elastic systems. As a result, inelastic bandages may be less likely to exacerbate pain or restrict arterial flow in patients with coexisting arterial disease. However, inelastic bandages can be challenging to use because of bandage slippage and a more rapid decrease of compression pressure over time. [Table I](#) shows examples of different available compression bandaging systems.

Subbandage pressure increases with the addition of each layer, supporting the notion that multiple layers are superior to single-layer compression. The principles of compression are based on the modified Laplace law⁸:

Subbandage pressure =

$$\frac{\text{No. of layers} \times \text{tension} \times \text{constant}}{\text{Bandage width} \times \text{limb circumference}}$$

Subbandage pressure can be increased with additional bandage layers, increased tension of the applied bandages, and decreased bandage width or limb circumference.⁹

Compression bandages can be applied using a number of techniques. A common practice is the application of bandages in a spiral fashion around the leg with a 50% overlap between turns, producing a double layer of wrapping with each component. Other application techniques, such as the figure 8 bandage technique, increase the number of effective overlapping layers, thereby increasing compression. Therefore, while a bandage may have 4 components, it may actually have many more layers. Any effective compression is dependent on accurate application of bandages by knowledgeable and skilled personnel.^{5,10,11}

Healing is influenced by patient and wound characteristics. Wound size and duration are the 2 most common characteristics affecting healing. Marston et al¹² reported that 57% of VLUs seen in clinical practice treated with compression healed in 10 weeks and 75% healed in 16 weeks. Larger ulcers (>20 cm²) and mixed arteriovenous ulcers were associated with delayed healing. Other risk factors for poor healing include long-standing VLUs, often associated with lipodermatosclerosis, and previous knee or hip surgery.

A recent analysis of 36 studies and 2 Cochrane systematic reviews found that overall there is no difference in ulcer healing, time to ulcer healing, or ulcer recurrence between compression stockings

Table I. Types of compression bandage systems⁵⁻⁷

Compression system	Examples	Advantages	Disadvantages
Long stretch (elastic) bandages	Surepress, Ace, Dauerbinde, and Biflex Thuasne	<ul style="list-style-type: none"> • Base of the toes to knees • Low working pressure • High resting pressure • >140% extensibility • Can be applied spiral or figure of 8 • Inexpensive, washable, and reusable forms available 	<ul style="list-style-type: none"> • Tend to unravel • Do not provide sustained compression • Risk of incorrect application
Short stretch (inelastic) bandages	Zinc paste (viscopaste/Unna), Comprilan, Circaid (Velcro), FarrowWrap (Velcro), Action, Panelast, and Porelast	<ul style="list-style-type: none"> • Comfortable/better tolerance • Minimal interference with daily activities • Generate high working pressure • Certain bandages with Velcro 	<ul style="list-style-type: none"> • Gauze impregnated with different products, such as zinc oxide • Not good for highly exudative wounds • Need to be applied by well trained staff
Intermittent compression devices	Pneumatic pump	<ul style="list-style-type: none"> • Enhance fibrinolytic activities 	<ul style="list-style-type: none"> • Expensive • Require immobility for a few hours a day
Multicomponent bandages	Coban 2 (and Coban2 lite), Profore, and Actico and Sofban	<ul style="list-style-type: none"> • Higher compression • Graduated compression • Sustain a high compression • Lite compression available for patients with mixed venous arterial disease 	<ul style="list-style-type: none"> • Need to be applied by well trained staff
Compression devices	Variable	<ul style="list-style-type: none"> • Adjustable compression • Easy to put on and remove 	<ul style="list-style-type: none"> • Expensive
Support system	Tubigrib	<ul style="list-style-type: none"> • Easy to use • Double layer to increase compression 	<ul style="list-style-type: none"> • Bulky • Low compression

Trade names remain property of their respective manufacturers.

and compression bandages. Compression stockings are most often used as a maintenance therapy after VLUs have healed (Fig 3). However, stockings represent a treatment option for some patients. An example of their potential healing benefit was shown in a recent study by Ashby et al¹⁰: 457 patients with VLUs were randomized into 2 groups; 1 group was treated with 2 layered stockings and the other was treated with 4-layer bandages. A high dropout rate was recorded in the stocking group because of discomfort and pain (38% in hosiery group vs 28% in the group with bandages), and healing rates of VLUs did not differ between therapies.¹⁰ The authors suggested that the use of stockings might result in higher quality adjusted life-years because patients who often preferred stockings and had an overall lower cost than those with bandages.¹⁰ In theory, the use of compression stockings during treatment also prepares patients for lifelong use of stockings as maintenance compression therapy.¹³ Table II shows the recommended level of compression stockings in patients with venous disease.^{16,17}



Fig 3. Compression stockings.

Intermittent pneumatic compression devices

Intermittent pneumatic compression (IPC) devices deliver sequential pressure to the limb and can be used in combination with bandages or stockings. Particularly in nonambulatory patients, IPC can be a beneficial adjunct to other forms of compression.^{2,18} An air pump and inflatable auxiliary boots in a closed system are used to provide

Table II. Compression stockings

Class	Pressure at ankle (mm Hg)	Indications
I	20-30	Mild edema, varicose veins, and venous ulcers
I	30-40	Moderate edema, moderate venous disease, varicose veins, and venous ulcers
III	40-50	Severe edema, severe venous disease, venous ulcers, and lymphedema
IV	50-60	Lymphedema

Adapted from Mosti¹⁴ and Woo et al.¹⁵

dynamic compression, thereby stimulating calf muscle contraction.¹⁹ IPC prevents lower limb edema and skin changes that are frequently seen on the legs of immobile patients.

Indications and contraindications for compression therapy

Key points

- **High compression of 40 mm Hg should be considered for a person with an adequate vascular supply indicated by an ankle brachial pressure index of 0.8 to 1.2**
- **In patients with mixed arteriovenous ulceration (with an ankle brachial pressure index >0.5 and an absolute ankle pressure of >60 mm Hg), inelastic compression <40 mm Hg does not impede arterial perfusion and treats impaired venous return**

Arterial supply may be evaluated by performing an ankle brachial pressure index (ABPI),²⁰ a screening tool with high sensitivity (85%) and specificity (97%) for the detection of arterial occlusive disease.²¹ The ABPI is calculated by the ankle systolic pressure divided by the best estimate of the central pressure (ie, the higher of each arm's brachial systolic blood pressure). Limbs with an ABPI >0.8 should have sufficient arterial supply to safely tolerate application of high strength compression therapy (Table III). An ABPI >1.2 usually indicates severe calcification or glycosylation of the tibial arteries leading to falsely elevated ankle pressure readings.

In patients with venous disease and coexisting arterial compromise (ABPI 0.5-0.8) compression therapy may need to be modified.²³ Recent studies have shown that inelastic compression may be superior to elastic compression in enhancing arterial circulation and healing.^{14,24,25} In patients with an ABPI >0.5 and an absolute ankle pressure of >60 mm Hg, Mosti et al²⁵ reported that inelastic

Table III. Compression therapy level based on ankle brachial pressure index²²

ABPI	Compression therapy
0.8-1.2	High compression therapy
0.5-0.8	Modified compression therapy (≤ 20 mm Hg)
<0.5	No compression therapy

ABPI, Ankle brachial pressure index.

Data from Briggs et al.²²

compression <40 mm Hg does not impede arterial perfusion and may lead to a normalization of venous function. While careful observation is warranted, inelastic bandages are recommended in the management for patients with mixed arteriovenous leg ulcers.²⁵ Alternatively, bandage systems with fewer components may also be applied, thereby modifying the compression force. However, inappropriately high compression can be harmful because it can lead to arterial compromise and subsequent distal gangrene and limb loss in individuals with severe arterial or arterial predominant disease.^{14,24,25} For this reason, compression in a patient with any degree of arterial insufficiency should be performed carefully and with a discussion of the risk of complications.

Patients with congestive heart failure may have difficulty tolerating compression therapy. Lower limb compression may increase the preload volume and worsen congestive failure.³ To prevent sudden exacerbation of heart failure, it is suggested to first apply modified compression therapy on 1 leg. If congestive failure is not exacerbated after 48 hours of observation, then increasing compression to both legs can be attempted.

Areas of inappropriate high pressure present as irregular pressure marks and deep or nonuniform erythema of the skin after removal of compression wraps. These areas may require the insertion of padding or other protective materials. Pain can alert patients and clinicians to problems associated with inappropriate compression therapy, which can indicate arterial compromise.

PAIN MANAGEMENT

Key points

- **Pain is subjective: "Pain is whatever the experiencing person says it is"**
- **Appropriate treatment is determined by the severity and specific types of pain: nociceptive, neuropathic, or a combination**

VLUs greatly affect quality of life, in large part because of pain. Table IV lists different pain etiologies in patients with VLUs. Appropriate

Table IV. Different pain etiologies in patients with venous leg ulcers

Pain in patients with venous leg ulcers
Ulcer-related
Neuropathy and nerve damage
Lower leg edema
Lipodermatosclerosis
Superficial and deep vein phlebitis
Infection
Contact dermatitis
Atrophie blanche

treatment of pain is determined by the severity and specific type of pain: nociceptive, neuropathic, or a combination.¹⁵ Stress induced by pain causes cortisol release and elevated cytokine levels, potentially delaying wound healing.²⁶ Pharmacotherapy continues to be the mainstay of treatment.

A patient-oriented multifaceted approach is recommended for the management of wound-related pain to provide relief and restore overall activities of daily living. The World Health Organization's analgesic ladder states that mild pain (1-3 on a 10-point scale) can be treated with acetaminophen, aspirin, or nonsteroidal antiinflammatory drugs (NSAIDs). However, these agents should be used with caution in people >65 years of age.¹⁵ Because of the risk of renal failure and worsening of congestive heart failure, narcotics are reserved for moderate (4-7 out of 10) or severe pain (8-10 out of 10), with initial use of short-acting and weak agents, followed by long-acting and stronger agents.¹⁵

Recent studies indicate that nociceptive and neuropathic pain may coexist in patients with VLUs.²⁷ Nociceptive pain is stimulus-dependent, incurred by tissue damage activating pain receptors in the skin, muscle, bone, joints, and ligaments, and is often described as tender, aching, throbbing, or gnawing. Neuropathic pain is spontaneous, not stimulus-dependent, and often described as burning, stinging, shooting, or stabbing. Neuropathic pain can initially be treated with the off-label use of tricyclic antidepressant medications. VLU size, duration, location, or severity of underlying venous disease does not predict the severity of the associated pain.²² The Krasner model²⁸ divides pain into 3 components: continuous chronic pain associated with underlying venous disease, acute recurrent pain with dressing change, and acute incidental pain associated with procedures, such as debridement or a secondary infection. Patients with early stages of venous disease, especially with prominent varicosities, often describe a dull aching or heaviness in their legs at the end of the day. Additional

aggravating factors include lower leg edema from prolonged periods of standing and pelvic venous disease, often associated with obesity.

Pain can peak during dressing changes with cleansing or debridement. Careful selection of dressings with atraumatic adhesives (eg, silicone and nonadherent wound contact layers) has been shown to limit skin damage and minimize pain during dressing changes.^{29,30}

Sealants, barriers, and protectants, such as wipes, sprays, gels, and liquid roll-ons, are designed to protect the periwound skin from caustic wound exudate and trauma induced by adhesive dressing removal. Pain from debridement can be alleviated by topical anesthetics or systemic pain medication 30 minutes before the procedure.³¹

Wound cleansing can also be painful, especially with the application of cold cleaning solutions. In addition to cytotoxicity, strong antiseptics may cause stinging and pain. Physical manipulation using forceps and gauze across wound beds can cause tissue damage. To reduce trauma during cleansing, compresses or soaks can be applied at room temperature and may be preferred to the physical trauma associated with wound irrigation.

Complications of venous disease

Lipodermatosclerosis (LDS) is the main clinical finding associated with long-standing venous disease. Although there is uncertainty regarding the exact pathogenesis of LDS, the most dramatic changes in histopathology include thickening and fibrosis of the septae with lipophagocytic changes and adipocyte necrosis (sclerosing panniculitis).³²

Chronic LDS commonly presents with hyperpigmentation and induration. Nearly half of patients with LDS experience pain, even in the absence of an ulcer. Acute LDS is characterized by intense pain and may occur even in the absence of other signs of venous disease. Management of acute LDS includes the use of intralesional corticosteroids, NSAIDs, fibrinolytic agents, and compression if tolerated. Stanazolol, oxandralone, or danazol may be useful for patients who do not respond to other therapeutic options.³²

Superficial or deep phlebitis must also be considered when patients describe new localized pain or a change in preexisting pain. Superficial phlebitis presents as bruise-like pain over a localized portion of an inflamed vein. The pain is often aggravated by palpation or standing, and the involved area may be warm to the touch. Deep phlebitis of the lower leg is often associated with more intense, often excruciating pain and swelling that must be distinguished



Fig 4. Debridement. Removal of biofilms and necrotic tissue with curettage.

from other conditions, including cellulitis or a ruptured Baker cyst.

Chronic venous insufficiency (CVI) promotes extravasation of inflammatory cells, rendering affected individuals prone to dermatitis. Dressings, bandages, and compression hosiery can cause local irritation and may aggravate the dermatitis. Allergic contact dermatitis to topical medications must be suspected in patients with dermatitis. Venous stasis dermatitis may be differentiated from allergic contact dermatitis by patch testing.

Regardless of the cause, patients with dermatitis may present with localized itching, pain, or increasing wound size despite wound treatment (Fig 4). Allergic contact dermatitis to wound and skin care products delays healing (Fig 5).^{33,34} Allergic contact dermatitis is more prevalent in individuals with VLU than individuals with any other dermatologic condition. Up to 80% of patients with VLUs have ≥ 1 positive patch test reactions, with most of the identified allergens relating to previous allergen exposure or a history of contact dermatitis.³³ This typically results from long-term exposure to allergens under occlusion and the impaired barrier function of the ulcerated skin.³³

Common allergens in perfumes and derivatives include colophony, Balsam of Peru, and perfume mix. Other common contact allergens associated with leg ulcers include preservatives, such as formaldehyde, quaternium 15 (a formaldehyde releaser), and propylene glycol. Hydroxybenzoate or other preservatives found in creams and some paste bandages are also potentially allergenic.³⁵ Preservative-free zinc bandages are an attractive alternative. Hydrogel is a common irritant/allergen because of the preservatives, including propylene glycol. In a study of 39 patients with chronic wounds, the rate of sensitization to hydrogel ranged from 9% to 23%.^{36,37} The most common allergens found in wound products are listed in Table V.^{20,36,38-51}



Fig 5. Allergic contact dermatitis to wound-related products.

Another cutaneous manifestation of venous disease is atrophie blanche,⁵² consisting of distinct white, stellate depressed atrophic scars frequently associated with local severe and sharp pain. Although the exact mechanism is unclear, in patients without associated venous disease it is often caused by small vessel thrombosis (livedoid vasculopathy).⁵²

LOCAL WOUND CARE

Debridement

Key point

- **Debridement is integral to wound care by removing devitalized tissue, foreign material, abnormal/dysfunctional cells, bacteria, and their byproducts, including biofilms**

Although routine debridement for VLUs is not yet supported by randomized clinical trials, the best available evidence suggests that debris on the wound surface should be removed.^{53,54}

Using a large retrospective dataset, Wilcox et al⁵⁴ documented faster healing with weekly debridement ($P < .001$) of a variety of chronic wounds compared to every 2 weeks. Wound debris can include devitalized tissue, foreign material, abnormal/dysfunctional cells (ie, nonresponsive or senescent cellular burden), and bacteria often associated with biofilms and bacteria byproducts (Fig 4). Necrotic tissue is rarely found in VLUs not complicated by arterial disease or infection. However, if present, debridement of necrotic tissue in chronic wounds can be achieved using a number of methods: surgical removal of slough or sharp debridement to bleeding tissue; autolytic dressings, including calcium alginates, hydrogels, hydrocolloids, or biologics (eg, maggots); and enzymatic methods (eg, collagenase [Table VI]).⁵⁵

Methods of debridement may be deployed as a single therapeutic modality or may be combined to optimize the debridement process. Selecting the proper combination of debridement techniques requires evaluation of the patient's individual needs while taking into account the available clinical resources.⁵⁴ Awareness of debridement options and the value of maintenance debridement

Table V. Contact dermatitis to wound products in patients with VLU

Allergen	Evidence	Dressing category	Product examples
PG	Freise et al ³⁸ (2008), Trookman et al ³⁹ (2011), and Renner et al ³⁶ (2013)	Hydrogel or emulsion	Hydrogels contain PG: • Intrasite gel: Has PG as backbone • Solugel: Benzoyl peroxide, PG • Saf-gel: Sodium alginate, PG • Biafine topical emulsion Honey dressings
Propolis	Pasolini et al ⁴⁰ (2004) and Garrido Fernandez et al ⁴¹ (2004)	Foam or gel	Honey dressings
Pentaerythroid ester of hydrogeneated rosin	Pereira et al ⁴³ (2007) and Renner et al ³⁶ (2013)	Hydrocolloid	NuDerm and DuoDerm
Sorbitan sesquioleate	de Waard-van der Spek et al ⁴³ (2007)	Nonadhesive dressings	Adaptic
Lanolin/paraben	Trookman et al ³⁹ (2011)	Cream or compress	Biafine topical emulsion and Seltouch
Colophony	Pereira TM et al ⁴²	Cream	Biafine topical emulsion
Carba mix	Isaksson et al ⁴⁴ (2004)	Rubber in elastic bandages	Tensor bandages
Povidone–iodine	Lachapelle ⁴⁵ (2005), Saap et al ⁴⁶ (2004), and Velazquez et al ⁴⁷ (2009)	Solution, paste, or PEG gauze	PVP-I and cadexomer iodine
Chlorhexidine digluconate	Shoji ⁴⁸ (1983)	Gauze, foam, or nonadhesive dressings	AMD and Bactigras
Silver	Renner et al ³⁶ (2013) and Ozkaya ⁴⁹ (2009)	Hydrofiber	Aquacel Ag
Benzalkonium chloride	Dao Jr et al ⁵⁰ (2012)	Creams/cleansers	Revitaderm wound care gel
Neosporin	Gehrig and Warshaw ⁵¹ (2008)	Cream/ointment	Neosporin
Bacitracin	Gehrig and Warshaw ⁵¹ (2008)	Cream/ointment	Baciquent and polysporin

Trade names remain property of their respective manufacturers.

AMD, Antimicrobial foam dressing; PEG, percutaneous endoscopic gastrostomy; PG, propylene glycol; PVP-I, polyvinylpyrrolidone of idoine.

procedures is a practice gap in contemporary dermatology.⁵⁶ High-quality studies are needed to elucidate the role of debridement in VLU care.⁵⁷

Dressings

Key points

- **A moist wound environment is essential to all phases of wound healing**
- **Moisture retentive dressings include foams, alginates, hydrofibers, hydrogels, and hydrocolloids**

A moist wound environment is essential to all phases of wound healing. It accelerates the reepithelialization process and collagen synthesis. It also facilitates the action of growth factors, keratinocyte and fibroblast proliferation, and promotes angiogenesis.

Venous ulcers are typically heavily exudative, and the exudate contains inflammatory proteases and cytokines capable of attacking surrounding healthy

skin if the exudate is not removed efficiently from the wound surface. In VLUs, the management consideration typically is not how to maintain a moist wound environment but how to avoid a macerated, overly wet wound environment in the presence of toxic mediators. The frequency of dressing changes should be chosen based on the absorptive capacity of the dressing applied. Once a dressing becomes saturated, it should be replaced.

Many dressings have been developed to maintain moisture balance. The major categories of moisture-retentive dressings include foams, alginates, hydrofibers, hydrogels, and hydrocolloids^{58,59} (Table VII). However, newer dressings require less frequent dressing changes and may be more cost effective with reduced nursing time.⁶² Dressing selection is based on the wound characteristics, control of exudate, odor, and protection of peri-wound skin.⁶³

Table VI. Debridement methods³⁹

Methods	Advantage	Disadvantage	Contraindication
Surgical/sharp	Fast; high selectivity	Painful; requires skilled person; expensive	Ischemic tissue and bleeding disorders
Autolytic	Less pain; inexpensive	Monitor infection closely; may promote anaerobic growth	Infected wounds and friable skin
Mechanical	Inexpensive	Nonselective; time-consuming; painful	Clean wounds
Biological: Maggot/Larva	Inexpensive; selective; safe; simple procedure	Short lifespan; time-consuming; not meant to be used under compression	Bleeding diathesis; deep, tunneled wounds; allergy: adhesives, eggs, fly larvae, and soy beans
Enzymatic	Nonselective; less painful; fast	Expensive; requires skilled person; may require secondary specific dressing; not meant to be used weekly	Allergy: the enzyme preparation

Infection control

Key points

- **Because of increasing bacterial resistance, antimicrobial drugs should be reserved only for cases of clinical infection or when bacteria are thought to be present in sufficient number to inhibit the healing process**
- **Topical antimicrobial dressings may contain silver, iodine, honey, polyhexamethylene biguanide, or a combination of methylene blue and crystal violet**

When bacterial growth reaches a critical threshold of $>10^5$ bacteria per gram of tissue, bacterial toxins can cause tissue damage in the superficial wound compartment and delay healing.⁵⁵ Soft tissue infection (deep and surrounding tissue) requires systemic antibiotics. No evidence currently supports the routine use of systemic antibiotics for VLUs.⁶⁴

Bacteria are thought to inhibit healing without inducing a host response as seen in cellulitis. These dressings are effective if the active antimicrobial barrier agent comes into direct physical contact with free-flowing (planktonic) bacteria. With the increasing problem of bacterial resistance, antimicrobial preparations should be reserved only for cases of clinical infection or antiseptic agents that have multiple antibacterial actions, lessening the chance of resistance. For example, ionized silver exerts its active antimicrobial barrier activity against cell walls, cytoplasmic membranes, and the DNA structure of microorganisms. The healing benefits of silver antimicrobial barrier dressings remain controversial.⁶⁵

Medical therapy

Key points

- **Pentoxifylline has several mechanisms of action, such as increasing the deformability**

of erythrocytes, the inhibition of neutrophil adhesion/activation, and the inhibition of tumor necrosis factor- α

- **Flavonoids and anticoagulants may have a role in the management of venous leg ulcers**

Pentoxifylline. Pentoxifylline improves VLU healing, especially in ulcers that have been present for >1 year. In an early systematic review performed by Jull et al,⁶⁶ pentoxifylline was found to improve VLU healing by approximately 50%.⁶⁷

Pentoxifylline is a methylxanthine derivative with good oral absorption and an extensive first-pass metabolism in the liver before excretion in the urine.⁶⁸ Peak plasma level is reached within 2 hours, with a half-life of 4 to 6 hours. The usual dose is 400 mg 3 times daily, with lower doses recommended in patients with significant renal failure. However, some investigators have reported higher doses of pentoxifylline (800 mg 3 times daily) to be more effective than the standard doses.^{69,70} Maximum benefits may be observed after 2 to 4 months of therapy.

Pentoxifylline has several mechanisms of action, including increasing the deformability of erythrocytes and inhibition of neutrophil adhesion and activation. It is also a known inhibitor of tumor necrosis factor- α , which has been hypothesized to impair healing of VLUs.⁷¹

Common side effects include nausea, gastrointestinal discomfort, dizziness, headache, and prolonged bleeding time.⁷⁰ Pentoxifylline has 2 primary contraindications: intolerance to methylxanthine derivatives and severe cardiac disease. The US Food and Drug Administration (FDA) pregnancy category for pentoxifylline is C.^{6,72,73}

Flavonoids. The FDA has not yet approved Daflon 500, a micronized purified flavonoid fraction

Table VII. Main categories of dressings. Adapted from Ficarelli et al⁶⁰ and Park et al⁶¹

Class	Description	Advantage	Disadvantage
Films	Semipermeable adhesive sheets	<ul style="list-style-type: none"> • Translucent • Impermeable to fluid and bacteria • Permeable to gas and water vapor • Less dressing change, less pain 	<ul style="list-style-type: none"> • Adherent, nonabsorbent • Not good for fragile skin • Risk of allergic contact dermatitis to adhesives
Hydrogels	Polymers with high water content	<ul style="list-style-type: none"> • Donates moisture • Nonpainful and soothing 	<ul style="list-style-type: none"> • Amorphous form needs secondary dressing • Caution in infected wounds • Risk of allergic contact dermatitis to propylene glycol or other components
Hydrocolloids	Hydrophilic colloid particles bound to polyurethane film, some composed of gelatin, pectin, and carboxy methylcellulose	<ul style="list-style-type: none"> • Autolytic debridement • Self-adhering • Long wear time • Impermeable to fluids and bacteria • Conforms to wound shape • Hemostatic 	<ul style="list-style-type: none"> • Nonabsorptive • Trauma with removal • Allergy to adhesives • Risk of maceration of surrounding skin • Malodor • Needs secondary dressing
Calcium alginates	Seaweed-based complex polysaccharide; sheets wick laterally and ropes wick upward	<ul style="list-style-type: none"> • Autolytic debridement • Semipermeable • Highly absorptive 	<ul style="list-style-type: none"> • Needs secondary dressing
Hydrofibers	Sheets or ribbons	<ul style="list-style-type: none"> • Highly absorptive • Nontraumatic in removal • Highly absorbent • Conforms to wound shape • Permeable to water and vapor 	<ul style="list-style-type: none"> • Needs secondary dressing
Foams	Polyurethane foam fluid exchange with partial fluid retention if variable pore size	<ul style="list-style-type: none"> • Absorbent and may be with an island and boarder configuration for central absorbency and peripheral adhesion 	<ul style="list-style-type: none"> • Bulky and may macerate surrounding skin, particularly with uniform pore size • Opaque • Bulky • Opaque
Composites	Multilayered combination to increase absorbency, fluid lock, and autolysis	<ul style="list-style-type: none"> • Absorbent and may be with an island and boarder configuration for central absorbency and peripheral adhesion 	<ul style="list-style-type: none"> • Bulky and may macerate surrounding skin, particularly with uniform pore size • Opaque • Bulky • Opaque
Collagen-based dressings	Bovine-derived collagen dressings	<ul style="list-style-type: none"> • Promote healing with oxidized reduced cellulose • Decrease matrix metalloproteinases 	<ul style="list-style-type: none"> • Not indicated for infected wounds

(MPFF), or other flavonoids for the treatment of VLUs, but these medications are available elsewhere. Flavonoids are a diverse group of naturally occurring phlebotropic compounds that are commonly used as food supplements. Daflon is a micronized flavonoid fraction used in the treatment of CVI. It improves venous tone, supports lymphatic drainage, and protects microcirculation.^{74,75} Daflon 500 mg twice daily for 6 months decreases the inflammatory response and the clinical symptoms of CVI.⁷⁴ Horse chestnut seed extract, derived from *Aesculus hippocastanum*, contains flavonoids. In several randomized controlled trials (RCTs), it was found to be safe and effective in the management of edema associated with venous disease.^{75,76}

A Cochrane review examined the role of flavonoids in the management of VLUs and found 9 studies with 1075 participants. MPFF (Daflon 500), consisting of micronized desomin and flavonoids, improved the healing rate in the treatment of VLUs through inhibition of the inflammatory cascade.^{77,78} However, the review concluded that the quality of the trials were poor and the observed increase in healing rate must be interpreted with caution.⁷⁹

Anticoagulants

Key points

- **Laboratory evaluation for thrombophilia may be considered in patients with a history of recurrent venous thrombosis and in**

young patients with chronic recurrent venous leg ulcers

- **A history of deep venous thrombosis may be detected in up to 60% of patients with venous leg ulcers**

A recent clinical trial reported that the use of low molecular weight heparin (LMWH) accelerated wound healing.⁸⁰ A RCT of 284 patients with VLUs treated with compression therapy, surgical intervention, and daily subcutaneous injection of LMWH for 12 months was found to accelerate wound healing.⁸¹ However; routine use of LMWH for VLUs, particularly if the patient does not have other reasons to be on anticoagulation.⁸²

Sulodexide is an oral antithrombotic and fibrinolytic agent with an active mixture of glycosaminoglycan polysaccharides. Sulodexide is used in the treatment of a number of vascular disorders associated with an increased risk of thrombosis, including VLU.⁸⁰ Sulodexide has a longer half-life than heparin but has less effect on systemic clotting and bleeding. In addition, sulodexide exerts antiinflammatory, endothelial-protective, and pleiotropic vascular effects, supporting its potential efficacy as an adjunct to compression therapy in patients with VLUs.⁸³

Doxycycline

Doxycycline has antiinflammatory actions, is antiapoptotic and antiangiogenic, and has inhibitory effects on tumor necrosis factor- α and matrix metalloproteinases.⁸⁴⁻⁸⁶ Doxycycline 100 mg twice daily, in combination with compression therapy, may improve the healing of recalcitrant ulcers.^{84,87} A subantimicrobial dose (40 mg daily), has also been used with success in the treatment of patients with VLUs in a small case series, but RCTs are lacking.⁸⁶

Zinc

A 2012 Cochrane review on the role of zinc sulfate in the treatment of patients with VLUs reported no beneficial effect.⁸⁸ Six small trials (N = 183) were included. Four trials considered only patients with VLUs and compared oral zinc sulphate with placebo; there was no statistically significant difference between the 2 groups (relative risk, 1.22 [95% confidence interval, 0.88-1.68]).⁸⁸

SURGICAL AND PERCUTANEOUS INTERVENTIONS

Key points

- **Invasive surgeries are being replaced by less invasive percutaneous procedures, such as radiofrequency therapy, endovascular laser**

ablation, and ultrasound-guided foam sclerotherapy

- **Recalcitrant venous leg ulcers may be associated with compression of the iliac venous system or vena cava (May–Thurner syndrome)**

Several studies suggest a role of venous intervention in the care of patients with VLUs. The compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR) trial compared compression alone to compression plus surgery for patients with VLUs. While both groups of patients had similar healing at 6 months, surgery reduced the recurrence of healed VLUs compared to compression alone. Overall, both groups had 65% healing at 24 weeks, but 12-month ulcer recurrence were significantly reduced in the compression and surgery group (12% vs 28%).⁸⁹ After 4 years, the recurrence rate was 56% in the compression group compared with 31% for the combined compression plus surgery group ($P < .01$).⁸⁹

Percutaneous procedures, such as endovenous ablation (EVA) and ultrasound-guided foam sclerotherapy, are replacing invasive surgery.⁹⁰ EVA either by laser or radiofrequency is minimally invasive and has a short recovery time. Rare complications include deep venous thrombosis (0.3-7% of cases), which typically resolves with short-term anticoagulation.⁹¹ In comparison to surgical procedures, EVA procedures have equivalent safety and efficacy to surgical ligation/stripping of saphenous veins.⁹¹ In addition to patients with ulcers, symptomatic patients with edema, varicose veins, and skin changes are candidates for endovenous ablation.^{92,93}

Understanding the venous anatomy is important for those performing vascular intervention; anatomic differences in disease may cause different clinical manifestations and require specific intervention(s). For example, great saphenous vein reflux is typically associated with varicosities of medial thigh and calf with medial ankle ulcers. Involvement of the small saphenous vein with reflux is associated with posterior calf and popliteal fossa varicosities and lateral ankle ulceration.⁹² Therefore, in patients who might be candidates for venous intervention, comprehensive assessments with venous duplex ultrasonography are required before intervention.^{93,94} One study found that 30% of patients with VLUs had a normal deep venous system, with their venous insufficiency related to saphenous or perforator dysfunction.¹² In patients with deep vein involvement, the ligation of the femoral or popliteal veins as a routine treatment is not recommended.⁸²

Table VIII. A review of literature on use of artificial skin substitutes in the management of venous leg ulcers (2004-2014)^{82,93,99-125,162}

Name	Description	Advantage	Disadvantage	Study	Study outcome
Epidermal Autologous EpiDex	Cultured from outer root sheath keratinocytes derived from plucked anagen hair follicles, (pluripotent stem cells for hair follicles)	Cost effective	<ul style="list-style-type: none"> • Easily damaged/torn during early wound healing • 30-min air drying required after application • Long preparation time (≤ 28 days) 	Ortega-Zilic et al ¹¹⁸ (2010) O'Donnell Jr and Lau ¹¹⁹ (2006)	No RCT available Systematic review
Allogenic HP802-247	Allogenic tissue made of growth-arrested, human keratinocytes and fibroblasts delivered in a fibrin matrix	Long shelf life (6 months)	Must be applied weekly	Goedkoop et al ¹²⁶ (2009) Kirsner et al ¹²⁷ (2012) Kirsner et al ⁷ (2013)	Patients were given 1 of 6 different doses of HP802-247 administered once per week over 12 weeks; mean complete closure was 40% for HP802-247 vs 33% for placebo patients 205 patients were assigned in a 1:1:1:1:1 ratio to 5.0×10^6 cells/mL every 7 or 14 days, 0.5×10^6 cells/mL every 7 or 14 days, or to vehicle alone. A higher mean wound reduction was found with active treatment vs vehicle ($P = .0446$), with dose of 0.5×10^6 cells/mL every 14 days having the largest improvement 24-week follow-up to previous study (Kirsner et al ¹²⁷); 183 patients followed up every 8 weeks; 43% of HP802-247 treated patients vs 35% vehicle patients had closure, while 10% and 17% had reopening of a previously closed wound
Connexin 43	Topically applied gap junction protein-specific antisense-containing gel			Mendoza-Naranjo et al ¹⁶⁷ (2012)	No RCT available

Dermal Xenogenic	Biobrane E-Z	Acellular porcine collagen type I	<ul style="list-style-type: none"> • Translucent • Long shelf life • Elastic • Immediately available 	<ul style="list-style-type: none"> • Expensive • Possible bovine allergy • May need multiple applications 	Barber et al ¹¹⁴ (2008)	Systematic review
	Oasis	Porcine intestinal collagen and extracellular matrix	<ul style="list-style-type: none"> • Long shelf life • Cost effective • Stored at room temperature 	<ul style="list-style-type: none"> • Applied weekly • Possible bovine allergy 	Romanelli et al ¹²⁰ (2010)	RCT: 55 patients received OASIS or petrolatum-impregnated gauze for 8 weeks. OASIS wounds healed faster than control group ($P = .02$), and had more complete wounds ($P < .05$), faster time to dressing change, and percentage of granulation tissue formed ($P < .05$)
					O'Donnell Jr and Lau ¹¹⁹ (2006)	Systematic review
					Plotner and Mostow ¹²¹ (2010)	No RCT
					Mostow et al ¹¹⁷ (2005)	RCT; 120 patients assigned to receive SGS plus compression therapy vs compression therapy alone for ≤ 12 weeks. 55% of SGS vs 34% of compression group healed ($P = .196$)
	Integra	Bovine tendon collagen and shark chondroitin	<ul style="list-style-type: none"> • Stored at room temperature • Flexible • Immediately available 	<ul style="list-style-type: none"> • Requires multiple applications 	Iorio et al (2012) ¹⁶²	No RCT available
Dermal Allogenic	Dermagraft	Neonatal foreskin fibroblast on a biodegradable mesh	Single application		Harding et al ¹²⁸ (2013)	RCT; 186 patients assigned to Dermagraft plus compression therapy vs compression therapy alone over 12 weeks; 34% of Dermagraft patients had healing vs 31% in control group ($P = .235$); complete healing observed in 57% of Dermagraft group vs 39% in control group ($P = .223$)
					Omar et al ¹⁰⁹ (2004)	No RCT available
					Landsman et al ¹²⁹ (2011)	No RCT available

Continued

Table VIII. Cont'd

Name	Description	Advantage	Disadvantage	Study	Study outcome
HAM	Inner layer of the amniotic sac, cryopreserved for transplantation	<ul style="list-style-type: none"> • Nonimmunogenic • Low cost 	<ul style="list-style-type: none"> • Long healing time • Unstratified epithelium—may be an obstacle for migration of keratinocytes • Closely resembles cutaneous basement membrane (ie, amniotic epithelium is at risk of being replaced by a reconstructed epidermis) • Does not survive in chronic wounds after 2-4 weeks 	Tauzin et al ¹³⁰ (2011) Mermet et al ¹³¹ (2007) Gutierrez-Moreno et al ¹³² (2011) Alsina-Gibert and Pedregosa-Fauste ¹³³ (2012) Pesteil et al ¹³⁴ (2007)	No RCT available No RCT available No RCT available No RCT available No RCT available
DCD	Cadaveric tissue skin with all epidermal and cellular components of the dermis removed	<ul style="list-style-type: none"> • Applied without immobilization • Single application 		Greaves et al ¹²³ (2013)	No RCT available
Composite					
Xenogenic and allogenic					
Apligraf	Neonatal foreskin keratinocyte and fibroblast bilayered with bovine collagen	<ul style="list-style-type: none"> • Self-repair ability • Single application • Stored at room temperature • Immediately available 	<ul style="list-style-type: none"> • Expensive • Minimal shelf life 	Karr ¹²⁴ (2011) Serena and Bialas ¹³⁵ (2009) O'Donnell et al ¹¹⁹ (2006) Plotner and Mostow ¹²¹ (2010) Landsman et al ¹²⁹ (2011)	No RCT available Case report Systematic review No RCT available No RCT available
Dermal artificial grafts					
Xenogenic					
Biobrane	Inner nylon mesh coated with porcine type I collagen attached to silicone membrane	Long shelf life	<ul style="list-style-type: none"> • Expensive • Possible bovine allergy • May need multiple application • Minimal shelf life 	Barber et al ¹¹⁴ (2008)	Systematic review
PriMatrix	Fetal bovine dermis with type I and III collagen	Long shelf life		Karr ¹²⁴ (2011)	No RCT available

Allogenic					
Hyalomatrix PA	A total ester derivative of hyaluronic acid, made of HYAFF* and coupled with medical grade silicone	<ul style="list-style-type: none"> • Immediate availability • User-friendly application 		Motolese et al ¹³⁶ (2013) Plotner and Mostow ¹²¹ (2010)	No RCT available No RCT available
CGS impregnated with bFGF	Collagen/gelatin sponge (CGS) with a 10 wt% concentration of acidic gelatin that releases positively charged growth factors for 10+ days in vivo	<ul style="list-style-type: none"> • Sustains and releases bFGF in a controlled manner • Applied less frequently than other growth factors 	Daily topical administration	Morimoto et al ¹³⁷ (2013)	RCT; 17 patients were assigned to CGS impregnated with bFGF with 7 or 14 $\mu\text{g}/\text{cm}^2$ after debridement and assessed after 28 days; wounds improved in 16 patients; no significant difference seen between groups
TheraSkin	Cryopreserved human skin allograft within 24 hours of death	Minimally processed to preserve native components of real human skin		Landsman et al ¹²⁹ (2011)	No RCT available
Skin grafts					
Pinch grafts	A small graft of skin, obtained by elevating the skin with a needle and excised from the base	<ul style="list-style-type: none"> • Readily obtained 	<ul style="list-style-type: none"> • Successful closure may require multiple attempts • End result can have cobblestone appearance 	Jones et al ¹³⁸ (2013) Jones et al ¹¹³ (2007)	No RCT available No RCT available
Split thickness graft	<ul style="list-style-type: none"> • Consists of epidermis and a portion of the dermis • Conform easily to irregular wound beds • Donor site can be reharvested 	<ul style="list-style-type: none"> • Easily expands 	<ul style="list-style-type: none"> • End result can have cobblestone appearance • Become hypo- or hyperpigmented • Have decreased thickness, which limits use 	Ross et al ¹³⁹ (2011), NPWT and grafts Høgsberg et al ¹⁴⁰ (2011)	No RCT available No RCT available

bFGF, Basic fibroblast growth factor; CGS, collagen/gelatin sponge; DCD, decellularized dermis; HAM, human embryonic membrane; NPWT, negative pressure wound therapy; RCT, randomized controlled trial.

*HYAFF is manufactured by Anika Therapeutics (Bedford, MA).

Phlebectomy and sclerotherapy have been performed for the treatment of varicose tributaries.⁹³ A systematic review and metaanalysis found 11 studies of surgical therapy versus conservative therapy in the management of VLUs.⁹⁵ The current study concluded that surgical intervention may improve the healing of VLUs, but cautioned that the quality of the available evidence is low.⁹⁵

Incompetent perforator veins

Patients with CVI are commonly found to have enlarged perforator veins with incompetent valves that allow reversal of flow from the deep venous system into the superficial system. The increased pressure transmitted into the superficial system contributes to inflammation and ulceration. Subfascial endoscopic perforator surgery (SEPS), a surgical technique to correct incompetent perforators, has been successful in multiple studies. In a metaanalysis comparing SEPS to the traditional Linton procedure (ie, ligation of all the perforating veins from ankle to proximal calf), the former was found to reduce the rate of VLU recurrence, secondary infection, and duration of hospital stay.⁹⁶⁻⁹⁸ Nelzen et al⁹⁹ found that SEPS of the superficial long saphenous vein was associated with less recurrence and positive long-term outcomes. Olivencia¹⁰⁰ reported that 79% of patients had a healing time of 2 to 3 months after SEPS.

In recent years, percutaneous methods to ablate incompetent perforators using laser or radiofrequency energy have emerged and have generally replaced SEPS in many venous practices. Percutaneous methods have the advantage of performance under local anesthesia with minimal morbidity.¹⁰¹ Success rates have been reported at 60% to 80% for an individual procedure, with 90% of perforators closed with multiple attempts. Early reports suggest benefit in improving ulcer healing, but data are limited.¹⁰¹⁻¹⁰³

Superficial venous ablation

Minimally invasive surgeries, such as superficial venous sclerotherapy or ablation, have been used in the management of patients with VLUs.^{104,105} Less invasive methods improve healing of VLUs with isolated superficial incompetence.³ In a series reported by Pang et al,⁹⁰ VLUs were treated with ultrasound-guided foam sclerotherapy combined with compression therapy.⁹⁰ Combined therapy led to 81% healing at 6 months and 5% recurrence at 2 years.

Venous compression syndromes

Patients with recalcitrant VLUs may present with compression of the iliac venous system or vena cava

(May–Thurner syndrome [MTS]). In a review of 75 consecutive patients with VLUs, significant compression of the venous outflow tract was documented in 37%.^{101,106} These patients may require venous intervention.

Obstruction of the venous outflow tract results in increased venous pressure, particularly with ambulation. This obstruction is a primary cause of poor adherence to compression therapy. Ambulation in a patient with MTS results in limb engorgement, leading to pain in the leg being treated with high-strength compression. Percutaneous stenting of the obstructed vein results in improved venous drainage, reduced limb edema, and pain alleviation. There is no current evidence that venous stenting results in improved ulcer healing or reduced recurrence.¹⁰⁷

USE OF ADJUNCTIVE THERAPIES: WHEN AND WHY

Key points

- **If a healable venous leg ulcer does not heal despite good standard treatment, adjunctive therapies should be considered**
- **Adjunctive therapies include skin grafts and bioengineered skin, growth factors, and electrostimulation therapy**

VLUs that have the ability to heal yet remain “stalled” despite good standard treatment disrupt the activities of daily life of the patient and increase costs.

Skin graft and bioengineered skin

Pinch graft and split-thickness grafts both have been successful in the treatment of patients with VLUs (Table VIII).^{69,108-110} Some studies report 50% healing after mesh skin grafting.^{111,112} However, limited data exist from RCTs. A Cochrane review supports bilayer artificial skin grafts for healing of refractory VLUs.¹¹³ A systematic review by Barber et al¹¹⁴ showed the importance of the dermal component in addition to the epidermal component in the improvement of venous ulcer healing rate. A bilayered skin equivalent (BSE; Apligraf, Organogenesis, Canton, MA) is the only skin equivalent therapy approved by the FDA for the treatment of VLUs.^{115,116} BSE is an allogeneic cultured bilayer skin construct derived from neonatal foreskin. It has a dermal layer comprised of human fibroblasts in a bovine type 1 collagen matrix, combined with an epidermal component of human keratinocytes. Data from a single RCT have shown that BSEs are effective for refractory VLUs and diabetic foot ulcers.¹¹⁶ Porcine small intestine submucosa (OASIS Wound Matrix; Healthpoint Ltd,

Table IX. A review of literature on use of growth factors in the management of venous leg ulcers (2004-2014)^{99,123,124,130,134-141,146-149,163-165}

Name	Description	Study	Study outcome
Autologous platelet-rich fibrin matrix membrane	Natural fibrin matrix obtained from autologous peripheral blood	O'Connell et al ¹⁵⁰ (2008)	No RCT available
Platelet gel/platelet-rich plasma	Hemocomponent obtained in vitro by pairing concentrated platelets with calcium chloride and thrombin to form a fibrin clot	Ficarelli et al ¹⁶⁰ (2008)	No RCT available
		Park et al ¹⁶¹ (2013)	No RCT available
		De Leon et al (2011) ¹⁶³	No RCT available
		Frykberg et al (2011) ¹⁶⁴	No RCT available
Granulocyte/macrophage colony-stimulating factor	Man-made form of granulocyte/macrophage colony-stimulating factor that is an hematopoietic growth factor and immune modulator	Cianfarani et al ¹²⁵ (2006)	No RCT available
		Da Costa et al ¹⁶⁵ (1999)	Systematic review (no RCT)
		Brem et al ¹¹⁶ (2008)	No RCT available
Basic fibroblast growth factor	A fibroblast growth factor	Seidman et al ¹⁴⁶ (2006)	No RCT available
Vitronectin: growth factor	Sterile combination of recombinant vitronectin, IGFBP-3, IGF-I, and EGF delivered in a solution comprised of disodium hydrogen phosphate, potassium dihydrogen phosphate sodium chloride, and potassium chloride	Upton et al ¹⁴⁷ (2011)	No RCT available
Platelet-derived growth factor	Platelet-derived growth factor is a protein commonly released by degranulating platelets, macrophages, endothelial cells, fibroblasts, and keratinocytes in the wound healing cascade	Trent et al ¹⁴⁸ (2005)	No RCT available
		Mwaura et al ¹⁴⁹ (2006)	No RCT available
		Margolis et al ¹⁵¹ (2009)	Phase I clinical trial; 15 patients received platelet-derived growth factor injections and were monitored over 24 weeks; 93% of patients had a decrease in wound size; 2 patients healed by day 28; 47% of patients healed at 24 weeks of follow-up
Calcitonin gene-related peptide and vasoactive intestinal polypeptide	Potent vasoactive and antiinflammatory peptide	Gherardini et al ¹⁶⁶ (1998)	66 patients were assigned to either standard treatment plus iontophoresis of calcitonin gene-related peptide and vasoactive intestinal polypeptide, or standard treatment plus placebo iontophoresis for 12 weeks; the results showed a surface area reduction of 74% in the treatment group vs 44% in the control group ($P < .05$), and complete healing was seen in 11 treatment patients vs 6 control patients ($P < .05$)

EGF, Epidermal growth factor; IGF-I, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein 3; RCT, randomized controlled trial.

Fort Worth, TX) accelerates healing of VLUs.¹¹⁷ In a study by Mostow et al,¹¹⁷ a total of 120 patients with VLUs were randomized to receive either weekly topical treatment of small intestine submucosa (SIS) plus compression or compression therapy alone. After 12 weeks, 55 % of wounds treated with SIS healed versus 34% in the control group ($P = .01$).¹¹⁷ A review of the literature on the use of artificial skin substitutes, including acellular matrix, is listed in Table VIII.^{109,113,114,117-124,128-141}

Growth factors

Granulocyte monocyte colony stimulating factor has been delivered by intralesional injection to accelerate VLU healing.¹⁴²⁻¹⁴⁴ Other growth factor delivery mechanisms exist, such as autologous platelet-rich plasma. Although case series have suggested that platelet-rich plasma may be used in the treatment of VLUs, evidence from RCTs have shown no significant benefit compared to standard care.¹⁴⁵ A review of evidence on the use of growth factors in the management of VLUs is listed in Table IX.^{7,60,61,125-127,146-151}

Electrostimulation therapy

Evidence for the use of electrostimulation therapy (EST) in the management of patients with VLUs is limited. On the whole, evidence for EST is limited. Jankovic et al¹⁵² noted improved healing in 35 patients treated with EST. However, a Cochrane review identified no statistically significant improvement of healing with EST compared to sham therapy.¹⁵³

Negative pressure wound therapy

A 2008 Cochrane review reported no beneficial effect of negative pressure wound therapy (NPWT) for the healing of VLUs.¹⁵⁴ However, NPWT has been used to promote granulation tissue before skin grafting.¹⁵⁵ Since the Cochrane review, Dini et al¹⁵⁶ reported that NPWT accelerates granulation tissue formation clinically and used immunohistochemical evaluation to demonstrate improved angiogenesis (CD31), lymphatic vessel formation (D240), and macrophage (CD68) and lymphocyte (CD3) proliferation after 1 week of therapy. Armstrong et al¹⁰⁴ found an ultraportable mechanically powered NPWT device to be equally efficacious to an electrically powered device in VLU management with less impact on daily activities, mobility level, social interactions, and sleep.¹⁵⁷

Other treatments

Low frequency (<100 kHz), low intensity (<100 mW/cm²) lasers have been used in the

management of patients with VLUs.¹⁵⁸ Increased cellular metabolism and subsequent cell proliferation were identified in the wounds exposed to laser therapy.^{158,159} Caetano et al¹⁶⁰ used phototherapy as an adjunctive therapy in the management of 20 patients with VLUs. A 2010 Cochrane review did not support that either lasers or phototherapy facilitates the healing of VLUs.¹⁶¹

In conclusion, VLUs are a growing health care burden. Dermatologists require the skills to diagnose, assess, treat, and prevent venous disease. Venous disease management can be optimized by treating pain and infection, reducing the bioburden, and through the routine use of compression therapy. The use of adjunctive systemic agents, skin grafting, biologic therapies, or venous intervention may promote healing in patients with refractory VLUs.

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