



PERSPECTIVE ARTICLE

Wound Healing Society (WHS) venous ulcer treatment guidelines: What's new in five years?

Jennifer C. Tang, MD¹; William A. Marston, MD²; Robert S. Kirsner, MD, PhD¹

1. Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, Florida, USA, and
2. Division of Vascular Surgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA

Reprint requests:

Dr R. S. Kirsner, Department of Dermatology & Cutaneous Surgery, University of Miami Miller School of Medicine, 1600 NW 10th Ave. RMSB, Room 2023-A, Miami, FL 33136, USA.
Tel: +1,305 243 4472;
Fax: +1 305 243 6191;
Email: rkirsner@med.miami.edu

ABSTRACT

Since the establishment of the guidelines for the treatment of venous ulcers by the Wound Healing Society in 2006, there has been an abundance of new literature, both in accord and discord with the guidelines. The goal of this update is to highlight new findings since the publication of these guidelines to assist practitioner and patient in appropriate health care decisions, as well as to drive future research endeavors.

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Guidelines for the treatment of venous ulcers were established by the Wound Healing Society (WHS) in 2006. Since then, there has been an abundance of new literature, both in accord and discord with the guidelines. Guidelines serve dual purposes. First, they are systematically devised statements to assist practitioner and patient in appropriate health care decisions. The second purpose is to demonstrate shortcomings of existing literature in order to guide further research. The goal of this update is to highlight new findings since the publication of the guidelines to drive future research endeavors.

METHODS

Data sources and searches

A key word search using MEDLINE, Embase, and Cochrane reviews for publications between January 2006 and January 2011 was performed. The search was further limited to only English publications and we excluded review articles and case reports. Key search terms and generated MeSH terms were derived from the existing guidelines. Studies included were classified as meta-analysis, systematic review, randomized control trial (RCT), retrospective series review, or clinical case series. Consistent with the existing guidelines, validated principles for other chronic wound types were included as well as animal studies.

Data synthesis and analysis

In a PubMed and Medline search, 4,382 articles were identified. Five hundred and seventeen articles met criteria for screening. In an Embase search, 4,686 articles were identified. Four hundred and eleven articles met criteria for

screening. Of note, among the articles that met criteria for screening, there was significant overlap as many were listed in at least two of the data sources. One hundred and sixty-seven articles relevant to the guidelines were selected. Seventy articles were reviews or special communications and were excluded. Ninety-seven articles were ultimately included. Similar to the original WHS guidelines, we have divided the literature into sections and summarized the new literature for each section.

RESULTS

Diagnosis

The clinical importance of correct diagnosis and exclusion of arterial disease has been confirmed (Table 1). A clinical case series found ankle brachial index (ABI) to have high specificity in detecting arterial occlusion.¹ Transcutaneous oximetry may be an alternative to ABI in screening for arterial disease in patients with venous leg ulcers.² Additional evidence exists to confirm the value of excluding sickle cell disease when encountering an apparent venous ulcer. There is a clinical case series that demonstrated that leg ulcers occur as a complication of sickle cell disease and this diagnosis should be ruled out in non-healing leg ulcers.³

Compression

Compression therapy remains the mainstay of initial treatment for venous leg ulcers (Table 2). An updated Cochrane review of compression therapy for venous leg ulcers highlighted increased healing rates compared to no compression, especially multicomponent systems.⁴ However, a systematic

Table 1. Guidelines for the diagnosis of lower extremity venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Rule out gross arterial disease	Lazareth et al. ¹	2009	Clinical case series	n = 100 patients with leg ulcers	Ankle arm index (AAI) < 0.09 has 84.7% sensitivity, 97% specificity in detecting arterial occlusive disease in patients with leg ulcers.	Support
	Bianchi et al. ²	2008	Clinical case series	n = 195 patients	Pulse oximeter is a comparable alternative to Doppler ABI in the screening of patients for arterial disease.	Support
Rule out sickle cell disease	Halabi-Tawil et al. ³	2008	Clinical case series	n = 20 patients	Leg ulcers are a major complication of sickle cell disease and may be prolonged and disabling.	Support

review and clinical case series reported that compression stockings improved healing rates and were easier to use compared to compression systems.⁵ Additional evidence confirms that intermittent pneumatic compression may be used alone or in conjunction with compression systems to aid in healing as demonstrated in a Cochrane review and small clinical case series.⁶ Overall, there is increased evidence to aggrandize the use of compression to combat venous hypertension.

Infection control

Debridement of wounds with devitalized tissue or high bacterial loads continues to be supported by an animal study.⁷ Regarding the method of debridement, a report suggested that larval therapy may not be the best debridement method.⁸ Quantitative swab culture and tissue biopsy remain valid techniques for detecting infection. As these are not often available to clinicians, one report found that swab culture provides a reasonable measurement of wound bioburden.⁹ In addition, tissue biopsy does not impede healing and could be performed to determine bacteria density, a predictor of non-healing.¹⁰ Despite consensus of using topical antimicrobial therapy to decrease bacterial levels, only cadexomer iodine was recommended as topical treatment for clinical infection in a Cochrane review¹¹ (Table 3).

In a randomized study of 213 venous leg ulcer (VLU) patients comparing silver donating and no silver dressings, there was no benefit of silver in ulcer healing and increased cost for its use. This was a significant study calling into question the routine use of topical antibiotics such as silver in dressings for VLUs.¹² Although no recommendations for the best treatment of cellulitis,¹³ trimethoprim-sulfamethoxazole and clindamycin are good options for initial empiric therapy if suspicion for community associated methicillin-resistant *Staphylococcus aureus*.¹⁴ However, both beta-lactam and non-beta-lactam antibiotics may be used for uncomplicated cases of cellulitis.¹⁵ Infection control to increase take of a skin graft or flap may be achieved by negative pressure therapy combined with sodium hypochlorite solution as seen in a small case series.¹⁶ Additional evidence to determine effective topical or systemic methods of decreasing bioburden for skin graft success is warranted.

Wound bed preparation

Examination of the patient as a whole by ensuring adequate nutrition and perfusion remain integral for optimal wound bed preparation (Table 4). Nutrition should be assessed in patients with venous leg ulcers as protein deficiency is associated with increased inflammation, greater wound area, and more frequent wound complications.¹⁷ In addition, protein requirements tend to be underestimated in wound patients.¹⁸ Smoking affects healing such that fibroblast proliferation is decreased, but collagen extracellular matrices may revert to normal with smoking abstinence.^{19,20} Initial and maintenance debridement have been reaffirmed as relevant procedures for wound bed preparation. Regular maintenance debridement is required to stimulate the wound and to persist in a healing state.²¹ In a large retrospective series review, surgical debridement was associated with greater wound surface area reduction compared to controls who did not receive debridement.²² Other forms of debridement, including collagenase

Table 2. Guidelines for lower extremity compression for treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Class 3 high compression system for treatment of venous ulcers	O'Meara et al. ⁴	2009	Cochrane review	n = 39 RCTs	Compression increases healing rates compared with no compression. Multi-component systems are more effective than single-component systems, especially when composed of elastic bandages.	Support
	Amsler et al. ⁹¹	2009	Systematic review and meta analysis	n = 8 RCTs (692 patients, 688 legs)	Leg compression with stockings is better than compression with bandages in terms of average time to healing, pain, and ease of use.	Contradict
	Szewczyk et al. ⁹²	2010	Clinical case series	n = 46 patients	Healing rate of 0.63 cm ² /week with four layered compression and 0.44 cm ² /week with compression stocking (difference not statistically significant). Compression stocking and multi-layered compression system have similar clinical effectiveness.	Support
	Nelson et al. ⁹³	2008	Cochrane review	n = 7 RCTs (367 patients)	IPC may increase healing compared with no compression. Unclear if IPC increases healing when combined with bandages or if can be used as sole therapy.	Support
Intermittent pneumatic compression with or without compression for patients non-compliant with adequate compression system	Betz ⁹⁴	2009	Clinical case series	n = 4 patients (2 with VLU)	Combination of standard wound care with IPC may aid closure of chronic, non-healing wounds.	Support

Table 3. Guidelines for infection control in the treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Remove necrotic or devitalized tissue by debridement	Payne et al. ⁷	2008	Experimental laboratory; animal study	n = 15 rats	Collagenase and papain-urea are beneficial and safe in wounds with high bacterial loads. These agents improve extent and rate of healing.	Support
	Dumville et al. ⁸	2009	RCT	n = 267 patients	Larval therapy did not improve rate of healing or reduce bacterial load compared to hydrogel. Larval therapy did significantly reduce time to debridement and pain associated with debridement.	Support
If suspicion of infection in debrided ulcer or non-progressing epithelialization within 2 weeks of debridement and initiation of compression, then tissue biopsy or validated quantitative swab technique	Gardner et al. ⁹	2006	Cross-sectional study	n = 83 wounds	Swabs collected using Levine's technique provides reasonably accurate measurements of bioburden.	Support
	Panuncialman et al. ¹⁰	2010	Retrospective study	n = 14 patients	Wound biopsy is a safe procedure and does not delay overall healing of chronic wound.	Support
	Davies et al. ⁹⁵	2007	Clinical case series	n = 70 patients	Bacterial density of wound surface area determined by swab or biopsy is independent predictor of non-healing. Biopsies are discouraged in clinically non-infected wounds.	Support
If $\geq 1 \times 10^6$ CFU/g of tissue or any tissue level of β -hemolytic strept following debridement, decrease bacterial level with topical antimicrobial therapy	O'Meara et al. ¹¹	2010	Cochrane review	n = 25 trials	Some evidence to support use of cadexomer iodine. Antibacterial preparations only for clinical infection and not for bacterial colonization.	Support

Robson et al. ⁹⁶	2007	Experiment	<i>n</i> = 85 rats	Stable form of hypochlorous acid (NVC-101) does not decrease tissue bacterial bioburden as much as silver sulfadiazine but associated with improved wound closure in chronically infected, granulating wounds.	Support
Michaels et al. ^{1,2}	2009	RCT	<i>n</i> = 213 patients	No difference between silver and non-silver dressings in the proportion of ulcers healed at 12 weeks.	Contradict
Kilburn et al. ¹³	2010	Cochrane review	<i>n</i> = 25 studies (2,488 patients)	Insufficient evidence to define best treatment for cellulitis.	Neither
Khawcharoenporn et al. ¹⁴	2010	Retrospective study	<i>n</i> = 405 patients	Bactrim and clindamycin are preferred empiric therapy for outpatient treatment of cellulitis in community associated MRSA prevalent settings.	Support
Madaras-Kelly et al. ¹⁵	2008	Multicenter, retrospective study	<i>n</i> = 2,977 patients (861 were included)	No difference between β -lactam and non- β -lactam antibiotics for treating uncomplicated cellulitis.	Support
Cenizal et al. ⁹⁷	2007	Clinical case series	<i>n</i> = 34 patients	Treatment failure rate of 9% seen in trimethoprim group, 0% in doxycycline group (not statistically significant).	Support
Raad et al. ¹⁶	2010	Clinical case series	<i>n</i> = 5 patients	VAC with Dakins solution eradicates bacteria and allowed 100% take and complete healing at 1 year.	Support
<p>Treat cellulitis with systemic gram positive bactericidal antibiotics</p> <p>Decrease level of bacteria to $\leq 10^5$ CFU/g of tissue, with no β-hemolytic strept before skin graft, skin equivalent, pedicled, or free flap</p>					

Table 4. Guidelines for wound bed preparation in the treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Examine and assess for (A) systemic diseases and meds, (B) nutrition, and (C) tissue perfusion and oxygenation	Legendre et al. ¹⁷	2008	RCT	n = 84 patients	Protein deficiency associated with inflammatory syndrome, greater wound area, and wound complications.	Support
	Pompeo ¹⁸	2007	Clinical case series	n = 150 patients	Protein requirements for wound patients tend to be underestimated.	Support
	Sorensen et al. ¹⁹	2010	RCT	n = 78 patients	Wound inflammation and fibroblast proliferation were decreased in smokers.	Support
	Sorensen et al. ²⁰	2009	RCT	n = 78 patients	Impaired wound healing in smokers and the potential reversibility of extracellular degradation with smoking abstinence.	Support
Initial debridement to remove necrotic tissue, excess bacteria, and cellular burden of dead or senescent cells. Maintenance debridement to maintain appearance and readiness of wound bed for healing	Falanga et al. ²¹	2008	Consensus of expert panel		Maintenance debridement helpful in stimulating a wound and to keep in a healing state.	Support
	Cardinal et al. ²²	2009	Retrospective series review	n = 376 ulcers (366 VLU, 310 DFUS)	Surgical debridement significantly increases wound surface area reduction compared to no debridement. Centers with greater debridement frequency had high rates of wound closure.	Support
	Marazzi et al. ²³	2006	Retrospective series review	n = 979 patients	Collagenase treatment is effective and well-tolerated in patients with chronic wounds. May improve wound healing and decrease wound care costs.	Support
	Ennis et al. ²⁴	2006	RCT	n = 23 patients	Low-frequency, noncontact ultrasound allowed shorter median time to healing, faster transition to secondary procedures, and decreased inpatient care.	Support
	Edwards et al. ²⁵	2010	Cochrane review	n = 6 RCTs	Hydrogel and larval therapy increases healing rate of DFUs compared to simple dressings. Surgical debridement showed no significant benefit.	Support
Clean wounds (initially and at each dressing change) using neutral, nonirritating, nontoxic solution	Fernandez et al. ²⁶	2008	Cochrane review	n = 11 trials	RR = 0.16 of wound infection when cleansing with tap water compared with normal saline. No statistically significant differences in infection rates if cleansed with tap water or not cleansed at all on tissue, amount of exudates, and edema.	Support

Andriessen et al. ²⁷	2008	Retrospective series review	<i>n</i> = 81 patients	Wounds cleansed with polyhexanide solution healed in 97% of patients compared to 89% of Ringer's or saline group (<i>p</i> < 0.0001). Time to healing for polyhexanide solution was 3.31 months vs. 4.42 months in Ringer's or saline group.	Support
Falanga et Fernandez et al. ²⁸	2006	RCT	<i>n</i> = 177 patients	Higher wound bed scores (healing edges, presence of eschar, greatest wound depth/granulation tissue, amount of exudates and edema, periwound dermatitis and callus/fibrosis, and pink/red wound bed) associated with increased complete wound closure.	Support
Cardinal et al. ²⁹	2009	RCT	<i>n</i> = 338 VLUs	VLUs with more convex wound shape, and sustained linear relationship between wound margin size and wound surface area had increased healing rates and greater likelihood of healing by 12 weeks.	Support
Cardinal et al. ³⁰	2008	RCT	<i>n</i> = 306 VLUs and 241 DFUS	Predictors of complete wound healing at 12 weeks: wound margin advance, initial healing rate, % wound surface area reduction, and wound healing trajectories. Poor healing progress as evaluated at 4 weeks will unlikely heal with 8 additional weeks of treatment.	Support
Kecejil Leskovec et al. ³¹	2008	Clinical case series	<i>n</i> = 81 patients	Horizontal initial healing rate (HHR), vertical initial healing rate (VHR), and ulcer duration are independent predictors of 24-week healing (area under ROC curve = 0.9).	Support
Cardinal et al. ³²	2008	Retrospective series review	<i>n</i> = 338 VLUs	35% of wounds that fit exponential model of surface area reduction healed vs. 21% of wounds that did not fit the exponential model (<i>p</i> = 0.018).	Support
Hon et al. ³³	2010	Descriptive, multicenter center	<i>n</i> = 98 ulcers (23 VLUs)	Pressure Ulcer Scale for Healing (PUSH) and surface area correlation coefficient was 0.66. Mean PUSH score significantly different between healing and non-healing VLUs (<i>p</i> = 0.000).	Support

and non-contact ultrasound, are well tolerated and effective in decreasing healing time and wound care costs.^{23,24} However, in a Cochrane review of debridement of diabetic foot ulcers, hydrogel and larval therapy increased healing rates but surgical debridement was not found to increase healing.²⁵ Debridement is accepted as mainstay in wound bed preparation, but high-level data are lacking and there are insufficient data to determine the most effective method for optimal healing. Currently, only Level III evidence is available to support wound cleansing as no RCT currently exists. A recent Cochrane review found no evidence supporting a difference in infection rate when wound cleansing was performed using tap water or saline.²⁶ In a retrospective analysis, cleansing with polyhexanide solution resulted in higher healing rates compared to Ringer's or saline solution.²⁷

The value of documentation and evaluation of rate of wound healing has been confirmed for the treatment of venous leg ulcers (Table 4). A wound bed score composed of healing edges, presence or absence of eschar, wound depth, presence and quality of granulation tissue, amount of exudates, periwound skin, and wound bed color has been developed based on data from an RCT comparing compression therapy alone or with a living bilayered skin construct.²⁸ Additional documentation of wound shape may contribute to healing probability as convex venous leg ulcers have greater likelihood to heal at 12 weeks.²⁹ In a large retrospective analysis of data from two large RCTs to compare topical wound treatments, predictors of healing at 12 weeks included wound healing trajectories, percent wound area reduction, margin advancement, and initial healing rate; if poor progress was assessed at 4 weeks, then likelihood of healing with 8 additional weeks of similar treatment is low.³⁰ Horizontal and vertical healing rates and exponential models of surface area reduction may be used to track wound size and determine if treatment is optimal.^{31,32} In a multicenter study, the pressure ulcer scale for healing was validated as a tool to determine healing vs. non-healing in venous leg ulcers.³³ Although optimal wound documentation method has not determined, the value recording wound characteristics and rate of healing has been fortified with new evidence.

Dressings

Despite consensus of choosing a dressing to maintain a moist wound-healing environment, limited literature supports one being superior (Table 5). In a systematic review, all modern dressings had the same efficacy with regard to healing and were comparable to saline or paraffin gauze.³⁴ There is additional evidence to support the selection of a dressing that manages wound exudate and protects peri-ulcer skin because chronic exposure to these are associated with delayed healing.³⁵ Wound fluid has been observed to contain elevated matrix metalloproteinase levels, correlating with worse clinical outcome and resistance to healing.^{36,37} Specifically, concentration of transforming growth factor beta in wound fluid had an inverse relationship with ulcer size.³⁸

Allergic contact dermatitis is recognized as a complication of venous disease. Polysensitization in venous leg ulcer patients is more prevalent with increasing duration of the ulcer; greater than twofold increase compared to controls was observed in a clinical case series.^{39,40} Fragrances, antiseptic agents, and parabens are among the most common allergens.⁴¹⁻⁴³ In a clinical case series, even advanced modern

dressings may cause contact sensitivity.⁴⁴ Dressing selection should continue to be based on costs and provider preference as additional evidence has not found superiority in healing. In a systematic review, the type of wound dressing utilized beneath compression systems was not shown to affect ulcer healing.⁴⁵

Surgery

Surgical procedures are often pursued when dressings and compression are unable to render healing in venous leg ulcers (Table 6). Additional literature suggests value of various procedures in improving healing, but high-level evidence remains lacking. Skin grafting, traditionally found to be a non-sustainable option, has new evidence for increased healing. In a Cochrane review, there was insufficient evidence to determine whether skin grafts enhanced healing of venous leg ulcers.⁴⁶ However, two clinical studies reported a heal rate of at least 50% after treatment with skin grafts.^{47,48} In one of these studies, the venous ulcers were all refractory in nature⁴⁷; and in the other, none of the ulcers receiving conservative treatment healed.⁴⁸ A surgical technique, subfascial endoscopic perforator surgery (SEPS), used to correct perforator disease, showed positive results in ulcer healing and preventing recurrence in four of four studies (one meta-analysis, three clinical case series). In a meta-analysis, SEPS produced significantly lower rate of wound infections, decreased hospital stays, and reduced rate of recurrent ulcers when compared to the Linton procedure.⁴⁹ Fewer skin complications and 100% heal rate were also seen in a small uncontrolled clinical case series.⁵⁰ Lateral SEPS in combination with routine surgery augmented ulcer healing and decrease recurrence rates vs. routine surgery alone.⁵¹ In a clinical case series, the addition of superficial venous surgery to SEPS resulted in high healing and low recurrence rates.⁵²

Venous surgery, while not shown to improve healing, seems to reduce or delay recurrence. Six of the seven studies (one systematic review, one RCT, two retrospective series review, and three clinical case series) involving less extensive surgery reported decreased venous ulcer recurrence (Table 6). One systematic review concluded comparable rates of healing but less recurrence when compared to compression alone.⁵³ In a retrospective case series, surgery was recommended for decreasing ulcer recurrence prior to ulcer becoming intractable to treatment.⁵ Two clinical case series and one retrospective series review demonstrated acceptable healing rates and recurrence rate of less than 9% in all.⁵⁴⁻⁵⁶ Valvuloplasty consisting of monocusp valve construction from viable vein wall led to 0% recurrence in a small clinical case series.⁵⁷ One RCT reported similar ulcer recurrence rates in patients treated surgically compared to conservative therapy.⁵⁸ However, the ulcer-free period was significantly greater in patients with recurrent ulcers or ulcers located on the medial aspect of the leg than those treated in the conservative group.⁵⁸ Current evidence supports the practice of venous surgery to decrease ulcer recurrence.

Free flap transfer with microvascular anastomoses remains an option for recalcitrant venous leg ulcers with concomitant lipodermatosclerosis (LDS). In a small retrospective series review, free flap transfer for ulcers with severe LDS was effective in preventing ulcer recurrence in all patients.⁵⁹

Table 5. Guidelines for dressings in the treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Use dressing that maintains moist wound-healing environment	Chaby et al. ³⁴	2007	Systematic review	n = 99 studies	No evidence that modern dressings were better than another or better than saline or paraffin gauze in clinical efficacy.	Support
Select dressing that will manage the wound exudates and protect peri-ulcer skin	De Mattei et al. ³⁵	2008	Clinical case series	n = 7 patients	Continuous exposure to chronic wound fluid causes cellular dysfunction and may delay wound healing.	Support
	Rayment et al. ³⁶	2008	Experiment	n = 9 patients	Excessive protease activity in chronic wound fluid is attributable to matrix metalloproteinases (MMP) and correlates with clinically worse outcome.	Support
	Moor et al. ³⁷	2009	Clinical case series	n = 4 patients	Recalcitrant VLU had elevated MMP-9 levels in wound fluid.	Support
	Gohel et al. ³⁸	2008	Clinical case series	n = 4 patients	Wound fluid volume correlated with ulcer size. Changes in wound fluid TGF- β ¹ inversely correlated with changes in ulcer size.	Support
Select dressing that stays in place, minimizes shear and friction, and does not cause additional tissue damage	Barbaud et al. ³⁹	2009	Clinical case series	n = 423 patients	Polysensitization increases with duration of ulcer. Avoid topical antiseptics and perfume containing ointments.	Support
	Jankićević et al. ⁴⁰	2008	Clinical case series	n = 157 patients	Polysensitization increases with duration of ulcer. Avoid topical antiseptics and perfume containing ointments.	Support
	Smart et al. ⁴¹	2008	Clinical case series	n = 7 patients	46% of patients had ≥ 1 positive patch test response. Most common allergens: fragrances, lanolin, antibacterial agents, and rubber-related allergens.	Support
	Tomljanović-Veselski et al. ⁴²	2007	Clinical case series	n = 60 patients	Positive reactions most commonly demonstrated: corticosteroid ointments, lanolin, and bethanone.	Support
	Zmudzinska et al. ⁴³	2006	Systematic review and meta analysis	n = 50 patients	Most common contact allergens: balsam of Peru, fragrances mix and parabens.	Support
	Motolese et al. ⁴⁴	2009	Systematic review and meta analysis	n = 116 patients	191 reactions were observed in baseline series, 13 reactions in leg ulcer series. 5 reactions to modern wound dressings.	Support
Dressing that is cost effective and appropriate to the setting and the provider	Palfreyman et al. ⁴⁵	2007	Systematic review and meta analysis	n = 42 studies	Type of dressing applied beneath compression does not affect ulcer healing. Decision of dressing should be based on costs and preferences.	Support

Table 6. Guidelines for surgery in the treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Skin grafting is not a long term solution and prone to recurrent leg ulceration	Jones et al. ⁴⁶	2007	Cochrane review	n = 15 RCTs	Insufficient evidence to determine whether skin grafting increases healing of VLUs.	Support
	Abisi et al. ⁴⁷	2007	Clinical case series	n = 62 patients	Wide local excision and meshed skin graft benefited ≥50% of refractory VLUs. Recurrence most likely to occur in first 2 months.	Contradict
	Jankunas et al. ⁴⁸	2007	Clinical case series	n = 71 patients	Ulcers treated with skin graft healed in 67.5% of cases. None of the ulcers in the conservative treatment group healed.	Contradict
Subfascial endoscopic perforator surgery (SEPS) is procedure of choice to prevent backflow from the deep to the superficial venous system	Luebke et al. ⁴⁹	2009	Meta-analysis		SEPS had significantly lower rate of wound infections, reduced hospital stay, reduced rate of recurrent ulcers compared to Linton procedure.	Support
	Kurdal et al. ⁵⁰	2010	Clinical case series	n = 20 patients	Ulcers healed in all patients. Fewer skin complications than Linton procedure and more sustainable ulcer healing.	Support
Less extensive surgery (superficial venous ablation, endovenous laser ablation, valvuloplasty) especially when combined with compression therapy can decrease recurrence of venous ulcers	Wang et al. ⁵¹	2009	Clinical case series	n = 63 patients	Routine surgery plus lateral SEPS resulted in 100% heal rate and 0% recurrence compared to routine surgery only with 87.9% heal rate and 12.1% recurrence rate. Lateral SEPS aids in ulcer healing and reduces recurrence.	Support
	Neizén et al. ⁵²	2007	Clinical case series	n = 90 patients	SEPS combined with superficial venous surgery resulted in 87% heal rate, 8% three year recurrence rate, and 18% five year recurrence rate.	Support
	Howard et al. ⁵³	2008	Systematic review	n = 61 articles	Superficial venous surgery has similar rates of healing compared to compression alone but associated with less recurrence.	Support

Obermayer et al. ⁵	2006	Retrospective series	<i>n</i> = 173 patients	Healing rate of 87% and recurrence rate of 5%. Recommend surgery for VLUs at any stage but before ulcer becomes intractable to treatment.	Support
Sharif et al. ⁵⁴	2007	Clinical case series	<i>n</i> = 20 patients	Cumulative healing rate of 95% at 22 months follow-up. ELVT effective in treatment and prevention of VLUs.	Support
Teo et al. ⁵⁵	2010	Clinical case series	<i>n</i> = 44 patients	Endovenous laser ablation yielded cumulative healing rate of 97.4% and 0% recurrence at 1 year post procedure. 5 recurrences in 52 month follow-up.	Support
Marrocco et al. ⁵⁶	2010	Retrospective series	<i>n</i> = 356 patients	Of 83 C5 and C6 patients, 7 patients did not heal or developed recurrent ulcer with endovenous laser ablation.	Support
Opie et al. ⁵⁷	2008	Clinical case series	<i>n</i> = 11 patients	Monocusp valves constructed using viable vein wall remained competent at four years follow-up and with no recurrence of ulcer in all patients.	Support
Van Gent et al. ⁵⁸	2006	RCT	<i>n</i> = 170 patients	Non-statistically significant greater healing rate in surgical group (83%) vs. compression only (73%). Equal rates of recurrence in both groups.	Contradict—no decrease in risk of recurrence compared to compression alone
Free flap transfer with microvascular anastomoses for recalcitrant venous ulcers with severe LDS	2007	Retrospective study	<i>n</i> = 11 patients	No ulcer recurrence in flap recipient site in 11 year follow-up period. 4 new ulcers at sites different from flap.	Support

Adjuvant agents

Topical cytokine growth factors continue to be explored as therapies for venous leg ulcers (Table 7). There is new evidence to suggest the efficacy of these agents, in contrast to previous conclusions of the guidelines. Three of three studies (one experimental laboratory study, two clinical case series) demonstrate the efficacy of growth factors for venous leg ulcers. One experiment found basic fibroblast growth factor to have proliferative effects on the fibroblasts of venous leg ulcers.⁶⁰ Granulocyte-macrophage colony stimulating factor was observed to increase blood vessel density in the wound bed.⁶¹ Gene therapy delivery system using platelet-derived growth factor beta in a small clinical series was found to be safe and effective in decreasing wound size in a phase I study.⁶² However, there is no high-level evidence to dispute past clinical trials that demonstrated lack of efficacy of topically applied growth factors for venous ulcers. Currently, there is no Food and Drug Administration-approved growth factor for VLU treatment.

Bilayered artificial skin, another advanced therapy, stimulates healing of venous leg ulcers (Table 7). A Cochrane review and systematic review confirmed that application of bilayered artificial skin improves healing outcome of venous leg ulcers compared to compression alone.^{46,63} In a clinical case series, skin substitute resulted in healing or substantial decrease in surface area of leg ulcers.⁶⁴ Recent studies (one RCT, one retrospective series review, two clinical case series) with epithelial autografts and allografts have shown benefit in ulcer healing. Human keratinocytes and fibroblasts stimulated wound healing and achieved complete closure in a phase II study.⁶⁵ Autologous epidermal cell effected closure in more than half of chronic wounds in a clinical case series.⁶⁶ Another clinical case series produced 90% closure rate in chronic leg ulcers with application of autograft.⁶⁷

Electrical stimulation is an adjuvant agent found to be effective in reducing venous ulcer size in three of four studies (one Cochrane review, one systematic review, two RCTs) (Table 7). Additional evidence exists to show rhythmic and pulsed therapy's ability to accelerate ulcer healing.^{68,69} Low-frequency pulsed electrical stimulation rendered non-statistically significant difference in healing compared to placebo.⁷⁰ However, a Cochrane review determined no statistically significant improvement of healing rate with electromagnetic therapy compared to sham therapy.⁷¹

Negative pressure wound therapy (NPWT) is typically not used as monotherapy in the healing of venous leg ulcers but often used to assist in skin graft take. Four of seven studies (one Cochrane review, one meta-analysis, one RCT, one retrospective series review, three clinical case series) found benefit of NPWT on promoting skin graft take (Table 7). Two clinical case series and one retrospective study resulted in increased graft take and ulcer healing.^{6,16,72} NPWT had no beneficial effect on wound healing compared to different dressings and topical treatments.⁷³ Contrastingly, some data support the use of NPWT in reducing healing time^{74,75} and hospital stay.⁷⁶ There remain insufficient data to support the use of NPWT venous leg ulcer healing.

Laser therapy, phototherapy, and ultrasound therapy are additional adjuvant therapies that have limited evidence that demonstrate efficacy in venous leg ulcer healing (Table 7). Laser therapy continues to be shown ineffective for the

healing of venous leg ulcers.⁷⁷ In an RCT, phototherapy increased healing rates of large, recalcitrant venous leg ulcers compared to placebo and control.⁷⁸ There is conflicting evidence of the effectiveness of ultrasound therapy for ulcer healing. Based on a Cochrane review, ultrasound does not increase healing of venous ulcers.⁷⁹ In other studies, ultrasound therapy has demonstrated efficacy in both venous leg ulcers^{80,81} and lower extremity ulcers of various etiologies.⁸² Sclerotherapy, another adjunct therapy, has shown healing rates of greater than 80% in two clinical case series.^{83,84} In addition, one study demonstrated rapid healing following sclerotherapy.⁸⁵

Pentoxifylline, an oral methylated xanthine derivative that improves microcirculation by reducing blood viscosity, is an established systemic agent that aids healing of venous ulcers (Table 7). Improved healing with addition of pentoxifylline to compression therapy was validated in a Cochrane review.⁸⁶ An RCT also confirmed increased healing but only after adjusted statistical analysis.⁸⁷ Convincing evidence does not exist that fibrinolytic agents improve venous ulcer healing, but rather have greater effect in treating the pain and other symptoms of LDS. However, new evidence showed intravenous iloprost to be effective in reducing healing time in patients with venous ulcers.⁸⁸

Long-term maintenance

Compression stockings remain imperative in the long-term maintenance of preventing venous leg ulcer recurrence (Table 8). However, there is new dissonant evidence that questions whether improving calf muscle pump function decreases risk of venous ulcer recurrence. Compression stockings to prevent venous ulcer recurrence was recommended in an RCT.⁸⁹ This trial found higher-grade compression to be associated with decreased recurrence but increased noncompliance.⁸⁹ Exercise to increase calf muscle pump function is often recommended to prevent venous ulcers. However, new evidence found no correlation between calf muscle volume and venous return.⁹⁰

In conclusion, this update is a reflection of new evidence regarding the treatment of venous leg ulcers. New data exist both in corroboration and contention with the current guidelines established in 2006. The level strength of evidence supporting each guideline has not been altered. This guideline update provides additional insight on treatment of venous ulcers to the clinical practitioner. More importantly, physicians and scientists may utilize this update to determine evidence gaps and direct new research to fulfill them.

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Study concept and design: Tang, Marston, and Kirsner.

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Analysis and interpretation of data: Tang, Marston, and Kirsner.

Drafting of the manuscript: Tang, Marston, and Kirsner.

Table 7. Guidelines for the use of adjuvant agents (topical, device, systemic) in the treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Cytokine growth factors have not been shown to demonstrate sufficient statistically significant results of effectiveness (potential usefulness only seen in isolated reports)	Seidman et al. ⁶⁰	2006	Experiment		Basic fibroblast growth factor (bFGF) down-regulates p21 and up-regulates phosphorylated tumor suppressor protein retinoblastoma to generate a proliferative environment for fibroblasts of VLUs.	Contradict
	Cianfarani et al. ⁶¹	2006	Clinical case series	n = 8 patients	Intradermal injections of granulocyte-macrophage colony stimulating factor increased blood vessel density in wound bed (action most likely mediated by vascular endothelial growth factor).	Support—underpowered
	Margolis et al. ⁶²	2009	Clinical case series	n = 15 patients	Mean reduction of ulcer size was 45.2% in 4 week period. Two patients healed after 4 weeks, 7 additional patients healed at 24-week follow-up.	Support—small sample size
Bilayered artificial skin (biologically active dressing) + compression bandaging to increase chance of healing	Jones et al. ⁴⁶	2007	Cochrane review	n = 15 RCTs	Bilayered artificial skin used with compression bandages increased the chance of healing a VLU compared with compression and a simple dressing.	Support
	Barber et al. ⁶³	2008	Systematic		Bioengineered skin substitutes with dermal component may improve healing outcome in VLUs, need better trials.	Support
	Gibbs et al. ⁶⁴	2006	Clinical case series	n = 14 patients	11/19 ulcers healed within 8 weeks of single application of skin substitute. Of remaining ulcers, 5 healed and 3 decreased in size substantially after 8-week follow-up period.	Support
Cultured epithelial autografts or allografts have not been shown to improve stable healing	Goedkoop et al. ⁶⁵	2010	Multicenter RCT	n = 36 patients	IHP802-247 was well-tolerated and displayed cell concentration dependent efficacy. Mean closure rate for treatment group was 40% vs. only 30% in placebo group.	Contradict
	Shukla et al. ⁶⁶	2010	Clinical case series	n = 15 patients	Autologous epidermal cell suspension rendered closure in 9 of 15 chronic, non-healing wounds in 20 week follow-up period.	Contradict
	Boggio et al. ⁶⁷	2008	Clinical case series	n = 20 patients	Minced autografts induces faster re-epithelialization than conservative therapy and achieved 90% closure rate.	Contradict
Electrical stimulation may be useful to reduce size of VLU	Jankovic et al. ⁶⁸	2008	RCT	n = 35 patients	Frequency rhythmic electrical modulation system (FREMS) accelerated ulcer healing and reduced pain in VLUs.	Support
	McGaughey et al. ⁶⁹	2009	Systematic review	n = 11 studies	Strong evidence pulsed electromagnetic energy (PEME) is more effective than sham PEME.	Support
	Jünger et al. ⁷⁰	2008	RCT	n = 39 patients	Non-statistically significant greater ulcer area reduction in Dermapause group compared to placebo group.	Support—not statistically significant

Table 7. Continued.

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict	
NPWT may be useful prior to skin graft or flap to promote growth of granulation tissue in wound base or post-operatively to prevent shearing and to remove exudates	Ravaghi et al. ⁷¹	2006	Cochrane review	n = 3 RCTs	No statistically significant improvement of healing rate between electromagnetic therapy and sham therapy.	Contradict	
	Raad et al. ¹⁶	2010	Clinical case series	n = 5 patients	VAC plus Dakins solution decreases bacterial load and resulted in 100% take and complete healing at 1 year.	Support	
	Kim et al. ⁷²	2007	Clinical case series	n = 47 patients	Addition of VAC to Alodermis and split thickness skin graft (STSG): 97.8% take at day 5 and mean complete healing time of 5.8 days. Alodermis and STSG only: 84% take at day 5 and mean complete healing time of 8.9 days.	Support	
	Körber et al. ⁶	2008	Retrospective series	n = 54 patients	Postoperative VAC reduces exudates and increases the take rate of mesh grafts (92.9% complete healing with addition of VAC vs. 64.9% complete healing in control).	Support	
	Ubbink et al. ⁷³	2008	Cochrane review	n = 7 RCTs	No beneficial effect of TNP on wound healing compared with 5 different dressings/topical treatments.	Neither	
	Sadat et al. ⁷⁴	2008	Meta-analysis	n = 3 RCTs	TNP significantly reduced healing times and increased the number of healed wounds.	Neither	
	Zielinski et al. ⁷⁵	2008	Clinical case series	n = 25 patients	Average healing time significantly shorter in group that received VAC (31 vs. 42 days, $p < 0.00002$).	Neither	
	Llanos et al. ⁷⁶	2006	RCT	n = 60 patients	Negative pressure closure (NPC) reduces the amount of STSG lost (0 cm in NPC group vs. 4.5 cm in control group) and hospital stay (13.5 days in NPC group vs. 17 days in control group).	Support	
	Laser therapy, phototherapy, ultrasound therapy have not been shown statistically to improve venous ulcer healing	Leclère et al. ⁷⁷	2010	RCT	n = 34 patients	Fewer patients healed in 980 nm diode laser group (3 patients) than control group (4 patients). Area reduction less in laser group (74.2%) than control group (94.3%). However, differences are not significant.	Support
		Caetano et al. ⁷⁸	2009	RCT	n = 20 patients	Phototherapy increases healing rate compared to placebo and control, especially in large recalcitrant VLUs non-responsive to conventional treatment.	Contradict
	Cullum et al. ⁷⁹	2009	Cochrane review	n = 8 trials	No reliable evidence that US hastens healing of venous ulcers. Weak evidence of increased healing with US but needs confirmation in larger, high-quality RCTs.	Support	

Taradaj et al. ⁸⁰	2008	RCT	<i>n</i> = 81 patients	Ultrasound is efficient and useful only in conservatively treated venous leg ulcers, NOT in surgical treated patients.	Contradict
Bell et al. ⁸¹	2008	Retrospective series	<i>n</i> = 76 patients	US had mean area reduction = 80% in VLUs. Appears to improve healing but no comparative assessment with other treatment options.	Contradict
Kavros et al. ⁸²	2007	Clinical case series	<i>n</i> = 51 patients	Low-frequency US improves rate of healing and closure of lower extremity ulcers. Mean % volume reduction: 37.3% for standard of care vs. 94.9% for noncontact low-frequency ultrasound therapy (<i>p</i> < 0.0001).	Contradict
Darvall et al. ⁸³	2006	Clinical case series	<i>n</i> = 68 patients	Sclerotherapy plus compression healed 96% of ulcers within 3 months; 2 healed ulcers (7%) recurred at 12 months. Good especially for the elderly and frail.	Support
Pang et al. ⁸⁴	2010	Clinical case series	<i>n</i> = 130 patients	Wound closure seen in 67/82 (82%) of C6 patients. Four recurrent ulcers in follow-up period (up to 32 months). Sclerotherapy had comparable healing rates compared to other surgical treatments but with lower recurrence.	Support
Hertzman et al. ⁸⁵	2007	Clinical case series	<i>n</i> = 9 patients	Two of 13 ulcers healed one week after sclerotherapy, suggesting response is rapid.	Support
Jull et al. ⁸⁶	2007	Cochrane review	<i>n</i> = 12 trials	Pentoxifylline is more effective than placebo in terms of complete ulcer healing or significant improvement (RR = 1.7).	Support
Nelson et al. ⁸⁷	2007	RCT	<i>n</i> = 245 patients	Pentoxifylline + compression is more effective than placebo + compression (RR = 1.56). Pentoxifylline associated with nonsignificant increased ulcer healing. Statistically significant greater proportion of healing in pentoxifylline vs. placebo only in secondary adjusted analysis (Cox regression).	Support
Ferrara et al. ⁸⁸	2007	RCT	<i>n</i> = 98 patients	Addition of IV iloprost to compression and local therapy reduced healing time. After 100 days, 0% of treatment group and 15.9% of control group remained unclosed.	Contradict
Sclerotherapy may be useful as adjunct to compression therapy					
Pentoxifylline and compression therapy improves healing					
Eicosanoids (prostaglandins) or prostaglandin antagonists lack sufficient data					

Table 8. Guidelines for long term maintenance in the treatment of venous ulcers

Guideline	Study	Year	Type of study	Sample size	Results	Support or contradict
Compression stockings constantly and forever for healed or surgically repaired venous ulcers	Nelson et al. ⁸⁹	2006	RCT	n = 300 patients	Recurrence occurred in 39% of class 2 compression group and 32% of class 3 compression group (difference not statistically significant). 42% of class 3 and 28% of class 2 group did not comply with randomized compression class. Patients should wear highest level of compression that is comfortable.	Support
Exercise to increase calf muscle pump function helpful in long term maintenance and ulcer prevention	Moloney et al. ⁹⁰	2007	Cross-sectional study	n = 9 patients	No correlation seen between calf muscle volume and hemodynamic venous return in response to voluntary contraction (with or without compression bandages). Calf muscle volume only may not accurately indicate muscle functioning capability.	Contradict

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