AUSTRALIA AND NEW ZEALAND CLINICAL PRACTICE GUIDELINE FOR PREVENTION AND MANAGEMENT OF VENOUS LEG ULCERS

The Australian Wound Management Association Inc

The New Zealand Wound Care Society

CONTENTS

1. INTRODUCTION

1.1 Venous leg ulcers in the community

In Australia, the prevalence of venous leg ulcers (VLUs) is 1% in the overall population[1] and approximately 4% in adults aged over 65 years.[2] Venous leg ulcers have a high rate of recurrence (approximately 56% recur within 3 months[3]), thereby increasing their health burden. In Australia it has been estimated that management of venous ulcers accounts for $400 million annually in health care expenditure.[1] Aside from the direct financial burden of treating VLUs,[1] they give rise to chronic pain, reduced participation in the workforce and social life and an overall reduced quality of life for people inflicted.[4]

Within the New Zealand context, an Auckland study demonstrated the risk of developing VLUs increases dramatically with age, with people over 60 particularly at risk.[5] A capture-recapture analysis that incorporates an estimation of missed cases estimated a point prevalence of 2.48 per 1000 adults.[6] Similar to Australian trends, statistics from the New Zealand Ministry of Health describe a rapid increase in the number of people over 65 years. By 2040 it is estimated the proportion of people over 65 will have risen from 12% to 24%, while the over 85 year olds will have increased fourfold from 1.3% to 5.5%.

There is no specific published data on the incidence of VLUs in Aboriginal and Torres Strait Islander people in Australia or Maori people in New Zealand. The health of Indigenous populations differs from that of the general population in both countries.[7-9] In New Zealand, this disparity has been directly related to poor socio-economic status leading to susceptibility of disease, poorer health outcomes and a higher rate of chronic disease.[8, 9] In Australia, there is a higher prevalence of most long term health conditions in people from Aboriginal and Torres Strait Island backgrounds compared with non-Indigenous populations.[7, 10] The introduction of evidence based guidelines for leg ulcer assessment and management will assist clinical decision making and may help reduce health inequalities for Australian and New Zealand Indigenous populations.

The Council of Australian Governments (COAG) recognises the desire of Australians to maintain and where possible improve the quality of their lives as they age.[11] There is significant growth in the population of adults aged over 65 years and this is projected to increase almost three–fold over the next four decades. The projected cost of management of VLUs is significant. Currently one in eight Australians is aged over 65 years. By 2044 those aged over 65 years will account for one in four of the Australian population.[12] Over the next 20 years the ageing population will lead to a tripling of demand for government–funded care provision for those aged over 80 years.

The COAG recognises the implications of an ageing Australia including demands on infrastructure and community support; the impact of ageing in regional areas; and the availability of accessible, appropriate health and aged care services.[11] Explicit costs include but are not limited to hospital admissions, domiciliary nursing services, nurse practitioners, consumables, pathology and radiology investigations, general practitioner

and specialist consultations, pharmaceutical costs, and additional adjuvant therapies. The financial cost to both the individual and the community is enormous. However, the implicit costs to individuals and their families are difficult to measure. Access to appropriate services for diagnosis and management of VLUs for all Australians will significantly improve health outcomes and quality of life.

Statistics from the New Zealand Ministry of Health describe a trend similar to Australia, with a rapid increase in the number of people over 65 years. By 2040 the proportion of people over 65 will have risen from 12% to 24%, while the over 85 year olds will have increased fourfold from 1.3% to 5.5%.[13]

The Australian Wound Management Association (AWMA) and the New Zealand Wound Care Society (NZWCS) aims to increase awareness of VLUs within the community. A priority is to optimise the prevention, assessment and management of VLUs via the dissemination of best available evidence and to simplify clinical decision–making processes for health care professionals.

1.2 Endorsement and expiry date for the recommendations

This guideline was developed by the AWMA in conjunction with the NZWCS. The guideline presents a comprehensive review of the diagnosis, assessment, management and prevention of VLUs within the Australian and New Zealand healthcare context, based on the best available evidence available up to September 2009.

Australian and New Zealand clinical practice guideline for the prevention and management of venous leg ulcers was approved by the CEO of the National Health and Medical Research Council (NHMRC) on XXXXX, under section 14A of the *National Health and Medical Research Council Act 1992*. Approval for the guidelines by the NHMRC is granted for a period not exceeding five years, at which the date of approval expires. The NHMRC expects that the guideline will be reviewed, and revised if necessary, no less than once every five years. Readers should check with the AWMA and NZWCS websites for any reviews or updates to this guideline.

The guideline is designed to provide information to assist in decision-making and is based on the best information available at the date of compilation. The guideline is not intended to have a regulatory effect.

This document is a general guide to appropriate practice, to be implemented by a qualified health professional subject to his or her clinical judgment of each individual case and in consideration of the patient's personal preferences.

1.3 Acknowledgements

This project was financed by the AWMA and conducted by the AWMA experts in conjunction with NZWCS.

The following experts were involved in the appraisal of evidence and the development of the recommendations contained in the guideline as part of the Expert Working Committee:

Donna Angel, RN; BN; NP; PGraddip (Clin Spec); MSc (Nur); MRCNA

Judith Barker, Vice Chair; RN; NP; STN; BHlthSc (Nurs); MN(NP)

Debbie Blanchfield, RN; Masters of Wound Care

Keryln Carville, A/Professor; RN; STN (Cred); PhD

Roy Cochrane, Consumer representative

Michelle Gibb, RN; NP; Wound Care MNrsgSc(NP)

Emily Haesler, BN; PGradDipAdvNsg (Ger)

Cathy Hammond, RN, MN

David Hardman, Chair; MBBS(Hons); LLB (Hons); GradcertHE ; FRACS; FACLM; A/Professor

Susan Hillier, BappSc(Physiotherapy); PhD; NHMRC Guideline Consultant

Suzanne Kapp, BN; PGDip (AdvNsg); MNSci

Deane Larkman, BSci(Hons); GradDipCompStud; MInfTech

Judith Manning, RN; MA; BEd.

Bill McGuiness,RN; DipT; BN; MNS; PhD; A/Professor; AWMA President

Robyn Rayner, RN; BSc (Nursing); Postgrad Health Admin; Master of Wound Care

Jan Rice, RN; AMWA Cert. Plastic & Reconstructive Surgery; MRCNA; FAWMA

Pip Rutherford, RGON; BN; GradDip CaseManage; GradCert Wound Care; MN

Juliet Scott, RN**;** BAppSci (Prim Hlth); Grad Cert; Grad Dip DN

Jill Sparks, RN; MWoundManage

Sue Templeton, RN; BN; MNSc(NP)

Carolina Weller, BN; MEd(Research); GradCertHlthEd

Peter Wilkins, Consumer representative

Michael Woodward, MB; BS; FRACP; A/Professor; Past AWMA President.

The Expert Working Committee would also like to thank the following people for their advice and assistance in the development of this guideline:

Julie Betts (RN, NP, MN) and Margaret Broadbent (Chronic Care & Health Promotion, Aboriginal Strategy & Consultation Unit)

1.4 Commonly used abbreviations

4LB	four layer bandages/ing
ABPI	ankle brachial pressure index
AWMA	Australian Wound Management Association
CEAP	clinical severity, (a)etiology, anatomy, pathophysiology
CI	confidence interval
CWIP	Cardiff Wound Impact Schedule
CVI	chronic venous insufficiency
CVIQ	Chronic Venous Insufficiency Qeustionnaire
DVT	deep vein thrombosis
EBO	expert based opinion
EMLA	eutectic mixture of local anesthetic
GIT	gastrointestinal tract
HCSE	horse chestnut seed extract
ITT	intention to treat
LLLT	low level laser therapy
MPFF	micronised purified flavanoid fraction
NHMRC	The National Health and Medical Research Council
NNT	number needed to treat
NS	not statistically significant
NSBF	No Sting Barrier Film
NZWCS	New Zealand Wound Care Society
QOL	quality of life
RCT	randomised controlled trial
RR	relative risk
SR	systematic review
VLU	venous leg ulcer

1.5 Glossary

antibiotic	Substance or compound administered systemically or applied topically that acts selectively against bacteria.
antimicrobial	A term used to encompass antibiotics and antiseptics. A substance that non-selectively reduces the possibility of infection by inhibiting the growth of, or eradicating micro-organisms.
arterial disease	Impaired blood flow in the arteries that generally occurs due to a build up of plaque. Plaque is made up of fat, cholesterol, calcium, fibrous tissue, and other substances found in the blood.
atrophie blanche	A type of scarring that infrequently occurs on the lower leg associated with healing that occurs when blood flow is impaired. It appears ivory/white depressed atrophic plaques with prominent red blotching within the scar.
bioengineered skin grafts	Manufactured skin replacement products not derived from human or animal skin cells.
chronic venous insufficiency (CVI)	Chronic venous insufficiency is an advanced stage of venous disease that occurs over the long term.
extensibility	The ability of a bandage to increase its length in response to an applied force.
Indigenous	Australians from an Aboriginal and Torres Strait Island background and New Zealanders from a Maori background.
lipodermatosclerosis	A condition that affects the skin immediately above the ankle in patients with long-standing venous disease. Is fibrosis of the underlying sub-cutaneous tissue.
microcirculation	The flow of blood or lymph throughout the system of smaller vessels (diameter of 100µm or less) of the body.
macrocirculation	The large blood vessels that transport blood to the organs.
patient	Any person receiving health assessment, care or treatment.
post-thrombotic syndrome	Post-thrombotic syndrome is a term used to describe signs and symptoms that occur due to long-term complications of lower limb DVT. Signs and symptoms include leg aching and cramping, itching, heaviness skin discolouration and VLU.
resting pressure	The sub-bandage pressure experienced whilst the patient is at rest
standard care	The definition of standard care varied amongst the trials reported in the literature and has been described in reports of individual studies. In most instances, standard care for VLU consisted of

	wound cleanse with normal saline and/or water and a non-adherent dressing, either with or without compression therapy.
venous disease	Venous disease is related to or caused by pathology or functional abnormality in the veins that leads to sluggish venous blood flow. Either superficial or deep veins may be affected. Pathology includes venous obstruction (eg. from blood clotting), swelling of the veins or stretched/weakened venous valves.
venous hypertension	Elevated blood pressure in the veins that occurs due to venous obstruction (eg due to plaque) or incompetent venous valves. Pooling of the blood in the veins leads to an increase in pressure and, in the long term, venous disease.
venous tone	The degree of constriction experienced by a blood vessel relative to its maximal dilated state.
venous leg ulcer	Full thickness defect of the skin that persists due to venous disease on the lower leg.
working pressure	The sub-bandage pressure experienced as the patient walks.

2. SUMMARY OF RECOMMENDATIONS

RECOMMENDATIONS FOR PRIMARY PREVENTION OF VLUs	Grade
Adequate prevention and management of venous hypertension includes: • early detection and management of deep vein thrombosis • deep vein thrombosis prophylaxis • access to venous surgery and phlebology interventions.	**EBO**
Applying compression therapy is effective in preventing the initial development of a VLU.	**EBO**
There is inconsistent evidence on the effectiveness of phlebotics in preventing the development of VLUs in patients with venous disease.	**C**
RECOMMENDATIONS FOR ASSESSMENT, DIAGNOSIS AND REFERRAL FOR VLUs	Grade
All patients presenting with a leg ulcer should receive a comprehensive assessment by a health professional trained in the assessment and management of VLUs.	**EBO**
A comprehensive assessment should be made of the leg ulcer on initial presentation and at regular intervals thereafter to guide ongoing management.	**EBO**
CEAP classification could be used to evaluate and classify venous disease.	**EBO**
Local guidelines should provide clear indication of appropriate circumstances for referral to specialist health professionals.	**EBO**
RECOMMENDATIONS FOR TREATMENT OF VLUs	Grade
There is good evidence that applying compression therapy is effective in promoting healing in VLUs.	**B**
There is excellent evidence that no specific dressing product is superior for reducing healing time in VLUs. Dressings should be selected based on clinical assessment of the wound, cost, access and patient/health professional preferences.	**A**
The use of dressings or bandages impregnated with water soluble zinc may provide comfort and promote epithelialisation of a healthy granulated superficial VLU.	**EBO**
There is some evidence that topical pale sulphonated shale oil is more	**C**

effective than standard care for promoting healing in VLUs.	
Cleansing the leg and wound when dressings and bandages are changed is recommended.	**EBO**
Venous eczema and impaired peri-wound skin should be treated promptly.	**EBO**
There is weak evidence that topical barrier preparations reduce peri-wound erythema in patients with VLU.	**D**
There is some evidence that cadexomer iodine is more effective than standard care in the treatment of VLUs.	**C**
There is good evidence that silver products offer no benefit over standard care in reducing the healing time for VLUs.	**B**
There is evidence that honey offers no benefits over standard care in promoting healing in VLUs.	**A**
There is some evidence that other topical antimicrobial agents offer no advantage over standard care in improving VLUs healing.	**C**
There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden.	**EBO**
There is a concern that the use of topical antibiotics is associated with antibiotic resistance and sensitivities. Topical antibiotics have a very limited place in management of VLUs. Their use should be judicious.	**EBO**
There is some evidence that systemic antibiotics offer no advantage over standard care for reducing healing time of VLUs that show no clinical signs of infection.	**C**
There is weak evidence that enzymatic debriding agents have no effect in promoting healing in VLUs.	**D**
There is evidence that the benefits of leg elevation are related to changes in microcirculation in patients with VLUs.	**D**
Elevation is recommended to reduce lower limb oedema and promote VLU healing.	**EBO**
There is evidence that exercise improves calf muscle function and promotes venous blood flow.	**D**
Exercise is recommended as part of a management plan to promote healing in VLUs.	**EBO**
Optimising nutrition and hydration is important to the healing of VLUs.	**EBO**
There is some evidence that bi-layered bioengineered skin grafts are more effective than standard care in promoting healing in persistent VLUs.	**B**

There is excellent evidence that EMLA® cream is effective in reducing pain associated with the debridement of VLUs.	**A**
There is some evidence that an ibuprofen impregnated dressing reduces pain associated with VLUs.	**C**
There is weak evidence that electrotherapy may have an effect in reducing pain from VLUs.	**D**
There is good evidence that therapeutic ultrasound therapy is not related to an improvement in total ulcer healing but may slightly improve the percentage of healed ulcer area when used in combination with compression therapy.	**B**
There is some evidence that health professionals benefit from appropriate education on VLUs and their management. Patient outcomes may be superior when ulcer care is conducted by an appropriately trained health professional.	**C**
There is weak evidence that patients with VLUs benefit from appropriate education on their condition and its management.	**D**
Psychosocial assessment and support is an essential component in the patient's management.	**EBO**
There is good evidence that pentoxifylline is effective in promoting healing in VLUs.	**B**
There is weak evidence that micronised purified flavanoid fraction may decrease the healing time for VLUs.	**D**
RECOMMENDATIONS FOR PREVENTING RECURRENCE OF VLUs	Grade
The risk of VLU recurrence is reduced through the maintenance of practices that promote the health of the legs.	**EBO**
There is some evidence that compression systems are effective in reducing the risk of recurrence of VLUs.	**C**

3. BACKGROUND

3.1 Venous leg ulcers

The most common causes of lower extremity ulcers are venous hypertension, arterial disease, neuropathy (usually due to diabetes), pressure injury and ischaemia. Venous leg ulceration is a debilitating, chronic condition that affects people of all ages. Venous ulceration is generally considered to result from venous occlusion, incompetent calf muscle pump function or venous valvular failure that give rise to venous hypertension.[14] Venous hypertension accounts for nearly 80% of all leg ulcers.[15] Venous ulceration is strongly related to risk factors such as family history of, or previous surgery for varicose veins; venous disease; phlebitis; deep vein thrombosis (DVT); congestive cardiac failure; obesity; immobility[16] and previous leg injury.[15]

Currently VLU management is a significant burden on patients, their families and the health care system. Venous leg ulcers are the most common clinical wound problem seen in general practice and community nurses spend some 50% of their time treating leg ulcers.[17-19] Viewed in the context of an ageing Australian population, the financial and time burden of managing VLUs will remain a significant burden on the Australian health system into the future. Development of strategies to both reduce the initial development of VLUs and more effectively manage their treatment should be considered a national health priority.

Australian data indicates that approximately 99% of individuals with a VLU are aged 60 years or over.[20] Treatment costs average at $AUD 2300 per individual.[20] In 1996 the private hospital cost for a mean stay of 23.9 days for management of chronic leg ulceration was estimated to be $AUD 8734.[20] In the Silver Chain study conducted in 1996–97 the mean cost of treating a VLU in the community was $AUD 2300.[21] In 2000–01 a similar survey found the mean cost to heal any leg ulcer was $AUD 1436 when comprehensive assessment was implemented. This study, which was conducted in Department of Veterans' Affairs clients predominately aged over 80 years, demonstrated that implementation of comprehensive assessment and management strategies has the potential to significantly reduce the cost of leg ulcer treatment to the health care system.[22]

3.2 The need for a guideline

The following points indicate there is a high degree of urgency for a guideline on management of VLUs:

- There is a high incidence of VLUs and recurrence within the Australian and New Zealand communities.[1, 2]

- Many rural individuals, who have a high rate of hard-to-heal wounds, are disadvantaged due to inadequate access to health care diagnostic and management services.[23]
- No current national clinical guidelines exist for the Australian and New Zealand health care context. Clinical guidelines have been developed in other regions including New Zealand (1999); Europe (2003); Canada (2004); UK (2006) and Scotland (2010).[24-27]
- There is a lack of awareness within the broader community regarding the assessment, prevention and management of VLUs.
- There is a need to address variability in professional knowledge and inequity in implementation of best practice in the management of leg ulcers.
- Venous leg ulcer research is not a funding priority.
- An anticipated increase in VLUs amongst the ageing population will result in a substantial increase in health costs.

The guideline seeks to assist health professionals to:

- accurately diagnose and assess VLUs;
- optimise management and promote self management;
- prevent or delay complications associated with VLUs;
- optimise quality of life; and
- reduce the risk of recurrence.

3.3 Scope and target population

The guidelines are intended for use by health professionals including but not limited to medical and surgical specialists, general practitioners, allied health professionals, nurse practitioners, nurses, pharmacists, and Aboriginal health workers. The guidelines could also be used as an informative source for consumers.

Guidelines are intended to refer to people of all ages. The guidelines are intended for use in health care settings in metropolitan, regional, rural and remote areas of Australia and New Zealand.

The guidelines will seek to address issues specific to special populations including:

- People living in rural and remote areas;
- People from an Aboriginal and Torres Strait Islander background;
- People from a Maori background; and
- People from ethnically, culturally and linguistically diverse (CALD) backgrounds.

3.4 Focus of the guideline

The guideline focus is leg ulcers of a venous origin. Research relating to other types of leg ulcers was not included in the literature review.

The Expert Working Committee alerts the users of this guideline to the importance of accurate diagnosis of the type of ulcer being treated before implementing recommendations on the management of VLUs.

3.5 Process

The Expert Working Committee (Appendix One) who has overseen the development of the guideline and supporting documents comprised of a vascular surgeon, geriatrician, nurse practitioners, registered nurses, three consumer representatives, a medical research consultant and a National Health and Medical Research Council (NHMRC) advisor. The process used to develop the guideline is outlined in full detail in the process report (Appendix Two). This guideline is based on an evidence-based literature review conducted to NHMRC requirements.

Evidence statements

A systematic search for literature published from 1985 to 2009 was conducted and studies providing Level I evidence or Level II evidence on the NHMRC Levels of evidence scale[28] (see Appendix Two) were considered for inclusion. Individual research papers that met the inclusion criteria were critically appraised using checklists developed by SIGN[29] and given an overall descriptive quality of high, moderate or low.

For areas considered important by the Expert Working Committee but for which there was limited level I or II evidence available (eg. assessment of VLUs) relevant lower level evidence, including expert opinion and consensus guidelines, was utilised.

A summary of the supporting evidence used to grade the recommendation is provided with each evidence based research recommendation.

Recommendations

Each recommendation statement is supported by a grading from A to D (evidence based research) or EBO (expert based opinion) that reflects the strength of the recommendation and the trust or confidence health professionals can place in the recommendation when it is implemented in clinical practice. The recommendation grades are based on *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (2005)*[28] presented in Table one.

Table one: Recommendation grades[28]	
Evidence based research	
A	Excellent evidence - body of evidence can be trusted to guide practice
B	Good evidence - body of evidence can be trusted to guide practice in most situations
C	Some evidence - body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Weak evidence - body of evidence is weak and recommendation must be applied with caution
Expert based opinion	
EBO	Consensus evidence – there was insufficient evidence to make a graded recommendation due to insufficient or no evidence from systematic reviews or RCTs or the literature search not locating research addressing the field. The EBO recommendations are supported by all members of the Expert Working Committee.

The overall grade of each recommendation is based on a summation of an appraisal of individual components of the body of evidence on which the recommendation is based, including volume and consistency of the evidence. Table 3 shows the body of evidence assessment matrix, listing all the components that were considered when assessing the body of evidence, together with the grades used.[28]

Expert based opinion recommendations were developed through group discussion and email. The topics are those that were raised by members of the Expert Working Committee as being significant to the prevention, assessment and management of VLUs. In most instances they cover topics for which there is no high level evidence available, often because RCT designs are inappropriate for evaluation of the intervention. Discussion continued until consensus was reached.

The full grading for each of the research based recommendations is available in the companion document *Grading of the Australian and New Zealand research based recommendations for the prevention and management of venous leg ulcers*.

The Expert Working Committee supports all the recommendations and intends that they are used in conjunction with clinical judgement and clinician and patient preferences.

Practice tips

Most recommendations are accompanied by practice tips to assist clinicians to implement the recommendation. The practice tips were developed by the Expert Working Committee and reflect their considerable experience in assessing and managing VLUs in a range of clinical settings.

3.6 Limitations of the guideline

Medication information

The literature search was not designed to retrieve safety trials for pharmacological interventions. The guideline does not seek to provide full safety and usage information on any medications, dressings, devices or antiseptic solutions; however commonly available safety and usage tips have been included. The selection of pharmacological interventions is complex, and should consider the specific patients' clinical profile and personal preferences. The Expert Working Committee recommends consulting the National Prescribing Service (www.nps.org.au), Australian Therapeutic Guidelines (www.tg.org.au) or New Zealand Medicines and Medical Devices Safety Authority (www.medfsafe.govt.nz) for detailed prescribing information including:

- indications and usage;
- drug dosage and route of administration;
- contraindications and interactions;
- supervision and monitoring requirements; and
- product characteristics.

Wound care therapies

The literature search was not designed to retrieve safety trials for wound care therapies including antimicrobials and other topical preparations. All products should be used according to manufacturer's directions.

Search date

The guideline is based on the best evidence published from January 1985 to September 2009. Evidence published before and after these dates has not been reviewed or considered for the guideline.

Interventions and types of research

The search strategy was limited to specific levels of evidence. Research on interventions for managing and preventing VLUs was limited to NHMRC Level 1 and NHMRC Level 2 evidence. Only interventions that have been investigated using a RCT design or that had been included in a systematic review or meta-analysis were considered in the grading of the recommendations addressing interventions. Lower levels of evidence have been incorporated into practice tips related to prevention, diagnosis, assessment and management of VLUs.

Interventions that may have been investigated using different study designs are not represented in the guideline. The guideline is not intended to confirm or refute the

effectiveness, nor provide guidance on the use of interventions that have not been included, as the evidence has not been reviewed.

The guideline does not include surgical interventions for managing venous disease.

Lack of evidence

For some interventions there was limited evidence from which to draw conclusions on potential effectiveness. Some interventions have received a lower grade, not due to a lack of support, but due to lack of research that has been conducted on the intervention's efficacy. In addition, some interventions may provide benefit for outcomes that have not been addressed in the research (eg. patient well being). The Expert Working Committee acknowledges that **lack of evidence is not evidence of lack of effect**.

Some interventions were not supported or received lower grades due to lack of evidence of effect. The Expert Working Committee acknowledges that this refers to **lack of evidence of effect over placebo or standard therapy**, that is; patients may receive beneficial outcomes from the intervention; however, these do not exceed beneficial effects that can be expected from a placebo therapy or standard care.

Cost effectiveness

This guideline does not address cost effectiveness or the economic feasibility of the recommendations.

4. RECOMMENDATIONS FOR PRIMARY PREVENTION OF VLUs

4.1 Management of venous hypertension

Prevention of VLUs requires the management of underlying venous disease. Early detection, management and prevention of deep vein thrombosis (DVT) and consideration of treatment of venous hypertension with surgery and phlebotic interventions are important in the prevention of VLUs. Surgical interventions were beyond the scope of this guideline; however, the Expert Working Committee acknowledges the role that venous surgery plays in treating venous hypertension and preventing the development of VLUs.

The literature search did not identify any research related to the management of venous hypertension with the specific objective of preventing VLUs. However, the relationship between venous hypertension and VLUs is acknowledged in the literature and detection and management of the former is highlighted by the Expert Working Committee as a priority in the prevention of VLUs.

Adequate prevention and management of venous hypertension includes:

- **early detection and management of deep vein thrombosis**
- **deep vein thrombosis prophylaxis**
- **access to venous surgery and phlebology interventions. (EBO)**

4.2 Compression therapy

Compression therapy aims to promote venous return, reduce venous pressure and prevent venous stasis. Commencement of compression therapy in patients with signs and symptoms helps reduce the long term effects of venous disease. More information on compression therapy is provided in the recommendation for the treatment of VLUs.

There was insufficient evidence to make an evidence based recommendation on the use of compression for primary prevention of VLUs because no appropriate studies were identified in the literature search, possibly due to the limitations on population types. The Expert Working Committee reached consensus that compression therapy has a demonstrated effect in improving venous return and is an effective therapy to prevent the initial development of VLUs.

Applying compression therapy is effective in preventing the initial development of a VLU. (EBO)

Caution

Refer to the caution statement in the recommendation for use of compression therapy in the treatment of VLUs.

Practice tips

- Commence primary prevention compression therapy after a patient experiences DVT or severe leg trauma, or during prolonged immobility, especially when there is a past history of DVT.
- There is insufficient evidence on the most effective degree of compression required to prevent an initial ulcer; however the Expert Working Committee's consensus is that compression should be **18—30** mmHg at a minimum.
- Further practice tips can be found in the section on compression therapy for the treatment of VLUs.

Evidence statement

The literature search did not identify any studies specifically investigating the prevention of VLUs using compression therapy. The search may have failed to identify relevant studies if they did not list VLUs as an outcome measure in the abstract, or if they were conducted in populations without diagnosed CVI. The Expert Working Committee considered that compression therapy is effective in preventing the development of VLUs, for patients at high risk of VLU.

One good quality, randomised cross over trial[30] (n=125) compared the effectiveness of low grade compression (10 to 20 mmHG) stockings in reducing painful discomfort in female patients with early stage chronic venous disease. Participants were randomised to wear either knee–high low compression or placebo stockings. Results showed compression stockings were associated with significant improvement in pain (p=0.0215), heavy legs (p=0.0025), cramps (p=0.0379), ankle swelling (p=0.0240), mood (p<0.01), and daily work (p<0.05), but there was no differences in ratings of paresthesia. There was no significant difference in any of the objective outcome measures; however, at commencement of the trial venous filling time and pump power were within normal limits so there was limited opportunity for significant improvement.[30]

4.3 Phlebotics

Phlebotics are venoactive drugs that are reported to have effects on both the macrocirculation (eg. improving venous tone) and microcirculation (eg. decreasing capillary hyperpermeability). The group of drugs known as phlebotics consists of both natural flavonoids that are manufactured from plant extracts and synthetic products.[31]

There is inconsistent evidence on the effectiveness of phlebotics in preventing the development of VLUs in patients with venous disease. (Grade C)

Evidence statement

A Cochrane review[31] investigated the effectiveness of oral and topical phlebotics for treating CVI. One of the primary outcomes of the SR was prevention of VLUs, which was reported in two trials. The trials, conducted in participants with moderate CVI, were of moderate to low quality and of short duration (1 to 3 months) and all participants used concurrent compression therapy. The trials compared the effectiveness of diosmine, hidrosmine or rutosides (n=80 over two trials) to placebo (n=80 over two trials). Pooled findings showed no statistically significant effect for phlebotics compared to placebo (59 ulcers vs. 60 ulcers, fixed effects model RR 0.95; 95% CI 0.80 to 1.13, p=0.56). When analysis was restricted to the higher quality trial, the effect for phlebotics in preventing VLU bordered on significance (39 ulcers vs. 46 ulcers; RR 0.83, 95% CI 0.69 to 1.00, p=0.056). The safety analysis included data from all trials included within the review, most of which did not report ulcer development as an outcome measure. Pooled data from 13 studies found no significant difference in the rate of adverse events between phlebotics and placebo. The reviewers concluded that there was insufficient evidence to suggest that phlebotonics are effective in treating CVI; and the findings regarding effect in preventing VLUs were inconsistent.[31]

5. RECOMMENDATIONS FOR ASSESSMENT, DIAGNOSIS AND REFERRAL FOR VLUs

5.1 Initial and ongoing assessment

The optimal outcome for the patient with a VLU is facilitated by a continuous process of general, wound and environment assessment. These factors determine ulcer aetiology and wound healing and can inform the ongoing development of a treatment plan.[32]

Using a formal ulcer assessment process such as the New Zealand Leg Ulcer Pathway can simplify ongoing monitoring and assessment of ulcer. The VLU pathway provides a model for national/international analysis on venous ulcer management, complications, outcomes and resources. Venous leg ulcer pathways enable clinicians to compare outcomes, based on this VLU guideline, from different practice settings, treatment options, and demographic groups.

5.1.1 Patient assessment

Only one trial investigating methods of assessing patients with VLUs was identified in the literature search. The trial provided low quality evidence on the efficacy of pulse oximetry that was insufficient to make a research based recommendation. The Expert Working Committee concurs with other expert groups[25, 33-35] that patient assessment is crucial to the appropriate management of VLUs.

All patients presenting with a leg ulcer should receive a comprehensive assessment by a health professional trained in the assessment and management of VLUs. (EBO)

CEAP classification could be used to evaluate and classify venous disease. (EBO)

Essential in comprehensive assessment is the identification of the aetiology of the leg ulcer. Specifically, the use of compression therapy—the most effective treatment for VLU—can result in damage to the lower limb if applied incorrectly or to a non-venous leg ulcer.[34, 35] Assessment should seek to identify co-morbidities that may influence treatment of the VLU and/or require concurrent management. Co-morbidities that require further investigation and management include peripheral arterial disease, rheumatoid arthritis, vasculitis, a past history of multiple skin cancers(lesions)and diabetes mellitus.[34, 35]

Assessment should be conducted and documented by a health professional with education and experience in the management of VLUs.[25, 33-35] Assessment should include a patient history, examination of the leg, vascular assessment, biochemical analysis, microbiology, nutritional assessment, psychological and social assessments and past treatments for the ulceration.

5.1.1.1 Patient history

A clinical history indicative of a leg ulcer of venous origin includes:[35]

- confirmed venous disease
- family history of leg ulceration
- varicose veins
- previous or current DVT
- phlebitis
- surgery or trauma of the affected leg
- chest pain, haemoptysis or pulmonary embolism
- occupations of prolonged standing or sitting

The patient's leg ulcer history helps develop a comprehensive picture of the disease history. Information that can assist in diagnosis and development of a treatment plan includes: [35]

- the duration of the current ulcer,
- previous ulcers and the time they have taken to heal,
- time spent free of ulcers
- strategies used to manage previous ulcers.

5.1.1.2 Examination of the leg

A bilateral limb assessment[25, 33, 35] and gait assessment should be conducted. Signs and symptoms that are indicators of VLUs are outlined in Table two.

Table two: Clinical indicators of venous leg ulcers[36]	
Signs or symptoms in isolation may not be clinical indicators of VLUs. A grouping of the following signs and symptoms is indicative of an ulcer of venous origin.	
Predisposing factors	History of deep vein thrombosis (DVT) Valvular incompetence in the perforating veins Obesity Familial history of venous ulcers Trauma or surgery to the leg/s Decrease in calf muscle pump function
Associated changes in the leg	Firm ("brawny") oedema Haemosiderin deposition (reddish brown pigmentation) lipodermatosclerosis Evidence of healed ulcers Dilated and torturous superficial veins Limb may be warm Atrophie blanche Eczema Altered shape -Inverted "champagne bottle" Ankle flare
Ulcer location	Anterior to medial malleolus Pretibial area Generally lower third of leg
Ulcer characteristics	Irregular shaped edges Ruddy granulation tissue Absence of non-viable tissue
Pain	Pain varying from nil, to mild or extreme Pain may be relieved by elevation of leg
Surrounding area	Leaking oedema may result in maceration, pruritis and scale Hot itchiness of the leg
Pulses	Normal foot/leg pulses

5.1.1.3 Vascular assessment

The aim of vascular assessment is to distinguish arterial aetiologies from venous and other aetiologies and assess the extent of venous insufficiency. Table three describes investigations that can assist in the diagnosis of ulcer aetiology.

Table three: Investigations	
Blood pressure (BP) [25, 33, 35, 37]	Blood pressure measures th pressure of the blood on the vessel walls using a spyphgmomanometer. It provides an indication of possible presence of a range or cardiovascular diseases. The systolic BP is used in calculation ABPI.
Ankle brachial pressure index (ABPI) [25, 32-35, 37]	Non invasive vascular test which identifies large vessel peripheral arterial disease in the leg. It provides evidence of adequate arterial blood flow in the leg before use of compression therapy. Systolic BP is measured at the brachial artery and also at the ankle level. Using these two measurements ABPI is calculated as the the highest systolic blood pressure in both ankles (either dorsalis pedis or posterior tibial pressures) divided by the higher brachial systolic pressure in both arms, which is the best estimate of central systolic blood pressure.[38] Patients with a leg ulcer and an ABPI less than 1.0 or greater do not have evidence of arterial disease. [38]
Duplex ultrasound[32]	A non invasive test that combines ultrasound with Doppler ultrasonography in which the blood flow through arteries and veins can be investigated to reveal obstructions.[39] An ABPI can be performed at the same time.
Photoplethysmography (PPG)[32]	A non invasive test that measures venous refill time by using a small light probe that is placed on the surface of the skin just above the ankle. The test required the patient to perform calf muscle pump exercises for brief periods followed by rest.[40] The PPG probe measures the reduction in skin blood content following exercise. This determines the efficiency of the musculovenous pump and the presence of abnormal venous reflux. Patients with problems with the superficial or deep veins usually have poor emptying of the skin and abnormally rapid refilling usually less than 25 seconds
Pulse oximetry[34, 37]	Non invasive test that measures the red and infrared light absorption of oxygenated and deoxygenated haemoglobin in the digit. Oxygenated hemoglobin absorbs more infrared light and allows more red light to pass through a digit. Deoxygenated hemoglobin absorbs more red light and allows more infrared light to pass through the digit. There is insufficient evidence to recommend this investigation as the primary diagnostic tool. [34, 37]
Toe brachial pressure index (TBPI)	A non invasive test which measures arterial perfusion in the toes and feet. A toe cuff is applied to the hallux (or second toe if amputated) and the pressure is divided by the higher brachial systolic pressure in both arms, which is the best estimate of central systolic blood pressure. The TBPI is used to measure arterial perfusion in the feet and toes of patients with incompressible arteries due to calcification as seen in patients with diabetes and renal disease or with an ABPI of greater than 1.3 mmHg.{Wound Ostomy Continence Nurses Society, 2008 #211}
Transcutaneous oxygen (TcpO2)[32]	Measures the amount of oxygen reaching the skin through blood circulation. There is insufficient evidence to recommend this investigation as the primary diagnostic test. 34, 37

The CEAP classification is an international consensus method of assessing venous disease. It incorporates clinical, (a)aetiological, anatomical and pathophysical evaluation. The scale consists of seven classifications from C0 to C6 that describe the severity of the patient's venous disease. Patients presenting with one of more active VLU would be classified as C6, which describes the most severe venous disease. Patients with evidence of healed VLUs are categorised as C5 due to the high risk of recurrent ulceration.

Doppler ultrasound measurement of ankle brachial pressure index (ABPI) is the investigation most frequently used to identify arterial aetiology.[25, 33-35, 37] However, results can be unreliable when ABPI is conducted by untrained health professionals and in patients with calcification or diabetes.[35] It may also be difficult to perform accurately in patients with severe oedema, lymphoedema, very painful ulcers or extensive ulceration.[37]

Toe brachial pressure index (TBPI) may prove more accurate for identifying arterial perfusion the in feet and toes of patients with diabetes and renal disease with an ABPI of greater than 1.3 mmHg.{Wound Ostomy Continence Nurses Society, 2008 #211}

Pulse oximetry could be considered to support the diagnosis of a venous ulcer; however there is insufficient evidence to recommend this investigation as the primary diagnostic tool. [34, 37]

5.1.1.4 Biochemical analysis

Appropriate biochemical analysis may include:

- blood glucose[25, 32, 33, 35]
- haemoglobin[32]
- urea and electrolytes[32]
- plasma albumin[32]
- lipids[32]
- rheumatoid factor[32]
- auto antibodies[32]
- white blood cell count[32]
- erythroctye sedimentation rate[32]
- C-reactive protein[32]
- liver function tests[32]

5.1.1.5 Microbiology and histopathology

Microbiology assists in the identification of infection and histopathology can identify malignant or other aetiologies. Investigations may include:

- bacterial wound swab or biopsy for bacterial status[32]
- wound biopsy if malignancy or other aetiology is suspected[32, 34, 35]

5.1.1.6 Nutritional assessment

A nutritional assessment should be conducted.[25, 33] This may include:

- weight and/or body mass index (BMI)[25, 33, 35, 37]

- food and fluid intake[32]
- hair and skin changes[32]
- mini nutritional assessment[32]

5.1.1.7 Pain assessment

A pain assessment that investigates pain intensity with a validated pain scale should be conducted.[25, 32, 33, 35]

5.1.1.8 Psychosocial, quality of life and social assessments

Conduct psychosocial and social assessments using appropriate assessment tools.[25, 33] Appropriate assessments include:

- Mini mental examination[32]
- Hospital anxiety and depression scale[32]
- Hamilton scale[32]
- Quality of life scales for specific health populations,[4, 32] for example the the Cardiff Wound Impact Schedule (CWIS) and Chronic Venous Insufficiency Questionnaire (CVIQ) that have both been validated in patients with venous disease.[4]

Practice tips

- Bacterial swabs should only be taken when the ulcer shows clinical signs of infection.[34, 35]
- A structured, systematic leg ulcer assessment tool can assist in accurate and comprehensive assessment that is clearly documented.

Evidence statement

A low quality observational cohort trial[37] investigated the reliability of pulse oximetry in assessing patients prior to commencing treatment of leg ulcers. Pulse oximetry was compared with the gold standard, Doppler ABPI. Participants (n=39) were attending a leg ulcer clinic; however their specific selection for inclusion in the trial was not reported. Pulse oximetry and ABPI were both measured after the patient had reclined at a 40 angle for 15 minutes. Pulse oximetry was conducted on the patient's toe and finger to determine a toe finger oximetry index (TFOI) that was reported to be analogous to an ABPI measurement. Analysis of the ratio of TFOI and Doppler ABPI showed only fair agreement (kappa 0.29, weighted kappa 0.39). The researchers suggested pulse oximetry could be used to determine whether compression therapy is appropriate for patients presenting with leg ulcers.[37]

A low quality SR[4] reported on the life impact of VLUs. Participants in the research included in the review were primarily older females. The review reports that two psychosocial assessment tools are particularly relevant to populations with VLU—the Cardiff Wound Impact Schedule (CWIS) and Chronic Venous Insufficiency Questionnaire (CVIQ). The CWIS is specific to, and has been validated in VLU populations. It includes sections on physical symptoms and daily living, social life, well being and overall health related QOL. The CVIQ has been validation in populations with venous insufficiency and for people with a VLU, offers the advantage of being able to compare scores to pre-ulceration psychosocial status. The review concluded that patients with VLU have a

significantly lower QOL compared with healthy populations and assessment with appropriately validated psychosocial tools is desirable.[4]

5.1.2 Wound assessment

A comprehensive assessment of the leg ulcer assists in developing the most appropriate management plan and ongoing monitoring of wound healing.

The literature search did not identify literature meeting the inclusion criteria. Identified papers that have been excluded from the review provided descriptive evidence for some assessment strategies; however the evidence was of low quality and provided an insufficient foundation on which a research based recommendation could be made. The Expert Working Committee concurs with other expert groups[25, 33-35] that patient assessment is crucial to the appropriate management of VLUs.

A comprehensive assessment should be made of the leg ulcer on initial presentation and at regular intervals thereafter to guide ongoing management. (EBO)

Ulcer assessment includes:

- measurement of the wound size[25, 33-35]
- amount and type of exudate[25, 33]
- appearance of the wound bed[25, 33, 34]
- condition of the wound edges[25, 33, 34]
- signs of clinical infection (eg. inflammation, increased pain, increased exudate, pyrexia)[25, 33, 34]
- peri-wound skin[32]
- woundodour[32]

Practice tips

- The acronym HEIDI can be used to guide assessment and diagnosis:
    - History
    - Examination
    - Investigations
    - Diagnosis
    - Indicators

- Measurement of the ulcer should include length, width[25, 33, 34] and depth and will be guided by experience, availability of resources and local guidelines.[35]
- Tracing the ulcer margins provide a reliable indication of the progress of wound healing.[25, 33, 34] Other tecniques for measuring ulcer size include measurement using a disposable ruler or photography including a scale strip.[41]

- Computerised calculation (planimetry) of the ulcer area from wound tracings or digital photography could be considered if resources are available.[41]
- The patient's position should be replicated as closely as possible when re-measuring the ulcer to increase the accuracy of results.[41]
- Characteristics of the wound and peri-wound should be documented regularly. The documentation system used should allow comparison of ulcer characteristics over time to evaluate progress.[41]
- When ongoing assessment indicates that the VLU is not healing at an optimal rate (25% improvement within 4 weeks[42]) dressing choice and overall management may need reviewing.

5.2 Differential diagnosis

The Expert Working Committee alerts the users of this guideline to the importance of accurate diagnosis of the type of ulcer being treated before implementing recommendations on the management of VLUs.

There are many conditions that are associated with leg ulcers. Some of the more commonly encountered differential diagnoses including:[43]

- Malignant ulcers
- Blood disorders
- Infection
- Metabolic disorders
- Iatrogenic
- Self-inflicted

Practice tips

- Other pathophysiology should be considered when VLUs fail to heal, recur, or remain persistently infected. Appropriate investigations include plain X-rays, bone scan or MRI but investigation is often best directed by a specialist with appropriate expertise in this area.
- When ongoing assessment indicates that the VLU is not healing at an optimal rate (25% improvement within 4 weeks[42]) the diagnosis may need to be reviewed.

5.3 Referral

A multidisciplinary approach to management is essential to optimise healing and the patient's long term outcomes.

No studies that met the inclusion criteria of the review addressed referral of patients with VLUs. The Expert Working Committee reached consensus that referral to specialists should be considered for some patients.

Local guidelines should provide clear indication of appropriate circumstances for referral to specialist health professionals. (EBO)

Recognised criteria for specialist referral include:

- diagnostic uncertainty[35]
- atypical ulceration distribution[34]
- suspicion of malignancy[34, 35]
- treatment of underlying conditions including diabetes, rheumatoid arthritis and vasculitis[34, 35]
- peripheral arterial disease indicated by an ABPI less than 0.8[34, 35]
- ABPI above 1.2[35]
- contact dermatitis[34, 35]
- ulcers that have not healed within 3 months[35]
- recurring ulceration[35]
- healed ulcers with a view to venous surgery[35]
- antibiotic resistant infected ulcers
- ulcers causing considerable pain that persists despite use of usual doses of simple analgesia.

Practice tips

- Early referral to appropriate specialists and/or a local leg ulcer clinic is essential to ensure appropriate management.
- Patients presenting with a traumatic injury and history of venous disease should be referred to a local leg ulcer specialist service or community nursing service immediately.
- In locations where specialist services are not readily available (eg. rural or remote) consultation could be made with a specialist using telecommunication services. One study indicated that advice from a specialist could be effectively implemented at a local level using digital images of the ulcer.[44] However, this is not to be considered a replacement for specialist review.
- Offer further investigations for venous hypertension for patients with healed VLUs and no previous diagnosis.

6. RECOMMENDATIONS FOR MANAGEMENT OF VLUs

As outlined in the limitations, for some interventions there was limited evidence from which to draw conclusions on potential effectiveness. Some interventions have received a lower grade, not due to a lack of support, but due to lack of research that has been conducted on the efficacy of the intervention. In addition, some interventions may provide benefit for outcomes that have not been addressed in the research (eg. patient well being). The Expert Working Committee acknowledges that **lack of evidence is not evidence of lack of effect**.

Some interventions were not supported or received lower grades due to lack of evidence of effect. The Expert Working Committee acknowledges that this refers to **lack of evidence of effect over placebo or standard therapy**, that is; patients may receive beneficial outcomes from the intervention; however, these do not exceed beneficial effects that can be expected from a placebo therapy or standard care.

6.1 Compression therapy

Compression therapy aims to promote venous return, reduce venous pressure and prevent venous stasis. To achieve this, bandages or stockings are applied to the legs, preferably with graduated compression with the greatest magnitude of compression at the ankle and pressure magnitude decreasing to the calf.

The recommendation on the use of compression in the management of VLUs was based on an excellent evidence base consisting of good quality SRs reporting moderate quality RCTs. The evidence was not always consistent, but generally showed that compression is effective.

There is good evidence that applying compression therapy is effective in promoting healing in VLUs. (Grade B)

Caution

Trials investigating the effectiveness of compression therapy were generally conducted in populations without diabetes, cardiovascular disease, malignancy or mixed aetiology ulcers. Compression should be used with greater caution in these populations.[24] Compression should be used with caution in patients with clinically infected ulcers and/or cellulitis. These ulcers require close monitoring that may not be adequately achieved with some compression systems. Although compression may relieve oedema, patients with oedematous limbs should be monitored carefully when compression therapy commences due to a risk of fluid overloading the systemic circulation. High levels of pain following application of compression should be assessed urgently.

Compression therapy should only be used in patients who can detect increasing pain or complications and for whom the compression system can promptly be removed (eg. by the patient or another person).[24] Potential modifications in the high risk patient include:

- Increased frequency of review by a health professional specialised in VLU management
- Increased frequency of assessment for signs and symptoms of complications (eg pain, pallor, paraesthesia, impaired capillary return)
- Reduction of the level of compression
- Increased padding/comfort layer under the compression
- Reviewing the initial diagnosis
- Referreral to a pain management specialist if the patient continues to experience severe pain.

6.1.1 Compression systems

Compression systems are categorised according to the amount of support applied to the leg. The description from the manufacturer may not accurately reflect the level of compression applied as other considerations will influence the pressure level, for example the extent to which the bandaging or hosiery system has been used (eg. number of times it has been washed), the application technique and the skill of the clinician applying the compression system.[45]

Table four: Examples of available compression systems

Compression system	Also referred to as	Description and function
Multi layer bandages	Two, three and four layer bandaging	Consists of several layers which use a combination of elastic and inelastic bandages. High resting pressure and high working pressure.
Elastic compression bandages	Long stretch bandages	Bandages with elastomers and high extensibility. High resting pressure and high working pressure.
Inelastic compression bandages	Short stretch bandages	Bandages with minimal or no elastomers. Low extensibility and high stiffness. Low resting pressure and high working pressure.
Single-component systems		Compression bandaging system that has only one layer or aspect to the system. Most bandage systems currently used in practice include a padding layer so are not described as single component systems.
Multi-component systems		A compression system with more than one layer or aspect. Most bandaging systems include at least a padding layer and bandages so are classified as multi-component systems.

Medical grade compression hosiery	Tubular stockings, compression stockings, tubular compression	Available in a range of compressions that are defined by manufacturers using various different scales. Two commonly used scales include: Scale one:[46] • extra light (5mm Hg) • light (15 mm Hg) • mild (18—24 mm Hg) • moderate (20—40 mmHg) • strong (40—60 mmHg) • very strong (>60 mmHg) Scale two: • Class I • Class II • Class III • Class IV
Unna boot	Unna's boot	Although there are several systems referred to as Unna's boot it is commonly a gauze bandage impregnated with zinc paste under a cohesive inelastic bandage.
Pneumatic compression	Pump compression	Pressure is applied via a boot inflated by a machine either continuously, intermittently or in sequential cycles.

Practice tips

- Incorrectly applied compression systems may not be effective. Clinicians and patients require education and experience to ensure that bandaging is applied correctly and to achieve an appropriate level of compression.[47]
- There is minimal evidence to suggest that there is a superior compression system. Moderate and low quality RCTs suggest that:
    - a single bandage component compression system is less effective than four layer bandaging[48, 49]
    - different variations of four layer bandage systems are as effective as each other[48, 49]
    - two layer medical grade compression hosiery is more effective than inelastic (short stretch) bandaging[48]
    - medical grade compression hosiery is comparable to multi layer bandaging systems in their effectiveness[50]
    - when using two or three layer component compression systems, an elastic component is more effective than an inelastic component.[48]
    - two layer and four layer bandaging systems have similar effectiveness[45, 51]
    - pneumatic compression is as effective as bandaging systems[52]
- In the absence of any good quality evidence supporting specific compression systems, the Expert Working Committee recommend that choice of a compression system should be made in consideration of:

- shape of the leg
- patient tolerance and preference
- clinician experience in application
- the environment (eg. temperature)
- ease of application and removal
- access to systems
- cost

- There is insufficient evidence on the most effective degree of compression required to achieve healing. The Expert Working Committee's consensus is that efficacy is related to the pressure of compression and should be attained through a garment designed for VLU management.
- Anti-embolic stockings are not designed for treating VLUs.
- Consider the shape of the patient's leg and comfort in selecting a compression system. For example:
  - Unusually shaped legs may require custom-made medical grade compression hosiery
  - Some patients benefit from additional support in particular areas (eg. the foot arch)
  - Adaptations such as the Southland Snail[53] or stasis pads can ensure pressure is applied evenly
- A sub-bandage pressure gauge can be used to determine the effectiveness of the bandaging application; however, ongoing monitoring of sub-bandage pressure does not influence the effectiveness of the bandaging.[47]
- There is some evidence that medical grade compression hosiery is associated with less pain than compression bandaging.[48]
- Compression stockings, socks and bandages should be replaced regularly. For most patients this will be two to three pairs of stockings or socks per year. Bandages should be applied, cared for and laundered according to manufacturers' instructions and replaced when bandaging integrity is compromised.
- Various devices and styles of stocking are available to assist in the donning and doffing of compression hosiery.

Evidence statement

One good quality systematic review[45] reported the results from 7 moderate and low quality RCTs investigating the effect of compression bandaging compared to usual care (primary dressing). The trials used different methods and compression techniques over different periods of time and results were not suitable for pooling. In one trial (n=36) Unna's boot was found to be more effective than a polyurethane foam dressing for completed healed ulcers after 12 months (RR 2.30; 95% CI 1.29 to 4.10, p=0.0047). In one trial comparing four layer bandaging (4LB) to usual care (n=36) compression therapy was related to greater healing at three months (RR 4.0 95% CI 1.35 to 11.82,

p=0.01). Another trial (n=36) found 4LB was no different to usual care for complete healing rate at 12 months (RR 1.18, 95% CI 0.96 to 1.47, p=0.12); however post-hoc analyses adjusting for patient age and baseline ulcer condition found healing was faster in the compression group. In a larger trial (n=200) comparing 4LB to standard care, there was significantly (p=0.06) faster healing in the participants receiving compression. A trial comparing short stretch bandage (SSB) to usual care (n=53) found greater numbers of complete healing at three months in those receiving compression (71% versus 25%). The other trials were small, had uneven groups and were at a high risk of bias.[45]

A second good quality systematic review and meta analysis[49] supported these findings. This earlier review[49] identified 8 trials, 5 of which are reported by O'Meara et al.[45] Pooled results from three trials showed no statistically significant difference between Unna's boot and other methods of compression (OR 5.8, p=0.16).[49]

One good quality cross-over RCT (n=81)[51] reported the effectiveness of two layer bandaging compression system compared to 4-layer bandaging in complete VLU healing. The trial was designed to measure the difference in bandage slippage. Although there was less bandage slippage for the two layer bandaging system there was no significant difference in ulcer healing rates. Patients preferred the two layer bandaging system. The trial was sponsored by a product manufacturer.[51]

One moderate quality RCT[52] (n=16) investigated the effectiveness of intermittent pump compression compared to compression bandaging. The researchers reported no significant difference between groups in ulcer size or leg volume, with both groups achieving a significant reduction (p<0.012) in ulcer size after 6 months. The trial was inadequately powered and did not report on adverse events.[52]

One low quality SR[47] reported on studies investigating training of nurses applying compression bandaging. The review included three pre-test post-test trials that assessed the amount of pressure applied. The three small studies reported that clinical bandaging skills can be improved through education programs however the effects may not be sustained beyond 10 weeks. None of the trials were randomised or adequately powered.[47]

6.2 Dressings and topical treatments

6.2.1 Dressings

Dressings or devices are applied to a wound in order to promote an optimal wound healing environment. Chronic wound healing is based on the principles of moist wound healing.[54]

There is no evidence to suggest that there is a superior dressing. There is also no evidence that there is a superior dressing for the management of heavily exudating ulcers. Dressings that are manufactured with absorption capacity for a heavily exudating wound are equally effective in promoting wound healing under compression.[55-57]

The recommendation that there is no specific superior dressing for managing VLUs is underpinned by five SRs[58-62] including over 40 moderate and low quality RCTs. Most trials showed that there was no difference between specific dressing products. When an

effect was shown the trial was more likely to be subject to bias. Dressing products should be used in conjunction with compression therapy unless there are contraindications.

There is excellent evidence that no specific dressing product is superior for reducing healing time in VLUs. Dressings should be selected based on clinical assessment of the wound, cost, access and patient/health professional preferences. (Grade A)

Caution

Trials investigating the effectiveness of primary dressings were generally conducted in populations without clinically infected ulcers or severe cellulitis or erythema on admission to the trial. Some of the trials were conducted in populations with heavily exudating ulcers.

Withdrawal from trials due to the experience of adverse events was high (above 20% for most trials). Adverse events commonly reported in RCTs included local infection, hypersensitivity, eczema, erythema and maceration. However, adverse events were not significantly more likely to occur with any specific type of primary dressing.[54, 57, 60, 63, 64]

Practice tips

- There should be some form of dressing between the compression layer and the VLU.
- Low quality RCTs suggested that clinicians and patients may have preferences for particular dressings over others, although preferences did not consistently support any specific dressing. Characteristics that are likely to influence preference include: [55-57, 64, 65]
    - ease of application and removal
    - ability to control exudate
    - pain experienced on dressing changes
    - appearance of the dressing
    - accessibility
- In the absence of any good quality evidence supporting specific primary dressings, the Expert Working Committee recommends that choice of a primary dressing should be made in consideration of:
    - amount of wound exudate
    - patient tolerance and preference
    - skill and knowledge of the health professional
    - level of bacterial burden
    - cost
    - presence of pain

- Select a dressing that does not adhere to the wound bed.
- Dressings that are less bulky in appearance will assist in maintaining optimal compression levels. One study showed less bulky dressings are preferred by patients and may increase quality of life.[56]
- If the wound is exudating heavily, select a dressing that is reported to have a high absorptive capacity.[55-57]
- Prolonged or continued heavy wound exudate should be investigated and managed appropriately.

Evidence statement

One good quality SR[62] of 42 primarily low quality trials including 3001 participants with VLU. The review concluded that there is no evidence that any dressing product is superior to others. The reviewers suggest that in light of lack of evidence of superiority of any product, choice of dressing should be based on convenience, access and cost effectiveness. [62] Results are summarised below.

Eight RCTs (n=792) comparing hydrocolloid dressings to low adherent dressings on total ulcer healing over 4 to 12 weeks were included in meta-analysis. The difference in complete healing was not significant (eight trials, significant heterogeneity, RR1.02 95% CI 0.83 to 1.25, p=0.88; seven trials, no hetergenity, RR 0.98, 95% CI 0.85 to 1.12).

Pooled results from four RCTs (n=311) compared hydrocolloid dressings to foam dressings for 12 to 13 weeks showed no difference in complete healing at 12 weeks (RR 0.98 95% CI 0.79 to 1.22, p=0.87). Two RCTs (n=80) compared hydrocolloid dressings to alginate dressings. Pooled analysis showed a high heterogeneity and no significant difference in healing (RR 0.92 95% CI 0.48 to 1.69). Two RCTs (n=69) comparing different hydrocolloid products to each other were pooled in meta-analysis. There was high heterogeneity and no difference between products for complete healing over 8 weeks. (RR 1.56, 95% CI 0.67 to 3.63). Five additional small (n = 28 to 153) trials comparing hydrocolloid dressings to hydrogel, gauze, lyophilised collagen and magnesium sulphate paste beneath gauze showed no significant differences in complete ulcer healing. [62]

The results from two RCTs (n=203) comparing foam dressings to low adherent dressings for 12 and 17 weeks were pooled in meta-analysis and showed no significant difference in healing (RR RR 1.35 95% CI 0.93 to 1.94). Pooled results of two trials (n=136) found no significant difference in ulcer healing between products (RR 1.2, 95% CI 0.77 to 1.87, no heterogeneity). [62]

Five trials investigated hydrogel compared to low adherent dressings, a miscellaneous dressing and other hydrogel products. The trial on miscellaneous dressings (porcine skin and aluminium foil dressing) was small (n=53) and did not report total ulcers healed. There was two RCTs comparing different types of hydrogel; however meta-analysis was not possible due to incomplete data. Results reported in the systematic review state there was no significant difference between different hydrogels. Pooled data for two trials (n=151) comparing hydrogels to low adherent dressings for 12 weeks showed no significant difference between the products in complete ulcer healing (RR 1.53, 95% CI 0.96 to 2.42, no heterogeneity). [62]

One trial (n=60) comparing alginate to low adhesive dressings and another trial comparing two types of alginate dressings both showed no difference in healing rates. [62] One low quality RCT (n=95) compared cadoximer iodine powder to standard treatment. There was a 34% reduction in

mean percentage of ulcer area cadoximer iodine group compared to a 5% increase in the standard therapy group after 6 weeks of treatment. One RCT (n=24 ulcers) compared a hyaluronan derivative fleece dressing to a paraffin gauze dressing used for 8 weeks. Individual ulcers were the end-point in the trial, with some participants (n=17) having more than one ulcer. The ITT analysis showed a significant reduction in the mean ulcer area ($p<0.002$) favouring the hyaluronan dressing; however comparability at baseline was not reported. One low quality RCT (n=40) compared a polyamide active charcoal dressing to a dressing applied according to the stage of healing showed no significant difference between the two dressing types over 6 weeks.[62]

Another good quality SR[66] supported the conclusions of the Palfreyman[62] review. This review included 48 studies investigating the effectiveness of dressing and topical preparations in the management of VLUs. The studies, many of which were included in Palfreyman[62] review, were generally of low to moderate quality. Nine RCTs compared hydrocolloid dressings to traditional dressings, of which one trial reported a significant result (hydrocolloids as superior to paraffin impregnated tulle); however the participants were not equivalent on baseline characteristics (ulcer size) in the trial. Eight of the trials provided data on ulcer healing and were pooled in a meta-analysis using a random effects model which showed significant heterogeneity. The pooled analysis showed no significant difference between hydrocolloids and traditional dressings (OR 1.4, 95% CI 0.83 to 2.34). Eleven RCTs made head-to-head comparisons of specific dressing types including collagen sponge dressing compared with dextranomer beads; lyophilised collagen dressing compared with hydrocolloid dressing; hydropolymer dressing compared with hydrocolloid dressing; hydrocolloid dressing compared to alginate dressing; four trials comparing different hydrocolloid types; and two trials comparing hydrocolloid to foam dressings. One trial (collagen sponge dressing compared with dextranomer beads) reported shorter healing times for hydrocolloid dressings, but results in the other trials were insignificant.[66]

A moderate quality SR[61] of low quality studies included 20 mostly low quality RCTs, of which five showed a statistically significant improvement in healing rate associated with the experimental dressing. Nine RCTs investigating semi-occlusive dressings were reported; however the trials were heterogeneous and results were unable to be pooled. Graphical reporting of the results from individual trials indicated that none of the 9 studies showed a statistically significant effect. Five RCTs investigating human skin equivalent (HSE) dressings were reported; however the trials heterogeneous and results were unable to be pooled in meta analysis. One of the trials showed a significant result in favour of HSE dressings. Eight trials investigated growth factor (GF) dressings, of which only two showed significant results. A pooled analysis from the eight RCTs using a random effects model favoured GF dressings over control dressings (eg. gauze pad, Adaptic™, hydrocolloid). GF dressings were superior for total healing, with a risk ratio of approximately 0.8 (reported graphically). Frequency of dressing changes and the control dressing varied between trials.[61]

A second moderate quality SR[60] investigating the effectiveness of dressing products included 26 primarily low quality RCTs, many of which were included in the review by O'Donnell and Lau.[61] Most of the trials excluded participants with ABPI < 0.80 and with chronic or serious disease including diabetes. Inclusion criteria for ulcers ranged between the trials, with some excluding ulcers greater than $10cm^2$ and other trials limiting inclusion to ulcers less than $100cm^2$. Some trials excluded infected ulcers. Although there was a range in the severity of ulcers being treated in these trials, there was no significant heterogeneity. Results from 8 RCTs (n=397) comparing hydrocolloid dressings to conventional dressings (e.g. gauze with paraffin or povidone iodine, non–adherent knitted viscose, paraffin–soaked gauze) for 10 weeks to 6 months were pooled. Most of the trials had non–significant results, and the pooled result for proportion of ulcers healed at

completion also showed no significant difference (RR 0.99, 95% CI 0.85 to 1.15, p=0.90). Six RCTs compared hydrocolloid dressings to either polyurethane, another hydrocolloid or alginate dressings for 6 to 16 weeks. Pooled results showed no statistically significant difference in number of ulcers healed (RR 1.13, 95% CI 0.86 to 1.47, p=0.40). Results from 3 RCTs (n= 238) investigating polyurethane dressings compared to traditional dressing types (moist gauze, paraffin–soaked gauze, and non–adherent knitted viscose) for 12 weeks to 12 months were pooled. No significant difference in proportion of ulcers healed at the completion was found (RR 0.92; 95% CI 0.14 to 1.98, p=0.80).[60]

One low quality SR[59] included 16 trials that reported on the use of dressing products for managing VLUs. Papers ranged from experimental studies to case reports and the quality of evidence was indeterminable. The reviewers concluded that simple, non-adherent dressings that are of low cost and acceptable to the patient are the most appropriate type for treating VLU. Polyurethane foam, hydrocolloid and calcium alginate are recommended as the best options, with hydrofiber and calcium alginate dressings recommended for heavy exudate and either polyurethane foam for low to moderate exudate. However, these recommendations should be considered cautiously due to the poor quality of this review, and the restriction of evidence to products available in Brazil in 2003.[59]

One low quality, unblinded RCT[58] investigated the efficacy of a biocellulose wound dressing (BWD XCELL®) compared to standard care of an Adaptic™ dressing in 24 patients diagnosed with CVI who had VLUs of at least 2 months duration that were considered to require debridement. After 12 weeks treatment with weekly dressing changes and concurrent compression therapy, the results showed no significant difference in wound healing time, oedema or exudate, and although pain was lower in those treated with the biocellulose wound dressing, this only reached significance at some time points.[58]

A low quality RCT[54] that failed to report methods of randomisation, allocation concealment or blinding or baseline comparability compared a lipidcolloid dressing (Urgotul®) to Duoderm® used in conjunction with compression for up to 8 weeks. Participants (n=91) had an ABPI of at least 0.8, ulcer duration of 2 to 18 months and ulcer size between 4 and 40cm^2. Ulcer area was measured weekly using wound tracings, photography and planimetry. At 8 weeks there was no significant difference in reduction of ulcer surface area (Urogtul 61.3 ± 39.7%versus Duoderm 52.1 ± 66.2%) or mean time to healing (Urgotul 33.3 ± 11.0 days versus Duoderm 29.8 ± 7.1 days).[54]

A low quality, unblinded RCT[65] compared the effectiveness of a lipidcolloid dressing impregnated with nano-oligosaccharide factor (NOSF) compared to an oxidised regenerated cellulose (ORC) dressing. Participants had an ABPI of at least 0.8 and had been compliant with compression therapy for at least 2 months, mean ulcer duration of 11 months, mean ulcer size at baseline of 10cm^2 and 61% of ulcers were recurrent. Wounds were redressed every 3 days following mechanical debridement as required for 12 weeks or until the wound was completely reepithelialised. More than 20% of participants withdrew from the trial, primarily due to local adverse events. The ITT analysis showed significantly greater reduction in wound area for the NOSF dressing compared to the ORC dressing (54.4% vs. 12.9%; p=0.00286). Complete wound healing was not significantly different between the two groups. Participants reported less difficulty in removing dressings and less pain during dressing changes in the NOSF group.[65]

A low quality, un-blinded RCT[67] investigated healing rate of VLUs treated with an oxidised regenerated cellulose collagen matrix dressing compared to a hydrocolloid dressing. The researchers did not provide a description of randomisation, allocation concealment or baseline comparability of participants. Participants were 27 patients with CVI who had a VLU of between 30

days and 3 months duration and no systemic inflammatory disease or malignancy. The trial lasted for 12 weeks and wounds were assessed on days 5, 14 and 28 for wound size (method not reported) and MMP-2, gelatinase, elastase and plasmin activity from exudates samples. It is unclear if any participants withdrew from the trial or if the analysis included all randomised participants and the trial was likely to be underpowered to measure a significant effect. The group treated with the oxidised regenerated cellulose collagen matrix dressing had a reduction in MMP-2, gelatinase, elastase and plasmin activity compared to the control group; however this did not translate to a significant difference in wound healing time. Adverse events were not reported.[67]

In a low quality RCT[64] researchers investigated the effectiveness of a hydrocellular foam dressing compared to composite foam dressing for managing VLUs. Participants had an ABPI of at least 0.8, no clinical signs of infection and a venous ulcer between 2 and 165 cm^2. Participants with diabetes were eligible if their condition was well controlled. In the experimental group VLUs were dressed with a foam composite dressing (Versiva; n=55) and control VLUs (n=52) received an adhesive hydrocellular dressing (Allevyn; n=52). Both groups wore compression bandaging and dressings were changed as required or every 7 days for 12 weeks or until complete ulcer healing was achieved. Wound tracing were performed every 14 days. There was no significant difference primary outcome measures related to wound healing including rate of healing (0.41cm^2 per week vs. 0.43 cm^2 per week, p=0.13); percentage change per week (median 7.3% vs. 6.1%, p= 0.27) or percentage of ulcers completely healed (38.2% vs. 38.5%; p= 0.96). Investigators reported significant preference for the hydrocellular foam dressing for some subjectively rated variables (e.g. conformability, p=0.05; ease of application, p=0.01) but there was no difference in ratings for exudate absorption, protection of surrounding skin, non-traumatic dressing removal, and ease of removal.

A low quality RCT[63] compared the efficacy of two different foam dressings, Allevyn (n=81) and Mepilex (n=75), for the healing of VLUs. Participants were 156 adult patients with an ABPI of at least 0.8 and a VLU of between 2 and 52 weeks duration. Participants were concurrently randomised to receive one of two types of compression bandaging. The primary outcome measure was complete ulcer closure, defined as complete re-epithelialisation of the reference limb, and pain assessed using McGill pain questionnaire and a VAS was a secondary outcome measure. After 24 weeks of therapy, the hazard ratio favoured Mepilex but the result was not significant (HR 1.50, 95% CI 0.86 to 2.62, p=0.16). There was a high withdrawal rate (29.5%), primarily due to mild adverse events, and the definition of complete healing to refer to the entire limb rather than the reference ulcer may have influenced the findings. It is unlikely the study was sufficiently powered to measure an effect given the concurrent randomization of compression therapy. Participants in both groups reported improved pain levels after dressing changes and progressively throughout the trial, with no between group differences.

Trials investigating ability of dressings to handle exudate

A low quality RCT[57] investigated ability of a hydropolymer dressing to manage heavy wound exudate from VLUs compared to an alginate dressing. Participants were 113 patients with ulcers of venous origin confirmed by an ABPI of at least 0.8 on Doppler ultrasound and ulcers less than 1cm in depth and less than 11cm wide. Exclusion criteria included wound necrosis, clinical signs of infection and hypersensitivity to dressing products. Participants received either a hydropolymer dressing (n=54) or an alginate dressing with a clear film (n=22) or a swab dressing (n=37). The ITT analysis included the more than 20% of participants who withdrew from the trial due to adverse events. The results found a significantly longer wear time for the hydropolymer dressing compared to the pooled alginate dressing groups (p=0.001) and no significant difference in healing rates. The findings should be considered cautiously due to the dressing change protocol that allowed for

dressing changes for reasons unrelated to the dressing ability to control exudates (eg. protocol included suspected infection, dressing displacement due to activity or dressing in place more than 7 days). Using subjective measures such as ease of application and removal, both investigators and participants ($p<0.01$ for both) were more likely to favour the hydropolymer dressing.[57]

A low quality RCT[56] compared an extra absorbent dressing, (n=10) to an alginate dressing (n=9) for the management of heavily exudating VLUs for a maximum of 6 weeks. Participants had an ABPI of 0.8 or higher, ulcers no larger than 28cm^2 and required dressing changes at least three times per week. The primary outcome measure was number of dressing changes required due to heavy exudate, subjectively assessed by a nurse. The researchers reported that 78% of ulcers dressed with kaltostat required dressing changes due to heavy exudate, compared to 8% of ulcers treated with the extra absorbent dressing. Due to a reduction in the bulkiness of dressings, the researchers proposed that extra absorption dressings may increase quality of life and decrease isolation for patients; however this was not formally assessed in the trial.[56]

A low quality RCT[55] compared the effectiveness of a hydrocapillary dressing to a hydropolymer dressing for healing VLUs. Participants were adults with an ABPI of at least 0.8 and a heavily exudating VLU of at least 4 weeks duration that had a maximum size of 8cm^2 who had no acute infection, severe eczema and disease or medications that may influence healing. Patients were treated with either the hydrocapillary dressing (Alione; n=49) or a hydropolymer (Tielle™ or Tielle™ Plus; n=48) until their ulcer healed, or for a maximum of 12 months. At the conclusion of the trial there were no significant differences for wound healing time, reduction in ulcer size, dressing wear time, or adverse events (infection, maceration or allergy). Subjective assessments from nurses significantly favoured the hydrocapillary dressing for absorptive capacity ($p<0.05$), although there was no significant difference noted in objective measures (numbers of times dressing leaked or estimates of absorption by weighing the dressing). Subjective ratings by patients of comfort favoured the hydrocapillary dressing ($p<0.001$).

Adverse events

Only one of the SRs reported an analysis on adverse events associated with primary dressings. A moderate quality SR pooled results from all trials comparing a modern dressing to a traditional dressing to compare withdrawal rates and adverse events.[60] There was no difference in withdrawal rates for participants receiving either type of dressing (modern 22% vs. traditional 17%; RR 1.20; 95% CI 0.76 to 1.89, p=0.40). The most commonly observed adverse events were deterioration of the wound and signs of local infection with or without cellulitis in both groups, and hypersensitivity in participants treated with modern dressings. There was no statistically significant difference in rate of adverse events between participants receiving modern and traditional dressing treatments (RR 1.21; 95% CI 0.76 to 1.96, p=0.40).[60]

A low quality RCT[54] reported significantly more (p=0.039) adverse events including eczema and infection were recorded in the group treated with Duoderm compared to those treated with Urgotul. (23 adverse events vs.10 adverse events).

One low quality RCT[57] reported significantly more adverse events for an alginate dressing compared to a hydropolymer dressing over a maximum treatment period of 4 weeks. The trial experienced a high withdrawal rate due to maceration, erythema and infection deemed to be related to the dressing type. The high level of adverse events (45%) experienced by participants treated with an alginate dressing covered with a clear film (Opsite) led to a change in the protocol whereby the clear film was replaced by a sterile swab; after which the adverse event rate was similar between the alginate group (19%) and hydropolymer dressing group (20%).[57]

A small, low quality RCT[64] investigating the effectiveness and tolerability of a hydrocellular foam dressing (Versiva®) compared to composite foam dressing (Allevyn*) reported on adverse events. Adverse events including maceration, erythema and eczema were experienced by 24% of participants treated with the hydrocellular foam dressing and 29% of those treated with the foam dressing, which was not statistically different between the groups.[64]

A low quality RCT[63] investigating the effectiveness of two foam dressings, Allevyn and Mepilex®, in 156 participants over 24 weeks reported a withdrawal rate of 29.5%. Withdrawals were primarily due to mild adverse events including maceration and eczema and the rate of events was not significantly different between the two products.

6.2.2 Zinc-impregnated bandages

Zinc-impregnated bandages are thought to have an effect in the treatment of chronic wounds by stimulating epithelialisation.[68]

There was insufficient evidence to make an evidence based recommendation on the use of zinc-impregnated bandages for treatment of VLUs because no appropriate studies were identified and no SRs specifically reported on the effect of zinc-impregnated bandaging. However, the Expert Working Committee recommends that these bandages could be used for managing VLUs in conjunction with compression.

The use of dressings or bandages impregnated with water soluble zinc may provide comfort and promote epithelialisation of a healthy granulated superficial VLU. (EBO)

Caution

Skin sensitivity may result from topical products used for extended periods.

Practice tips

- Zinc-impregnated bandages can be used to soothe venous eczema and associated inflammation.[69] (see recommendation 6.10)
- Zinc impregnated bandages alone do not provide therapeutic compression.
- All previous zinc should be carefully removed from the patient's VLU and surrounding skin before a new zinc-impregnated bandage is applied. Moisturiser can assist removal to prevent skin damage.
- Apply zinc-impregnated bandages according to the manufacturer's directions.

6.2.3 Micellaneous topical treatments

The literature search identified two trials investigated the application of miscellaneous topical treatments—pale sulphonated shale oil (PSSO) and a bark product— for promoting healing in VLUs.

Pale sulphonated shale oil (Ichthammol) derives from marine sediments in carbonised rock. It is has a high hydrogen/carbon ratio and low nitrogen content. Pale sulphonated shale oil is also known as ichthammol, ammonium bituminosulphate and ichthyol. Although there is minimal evidence to support its use, PSSO has been used as an antibacterial; to reduce inflammation, pruritus and eczema; and to increase blood flow to wounds.[70]

The evidence underpinning the recommendation that pale sulphonated shale oil (PSSO) is effective for treating VLUs was one good quality trial showing an effect in reducing VLU size, but no effect on rate of epithelialisation or management of fibrinous discharge, necrosis or pain. There was insufficient evidence to make a recommendation for use of bark products in treating VLUs.

There is some evidence that topical pale sulphonated shale oil is more effective than standard care for promoting healing in VLUs. (Grade C)

Caution

Pale sulphonated shale oil may cause minor skin irritation and has been reported as a flammable agent.[70] In the trial reported in the evidence base, participants experienced adverse skin reactions at the same rate as those treated with a placebo gel. [71]

Evidence statement

A good quality trial[71] investigated the effectiveness of a topical PSSO for healing VLUs. Participants were adults with an ABPI over 0.8 and ulcer size of at least 3cm^2. Severe cardiac, respiratory, gastrointestinal, liver, or renal disease, malignancy, signs of wound infection and pregnancy or lactation were exclusion criteria. Participants were randomised to receive either 10% Leukichtan (a PSSO) (n=62) or a placebo gel (n=57) applied at 2 to 2.5 mm thickness under a non-adherent dressing and compression. Frequency of dressing changes was not reported. Patients were treated for 20 weeks, with wound assessments conducted every 2 weeks. At the final assessment after 20 weeks of treatment the group treated with PSSO achieved a significant reduction in overall ulcer area compared to the placebo group (mean 6.2cm^2 vs. 10.8cm^2, $p<0.0005$). Relative change in ulcer area was significantly greater in the treatment group (-72% vs. -18%, $p<0.0001$). There were no differences in complete epithelialisation (53% vs. 34%), fibrinous discharge, necrotic tissue or pain levels. Qualitative assessment of the overall treatment conducted by both patients and physicians favoured the PSSO ($p<0.001$ for both). Adverse events were equivalent between groups (12% vs. 11%). This trial provided good quality evidence that 10% Leukichtan (a PSSO) is more effective than placebo in promoting healing of VLUs if used in conjunction with compression for 12 weeks.[71]

A low quality double blind RCT[72] investigated the effectiveness of *Mimosa tenuiflora* bark extract in healing VLUs. Forty participants with a mean VLU duration of 8.5 years who showed no clinical signs of infection were randomised to receive *Mimosa tenuiflora* bark extract 1.8g tannins/100g hydrogel or regular hydrogel daily for 12 weeks. Patients attended their own dressings on a daily basis and wore concurrent compression bandaging. Ulcers were measured weekly using digital photography and a data processing image analyser to determine ulcer area. The reliability of this measurement technique was not reported, nor was it clear whether mean ulcer size was equivalent between

groups at baseline. Treatment effect became evidence after 3 weeks when 25% of the experimental group had at least 80% of VLU area healed compared to 0% in control group (p=0.001). By the study completion at 12 weeks 100% of the experimental group had at least 80% healed ulcer area compared to 18% in control group (p=0.0001). Almost half the control participants withdrew from the trial (11/20) and were not considered in the analysis. Only 1 participant withdrew from the *Mimosa tenuiflora* group. No adverse events or abnormal blood results were experienced during the trial. The results may have been influenced by the self-administration of treatment, including compression bandaging. Randomisation and allocation concealment methods were not reported. The results of this low quality trial suggested that topical *Mimosa tenuiflora* bark extract administered daily for 12 weeks may be more effective than regular hydrogel when used in conjunction with compression bandaging to treat VLUs.[72] This was considered insufficient evidence on which to make a recommendation on the products use for treating VLUs.

6.3 Skin management

6.3.1 Skin and wound hygiene

Ongoing attendance to leg and wound hygiene is important in maintaining overall skin integrity. Regular washing of the wound removes exudate and topical product residue that may aggravate peri-wound skin. Compression bandaging often restricts the patient's ability to maintain regular hygiene of the leg so it is important this is attended to at bandaging changes to reduce odour and promote skin integrity.

Cleansing the leg and wound when dressings and bandages are changed is recommended. (EBO)

Practice tips

- Aseptic wound management techniques should be considered when:[32]
    - The patient is immunosuppressed
    - The wound healing environment is compromised
- Avoid the use of alkaline soaps and cleaners to maintain optimal wound and skin pH.[32]
- Normal hygiene of the leg should be attended at each dressing change and the leg dried gently with a clean towel. Hygiene could be achieved through:
    - showering
    - washing the leg in a dedicated bowl
    - wiping the leg with a moist washer
- Cleansing the leg with a pH appropriate skin cleanser and appllying a moisturiser contributes to the maintenance of leg hygiene.

- The leg may be moisturised.

6.3.2 Management of venous eczema

Prevalence of venous eczema in patients with venous hypertension is between 3 and 12%.[73] Red inflamed skin with flakiness or scaling indicates venous eczema. The skin may have blistering or cuts. Venous eczema can result from increased venous pressure due to poor venous blood flow related to venous hypertension. Hypersensitivity to topical products also occurs frequently in patients with VLU, particularly those with VLUs of long duration requiring ongoing dressings.[74]

No SRs or RCTs addressing the management of venous eczema met the inclusion criteria for the literature review. The Expert Working Committee recommends venous eczema be investigated and managed promptly to prevent skin breakdown, relieve discomfort and promote overall healing of VLUs.

Venous eczema and impaired peri-wound skin should be treated promptly. (EBO)

There is weak evidence that topical barrier preparations reduce peri-wound erythema in patients with VLU. (Grade D)

Practice tips

- Red skin near the wound may be related to infection that requires further investigation.
- Red skin near the wound may be related to venous eczema.
- Review current topical agents with consideration to hypersensitivity.
- Consider applying a topical barrier preparation to the peri-wound skin to protect from wound exudate.
- Venous eczema may be treated with a wide range of products including:
    - topical corticosteroids
    - topical zinc impregnated bandages (see recommendation 6.2.2)
    - other dermatological preparations.

Evidence statement

A low quality trial[75] compared the effectiveness of Cavilon™ No Sting Barrier Film (NSBF) to a zinc compound paste as barrier preparations. Patients eligible for inclusion were those with VLUs with maceration or peri-wound irritation, a VLU of at least 4 week duration and an ABPI above 0.8. Exclusion criteria included insulin dependent diabetes, systemic therapy that may influence ulcer

healing and ineligibility for compression therapy. Participants were randomly assigned to treatment for 12 weeks with either NSFB (n=18) or zinc paste (n=18) applied to peri-ulcer skin at each dressing change. The analysis at 12 weeks showed no significant difference in wound healing rates, exudate level or condition of peri-ulcer skin between the groups. Both products were deemed to be effective barrier creams to protect the skin around VLUs.[75]

A second low quality RCT[76] investigated the effect of Cavilon™ NSBF in controlling peri-wound erythema in 239 patients with heavily exudating VLUs. Participants had VLUs that had persisted for at least 2 years and were not clinically infected. Each VLU was treated with NSBF on one side of the wound and saline on the opposite side of the wound, with application of each performed. The NSBF and saline were applied daily for four days using applicators of different appearance and the patients and clinicians were not informed of which was the active treatment. Erythema was assessed using a chromometer that was reported to be a reliable measure of wound colour. The presented analysis for 200 of the participants showed the extent of erythema on the fourth day was 0% for parts of the VLU treated with NSBF and 99% for parts receiving saline. Statistical analysis was not performed. Participants who developed infection (n=12) were excluded from the analysis, as were those who did not respond to the NSBF. The trial provided low quality evidence that NSBF may contribute to a decrease in peri-wound erythema in patients with VLU.[76]

6.4 Antimicrobial therapy

Antimicrobial therapy includes topical agents such as cadexomer iodine, silver, honey and other topical antiseptics, as well as systemic antibiotics. **All products should be used in accordance with manufacturer's directions.**

6.4.1 Cadexomer iodine

Cadexomer iodine products include ointments, powders and impregnated dressings that have the ability to absorb exudate within the wound. They also provide a slow release of iodine, have broad spectrum antimicrobial properties and facilitate the debridement of the wound bed.[77]

The evidence supporting the recommendation on the topical antimicrobial agent cadexomer iodine comes from a good quality Cochrane SR that reported the results from 10 moderate quality RCTs in a narrative summary.[77] Results were generally consistent that there is a moderate effect on ulcer healing.

There is some evidence that cadexomer iodine is more effective than standard care in the treatment of VLUs. (Grade C)

Caution

Unless the patient has a hypersensitivity to iodine, cadexomer iodine is usually not associated with significant adverse events.[78, 79] Cadexomer iodine ointments and impregnated dressings should not be used in patients with a history of Hashimoto's

thyroiditis, Graves disease, non-toxic nodular goitre or thyroid disorders or impaired renal function, in children or in pregnant or lactating women. Risk of systemic absorption increases when cadexomer iodine products are used on larger wounds or for prolonged periods.[79] In some trials, patients treated with topical cadexomer iodine have experienced local burning sensations;[78] however, this was not reported in the trials included in this review.

Practice tips

- Cadexomer iodine should not be used for longer than 3 months continuously.
- Cadexomer iodine dressings should only be used when there is evidence of heavy bacterial load/local wound infection and stopped once local infection has been controlled.
- The dressing product will change from brown to white (mashed potato appearance) when all the available iodine has been used. The product is no longer efficacious when the brown colouring has gone.
- When replacing the product, the the wound should be completely cleansed of residual cadexomer iodine.
- Cadexomer iodine should not be covered with povidone iodine impregnated tulle gras as this practice results in the dumping of iodine, increasing toxicity.
- The pro-inflammatory properties of cadexomer iodine may increase inflammation when used in inflammatory wounds.

Evidence statement

One good quality Cochrane review[77] reported the results of ten moderate quality RCTs investigating the use of the antimicrobial agent cadexomer iodine for the treatment of VLUs.

Ten RCTs investigated the use of cadexomer iodine. Four trials compared cadexomer iodine to standard care, with none reporting baseline infection status. In one trial (n=28) patients received alternate day dressings. After 4 weeks there was no significant difference in number of ulcers healed (RR 4.33, 95% CI 0.56 to 33.53); however there was significantly greater reduction in ulcer area in the treatment group (33.6% vs. 4.2%, p<0.005). In a second trial (n=67) participants were admitted to hospital, maintained on bed rest for six weeks and had dressings changed daily. At 6 weeks there were significantly more ulcers healed in the cadexomer iodine group (RR 2.29, 95% CI 1.10 to 4.74) and a significantly greater reduction in ulcer area (71% vs. 54%, p<0.001); however, more than 10% of participants were excluded from the final analysis. In a third trial 61 participants treated with either cadexomer iodine or standard care showed no significant difference in numbers of ulcers healed at 12 weeks (RR 1.71, 95% CI 0.78 to 3.75). The fourth trial (n=75) did not report total healing rates. Results for rate of reduction in ulcer area were pooled with findings from the third trial and showed that ulcers treated with cadexomer iodine healed at a significantly faster rate (WMD 0.47cm^2 per week, 95% CI 0.26 to 0.69, p=0.00002).[77]

Three trials compared cadexomer iodine with compression to compression alone. The first two trials (total n=132) reported complete healing at 4 and 6 weeks. Pooled results favoured cadexomer

iodine (RR 6.72, 95% CI 1.56 to 28.95). The third trial did not report complete ulcer healing, but its analysis showed a significant decrease in colonization with *Staphylococcus aureus* in ulcers treated with cadexomer iodine (RR 31.31, 95% CI 1.95 to 503.29, p=0.015).[77]

Two trials compared cadexomer iodine with dextranomer. Both trials were small, and although one had results for complete healing that bordered on significance (p=0.54) between groups, there was only 27 participants and 30% were excluded from the final analysis. One trial (n=153) compared cadexomer iodine to a hydrocolloid dressing for participants with non-infected VLUs. After 12 weeks there was no significant difference in complete healing (RR 1.37, 95% CI 0.48 to 3.91, p=0.55) or rate of ulcer reduction (WMD 1.00%, 95% CI -2.52 to 4.52, p=0.58); however, the mean reduction in ulcer area was larger in the cadexomer iodine group (WMD 20.90%, 95% CI 2.22 to 39.58, p=0.028). The same trial had a third arm treated with paraffin gauze. This group had no difference in complete healing to the cadexomer iodine group but cadexomer iodine was superior for mean reduction in ulcer area (WMD 37.70%, 95% CI 8.77 to 66.63, p=0.011) and rate of ulcer reduction (WMD 6.00%, 95% CI 1.56 to 10.44, p=0.0082).[77]

6.4.2 Silver

Silver has been used throughout history as a wound dressing product to promote healing. Silver reacts to moisture, releasing silver ions that are thought to have a wide-spectrum antimicrobial effect. Silver treatments include topical silver creams and silver impregnated dressing products. The composition and amount of silver delivered via different systems varies.[80, 81]

Although reported to reduce wound infection and promote healing, the studies included in this review were unable to demonstrate a healing effect of silver-containing products above standard dressing products. This supports the findings of another Cochrane review that investigated the effect of silver in chronic infected wounds, primarily burns.[82]

The recommendation that silver products do not improve healing times for VLUs is underpinned by one good quality SR reporting nine RCTs with consistent findings. The RCTs did not report bacterial load as an outcome measure.

There is good evidence that silver products offer no benefit over standard care in reducing the healing time for VLUs. (Grade B)

There is insufficient evidence regarding the ability of silver products to decrease bacterial load in VLUs.

Caution

Potential renal toxicity should be considered when using topical silver agents for extended periods (eg. greater than 4 weeks) on large wound beds. The risk appears to be low but caution is warranted. As with other anti-microbial therapies there is a risk of bacteria resistance with extended use of silver products.[83]

Practice tips

- Silver-containing based topical products could be considered:
  - when there is evidence of an increase in microbial burden at the wound base; or
  - when there is wound inflammation.
- Colloidal silver, either internally or topically, is not recommended.
- There is insufficient evidence to indicate if any specific silver product is superior to others.

Evidence statement

A good quality SR[80] investigating the effectiveness of silver products in treating VLUs identified nine RCTs meeting inclusion criteria for the review. The reviewers searched major databases, wound journals, conference proceedings and contacted manufacturers to identify literature. Six of the included studies investigated silver dressing products and three trials focused on topical silver treatment. All of the studies were of low quality.[80]

One RCT in participants with ulcers of at least 3 month duration compared silver sulphadiazine cream (n=28) to both tripeptide copper-complex cream (n=29) and placebo cream (n=29) applied to VLU for a treatment period of 4 weeks. None of the ulcers treated with tripeptide copper-complex cream and one ulcer treated with placebo cream healed, compared to six ulcers treated with silver sulphadiazine cream. Mean reduction in ulcer area was 18.7% for tripeptide copper-complex cream, 22.5% for the placebo cream and 44% for the ulcers treated with silver sulphadiazine cream. RR for silver sulphadiazine cream compared to placebo cream was 6.21 (95% CI 0.8. to 48.38, p=0.08). A second low quality trial compared VLUs treated with compression bandaging and either silver sulphadiazine cream (n=30) or a non-adherent dressing (n=30) over a period of 12 weeks. Nineteen ulcers (63%) treated with the ordinary dressing healed compared to 24 ulcers (80%) in the silver sulphadiazine cream group healing. Relative risk was 0.79 (95% CI 0.57 to 1.10; p=0.16). The results of these two studies were pooled using a random effects model with the results showing no significant effect of silver sulphadiazine cream compared to placebo or non-adherent dressing (n=117; pooled RR 1.8; 95% CI 0.19 to 17.11; p=0.63). A third low quality (n=51) study reported no significant difference in median time to heal chronic ulcers treated with silver sulphadiazine cream compared to hydrocolloid dressing alone.[80]

Six trials in this review compared silver-containing dressings to conventional dressings, a calcium alginate dressing or different types of silver dressings. One low quality study compared a silver foam dressing (n=65) to a hydrocellular foam (n=64) in patients with leg ulcers of mixed aetiology. Although the median relative reduction in ulcer area was significantly shorter in the group treated with the silver product (45 vs. 25% p=0.034) after 4 weeks, there was no difference in the proportion of ulcers that completely healed (silver 10%; control 9%; RR 1.10; 95% CI 0.34 to 3.57; p=0.88). In a follow-on study, 45 of the participants were then re-randomised and the results continued to show no significant difference in the proportion of ulcers that were completely healed (silver 8%; control 5%; RR 1.6; 95% CI 0.16 to 16.40; p=0.67). These results were supported in a third low quality trial (n=40) that compared a silver impregnated-activated charcoal dressing to a range of conventional therapies. No significant difference was shown for proportion of ulcer area healed or number of ulcers completely healed (RR 3.0; 95% CI 0.69 to 13.03; p=0.14). Pooled results from two

of these trials using a fixed-effects model showed no significant difference in the proportion of ulcers completely healed (RR 1.66; 95% CI 0.68 to 4.05; p=0.27).[80]

One large trial (n=415) that compared the treatment of mixed aetiology ulcers with silver foam dressings compared to conventional treatment found the area of ulcer healed was significantly better for the silver dressing (45.5 vs. 28.8%, p=0.0001); however, the groups were not equivalent at baseline with respect to median ulcer sizes.[80]

Another low quality trial compared silver dressing (n=38) to a calcium alginate dressing (n=33) for treating VLUs for 4 weeks. No significant differences were found in either reduction of wound size (WMD –3.5; 95% CI 10.45 to 3.45, p=0.34) or healing rate (WMD 0.13; 95% CI 0.13 to 0.12; p=0.31).[80]

A moderate quality SR[84] reported findings from three RCTs investigated silver–based products. In one trial in which wounds were also debrided there was no significant difference between silver–impregnated activated charcoal dressing and dressings targeted at stage of wound healing. Silver sulphadiazine was not superior compared to saline cleansing and ulcers in the treatment group that were contaminated at baseline remained so throughout the 12 week trial. However, another trial investigating silver sulphazine reported it to be more effective for reducing mean ulcer area than both tripeptide–copper complex (ES 25.30 (95% CI 20.82 to 29.78, p=0.03) and placebo (ES 21.50, 95% CI 16.66 to 26.34, p=0.05). In the same trial there was no difference in treatments for complete ulcer healing.

In addition, a low quality RCT[85] investigated the effectiveness of a silver dressing compared to a regular foam. Participants had VLUs with clinical signs of infection and a mean size of 2cm^2. Patients with diabetes, taking systemic corticosteroids and with an ABPI less than 1.0 were excluded. Participants were randomised to receive a twice weekly dressing with either silver releasing foam (n=21) or a regular foam (n=21) covered in short stretch bandaging for 9 weeks. Randomisation and allocation concealment techniques were not reported and baseline equivalence for ulcer duration and concurrent medical conditions was unclear. After 9 weeks 81% of the treatment group compared to 48% of the control group (p=0.002) had achieved full ulcer healing (method of ulcer measurement was not reported). Patients treated with the silver releasing dressing achieved reduction in pain earlier in the trial period than the control group. No systemic or local effects were experienced. This low quality trial provided some evidence that silver dressing may be more effective at healing infected VLUs, although the trial was small and methods were not clearly reported.[85]

6.4.3 Topical honey

Honey is a supersaturated sugar solution containing glucose, fructose, sucrose and water. Honey has been used for treating wounds for centuries.[86] Honey is thought to aid in wound healing through an osmotic effect that draws fluid from the wound cavity to the wound tissue surface, through the promotion of a moist healing environment and through the lowering of wound pH, all of which aid in autolysis.[87] More recently it has been proposed for use due to potential antibacterial properties, particularly Manuka honey, a variety found in Australia and New Zealand.[86]

The recommendation that honey offers no benefits over standard therapy in treating VLUs is underpinned by a good quality SR reporting two good quality RCTs that had consistent results.

There is evidence that honey offers no benefits over standard care in promoting healing in VLUs. (Grade A)

Caution

Treating VLUs with honey has been reported to lead to ulcer pain, deterioration of the ulcer and an increase in wound exudate.[88] A SR found that adverse events were more likely to occur in VLUs treated with honey compared to those treated with hydrogel or standard dressings, but that infection was not more likely for wounds treated with honey.[86]

Practice tips

- The Expert Working Committee acknowledges that more research is required. Anectodatal evidence suggests honey could be considered:
    - when there is evidence of an increase in microbial burden at the wound base; or
    - when there is wound inflammation.
- The honey should be specifically indicated for application to wounds.
- Manuka honey should be rated UMF (Unique Manuka Factor) +12 or above for topical dressing products.
- Use gamma irradiated honey as other sterilizing processes will destroy the UMF in the honey.
- Honey may increase exudate levels thus warranting more frequent dressing changes.

Evidence statement

A good quality Cochrane review[86] included trials investigating the effect of honey used to treat wounds. A search of major databases was conducted and studies were appraised by two reviewers. Appraisal included consideration of randomisation and allocation concealment methods, loss to follow up, blinding and use of ITT analysis. Complete healing at 12 weeks was the primary outcome measure for the review. Two good quality trials considering the use of honey for treating VLUs were included in the review. Pooling of results using a fixed effects method found no significant difference between honey and control therapy (regular dressings) for treating VLUs (RR 1.15, 95% CI 0.96 to 1.38, p=0.12). Pooling using a random effects model showed there was significantly more adverse events in participants treated with honey (111vs 84, RR 1.27, 95% CI 1.05 to 1.55, p=0.016) although one trial reported all adverse events including those that may not have been related to therapy. These findings were based on two trials with good methodological quality, one of which was a large study. In both trials honey was used in conjunction with compression. The results suggest there is no evidence suggesting honey used for between 4 and 12 weeks is more effective than standard care for treating VLUs.

6.4.4 Other topical antimicrobials

Topical antimicrobial preparations (antiseptics and antibiotics) are used either as an irrigation agent or designed to remain in contact with the wound for longer periods (eg. until the next time the dressing is changed). Most products come in a range of forms or concentrations, all designed to promote healing through the eradication of bacteria in the wound.[77]

Agents reported in the research included:

- benzoyl peroxide
- chlorhexidine
- dimethyl sulphoxide powder
- ethacridine lactate
- hydrogen peroxide
- mupirocin
- povidone iodine

The evidence supporting the recommendation on other topical antimicrobial agents comes from ten moderate quality studies with small numbers of participants that were reported in narrative summary in a good quality Cochrane SR.[77] Results were consistent that there is a moderate effect on ulcer healing. However, the Expert Working Committee recommends that there may be a role for some topical antimicrobials where there is known increased microbial burden.

There is some evidence that other topical antimicrobial agents offer no advantage over standard care in improving VLUs healing. (Grade C)

There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden. (EBO)

Caution

The Working Committee does not recommend the use of hydrogen peroxide in wound care. Deaths have been reported as a result of irrigation of closed cavity wounds with hydrogen peroxide.[89-91]

Skin sensitivity may result when products are used for extended periods.

Toxic effects of antimicrobial/antiseptic solutions on fibroblasts and macrophages in vitro are well documented. [91-93]

Acetic acid has been associated with pain at the ulcer site and skin irritation at higher concentrations. There is a risk of acidosis when used for extended periods over very large wound surfaces.[94] It has been demonstrated that there is no dilution of acetic acid that is toxic to bacteria without being toxic to fibroblasts.[93]

Practice tips

- When using povidone iodine solution it should be used at full concentration and rinsed off after two to five minutes.[95]
- Topical antiseptic solutions should generally only be used for treatment of topical contamination or minor skin infections and their use avoided on clean, healing ulcers.[96]
- The length of treatment with topical antimicrobials should be determined by the response of the VLU and the patient.[96]
- Acetic acid at 3% concentration may be considered for treatment as a topical wash to reduce the burden of pseudomonas where other topical interventions are unavailable or have been ineffective.

Evidence statement

One good quality Cochrane review[77] reported the results of 10 moderate quality RCTs investigating the use of a range of topical antimicrobial agents for the treatment of VLUs. When trials were clinically homogenous the results were pooled using appropriate techniques; however, for the most part differences in interventions and trial lengths precluded pooling and results were presented in a narrative summary.

Povidone iodine

Five trials reported the effectiveness of povidone iodine. Three trials compared povidone iodine plus compression to hyrocolloid dressing plus compression. In the first trial (n=200) participants were stratified according to ulcer size. For ulcers over 4cm in diameter, the hydrocolloid dressing was more effective for total healing than povidone iodine (p=0.02) and there was no significant difference in the rate of healing. Total healing was not reported for smaller ulcers. Thirty percent of participants withdrew from this trial. In the second trial (n=51) participants with more than one ulcer acted as their own controls. Ulcers treated with povidone iodine (17 patients) healed significantly faster (p<0.01). The third trial (n=74) compared povidone iodine with hyaluronic acid plus compression to either hydrocolloid or paraffin gauze and found no differences in rate of healing.[77]

One trial (n=100) compared povidone iodine to dextranomer in participants with ulcers colonised with bacteria at baseline. Mean time to healing was significantly shorter in those treated with dextanomer (4.4 weeks vs. 5.3 weeks, p<0.05) and time to eradicate *Staphylococcus aureus* was also shorter with dextranomer (14.7 days vs. 18.7 days, p<0.01). One low quality trial (n=63) compared povidone iodine and sugar ointment applied once or twice daily to recombinant tissue growth factor applied as a spray solution. After 4 weeks there was no significant difference in number of ulcer healed (RR 0.57, 96% CI 0.22 to 1.52, p=0.26).[77]

Peroxides

Three trials reported on the use of peroxides. One trial (n=31) had a three different arms comparing different concentrations of benzoyl peroxide with saline dressing in VLUs with unknown infection status at baseline. After 42 days, days, benzoyl peroxide lotion 10% was significantly more effective than saline in reducing ulcer area (WMD -30.40%, 95% CI -42.12 to -18.68) and benzoyl peroxide lotion 20% was also significantly more effective (WMD -34.10%, 95% CI -46.22 to -21.98). Two trials compared hydrogen peroxide plus compression to standard care plus compression. In both trials

patients received systemic antibiotics prior to commencing the trial and were then randomised to receive hydrogen peroxide 1% cream or placebo cream for 10 days. In one of the trials (n=20) there was a significant reduction in ulcer are in those treated with peroxide ($p<0.05$) and the second trial also favoured peroxide ($p<0.005$).[77] Deaths associated with hydrogen peroxide used in wound care have been reported in the literature.[89-91]

Other treatments

One trial (n=253) investigated daily treatment with ethacridine lactate 0.1% lotion plus compression compared to placebo lotion plus compression and found ethacridine lactate was associated with significantly greater reduction in ulcer are after 21 days (RR 1.47, 95% CI 1.24 to 1.74, $p<0.00001$). Complete healing was not reported and the follow up period was short. Another trial compared of 2% mupirocin in paraffin tulle gras with vehicle (all participants also received compression). After 12 weeks there was no significant difference in complete ulcer healing (RR 1.14, 95% CI 0.56 to 2.35, $p=0.72$), rate of healing or eradication of gram positive bacteria. The third trial compared chlorhexadine to hydrocolloid dressing, with all participants receiving compression and acting as their own controls. After 6 weeks there was no significant difference in time to healing.[77]

Overall, the SR provided evidence from moderate quality trials that most topical antimicrobial agents have no significant effect in the healing of VLUs. [77] Few of the trials reviewed reported the clinical infection status of ulcers and it remains unknown if this is an important prognostic factor for healing. In studies that investigated bacterial resistance as an outcome, there was significantly more emerging bacterial resistance in ulcers treated with systemic or antimicrobial products.[77]

An additional moderate quality SR[84] investigated the effectiveness of antimicrobial agents. The critical appraisal suggested the included trials were not of high quality. Due to variations in populations, interventions and trial durations, results were not pooled. A narrative summary presented the findings.[84]

The review[84] reported seven small (less than 40 participants) trials in which topical antimicrobials were investigated, five of which were randomised and all of which were placebo controlled. Most trials excluded participants with clinical signs of infection and few reported wound colonization culture testing. In all trials, participants received concurrent compression therapy. There was no difference in healing rate and/or complete healing for polynoxylin paste, povidone iodine or mupirocin tulle gras compared to placebo or no therapy. Dimethyl sulphoxide powder and allopurinol powder were equivalent and both superior to placebo powder for complete healing (OR 10.67, 95% CI 2.30 to 49.39, $p<0.01$) when used in conjunction with compression therapy for at least 12 weeks in participants with VLUs less than $10cm^2$. Withdrawals due to local irritation were similar between the groups (allopurinol=1, placebo=1, dimethyl sulphoxide=2).[84]

6.4.5 Topical antibiotics

The overuse of topical antibiotics has contributed to the development of antibiotic resistant bacteria.

The literature search did not identify any SRs or RCTs reporting on the effectiveness of topical antibiotics for treating VLUs. The Expert Working Committee recommends the use of topical antibiotics only when there is an identified microbial burden present at the ulcer site and other treatment options have failed to eliminate the bacterial burden.

There is a concern that the use of topical antibiotics is associated with antibiotic resistance and sensitivities. Topical antibiotics have a very limited place in management of VLUs. Their use should be judicious. (EBO)

Caution

Skin sensitivity may result from topical products used for extended periods.

Practice tips

- Topical metronidazole may be used for a short period to reduce odour related to anaerobes.

6.4.6 Systemic antibiotics

Systemic antibiotics include penicillins, cephalosporins, aminoglycosides, quinolones. clindamycin, metronidazole, and trimethoprim. Cephalosporins and penicillin based antibiotics interfere with formation of bacterial cell walls. Aminoglycosides interfere with normal protein synthesis, whilst quinolones prevent cell nucleus DNA.[77]

Antibiotic resistance is a significant concern due to the over use or inappropriate use of antibiotic therapy.[77, 97] Pooled results from two of the trials reported in the literature related to VLU management identified that antibiotic resistant strains of bacteria were seen more often in patients treated with systemic antibiotics compared to placebo.[77] Selection of antibiotics should generally be made after wound swabs and sensitivity testing to determine the bacteria against which treatment should be directed. Patients should be advised to complete their antibiotic therapy as prescribed to reduce the risk of antibiotic resistance.

The evidence supporting the recommendation on systemic antibiotics comes from five moderate and low quality studies with small numbers of participants that were reported in narrative summary in a good quality Cochrane SR. Results were generally consistent that there is no effect on ulcer healing, and the one RCT that found an effect was small and of low quality.

There is some evidence that systemic antibiotics offer no advantage over standard care for reducing healing time of VLUs that show no clinical signs of infection. (Grade C)

Caution

Adverse effects for systemic antibiotics were not reported in the trials reported in the included literature. Side effects include GIT signs and symptoms and signs of allergic reaction (eg. skin rash, itching and rarely, difficulty breathing). Interactions with other medications are common.[97] The development of antibiotic resistance due to overuse of antibiotics is also of major concern.

The Expert Working Committee recommends consulting specific product information, the National Prescribing Service (www.nps.org.au), Australian Therapeutic Guidelines (www.tg.org.au) or New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz) before prescribing systemic antibiotics.

Practice tips

- All wounds should be assessed regularly for indicators of infection.[96]
- Systemic antibiotics only have a role when the ulcer is clinically infected. A wound swab should generally be taken to guide appropriate antibiotic therapy, although the results are not to be considered as binding.[96]
- The length of treatment with systemic antibiotics should be determined by the response of the wound and the patient.[96]
- For complex, unresponsive, recalcitrant or recurrent VLU infection, consider consulting a microbiologist or infectious disease specialist.[96]

Evidence statement

One good quality Cochrane review[77] reported the results of 5 moderate and low quality RCTs investigating the use of systemic antibiotics for the treatment of VLUs. Only one trial selected antibiotics based on wound swabs and sensitivity testing. Wounds were not clinically infected at baseline.

In one RCT participants (n=48) received either co-trimoxazole, gentamicin or amikacin (according to sensitivities) for 10 days. At 20 day follow up there was no statistically significant difference in number of ulcers healed or mean ulcer area between those receiving standard care and those receiving antibiotics. There were more ulcers with bacterial eradication in the group receiving systemic antibiotics (RR 1.67, 95% CI 0.64 to 4.36, p=NS). [77]

Two trials compared ciprofloxacin to standard care or placebo. In the first trial, participants (n=26) were eligible if they had VLUs colonized by bacteria sensitive to ciprofloxacin. Participants were unevenly assigned between treatment and control groups and the treatment group had ulcers that were of significantly longer duration at baseline, possibly biasing the control group. At three months, more ulcers were completely healed in the group receiving antibiotics (RR 3.32, 95% CI 0.19 to 57.61, p=NS). There was no significant difference in number of patients with at least 10% reduction in ulcer length and width (p=0.08) and no significant reduction in bacterial eradication rates (p=0.32). The second trial compared ciprofloxacin (n=12) and placebo (n=10) for 12 weeks; however, those receiving the antibiotic therapy had larger ulcers of longer duration at baseline. At 16 weeks follow up there was no significant difference in number of ulcers healed (RR 1.39, 95% CI 0.44 to 4.43). Pooling of the data from these two studies found that antibiotic resistant strains of bacteria were more commonly seen in participants treated with ciprofloxacin compared to placebo (RR 8.65, 95% CI 1.76 to 42.60, p=0.008). [77]

One trial compared trimethoprim (n=12) to both placebo (n=10) over 16 weeks. Although there was no statistically significant difference (RR 1.25, 95% CI 0.40 to 3.91, p=0.70) between healing between the two antibiotic groups, those receiving ciprofloxacin had larger ulcers of longer duration at baseline. There was no difference between the groups in emergence of antibiotic resistant strains of bacteria. There was also no statistically significant difference between

trimethoprim and placebo (RR 1.11, 95% CI 0.30 to 4.17, p=0.88) for complete healing, although the ulcers in the antibiotic group were of longer duration on entry into the trial. Difference in rates of development of antibiotic resistant bacteria strains bordered on significance (RR 6.67, 95% CI 0.98 to 45.29, p=0.052). [77]

One trial compared systemic amoxicillin to topical povidone iodine. In this three-arm trial, those receiving amoxicillin also received an undefined type of compression (n=21), a second group received povidone iodine and compression (n=21) and the third group were treated with povidone iodine alone. (n=21). There was no significant difference in complete healing rates between amoxicillin and either of the povidone iodine groups (with compression RR 1.06, 95% CI 0.81 to 1.39, p=0.68; without compression RR 1.38, 95% CI 0.95 to 2.02. p=0.092). [77]

One trial (n=59) compared levamisole two days per week for 20 weeks to placebo on the same regimen for the treatment of ulcers, the majority of which were venous in origin (baseline infection status not reported), There was a statistically significant greater rate of complete ulcer healing in the levamisole group compared to placebo (RR 1.31, 95% CI 1.06 to 1.62, p=0.012); however almost 20% of participants withdrew from the trial and were not included in the analysis. [77]

The SR[77] concluded that there is no evidence that systemic antibiotics are useful for the treatment of VLUs. The one trial that achieved a significant result in favour of systemic antibiotic treatment was small and of low methodological quality.

6.5 Wound debridement

Debridement is commonly performed on chronic wounds to remove non-viable tissue that includes superficial necrotic, poorly vascularised tissue and debris. Non-viable tissue can prolong the healing process by increasing inflammation, levels of bacteria and toxins and inhibiting re-epithelialisation.[98] The most commonly used methods of debridement are surgical (sharp), conservative sharp, autolytic, larval, enzymatic and mechanical.[99] Surgical debridement, which is beyond the scope of this guideline, is rapid, although it requires either general or topical anaesthetic and can be painful.[98, 99] Conservative sharp debridement is the removal of loose vascular tissue without pain or bleeding. Autolytic debridement is a process whereby the body releases endogenous proteolytic enzymes and phagocytes that gradually degrade non-viable tissue. Although this process occurs naturally in wounds, it may not be sufficiently rapid to promote wound healing.[98, 99] Autolytic debridement can be facilitated with the use of appropriate dressings that retain or donate moisture to the necrotic tissue. Enzymatic debridement requires the use of chemical products containing proteolytic enzymes designed to enhance naturally occurring wound debridement.[98-100] Larval debridement is the application of sterile, irradiated blue-bottle fly maggots to the wound.

The literature search identified few trials that investigated the efficacy of debridement in healing VLUs. Evidence was limited to RCTs investigating the efficacy of various enzymatic debriding agents. A small number of low quality trials consistently indicated that these products are not more effective than placebo or autolytic products in healing VLUs.[101]

There is weak evidence that enzymatic debriding agents have no effect in promoting healing in VLUs. (Grade D)

There is insufficient evidence to make a recommendation on the effectiveness of other debriding methods for VLUs.

Caution

Adverse events do not commonly occur with enzymatic debriding agents. Collagenase debriding agents are contraindicated in patients with hypersensitivity due to the risk of allergic reaction.[102]

Practice tips

- Mechanical debridement methods such as utrasound or high pressure irrigation may be useful for reducing non-viable tissue, bacterial burden and inflammation.
- When debriding a VLU, the goal is to remove all excess non-viable tissue; however for patient comfort smaller amounts of non-viable tissue may be removed in each session.
- Conservative sharp debridement should only be performed by health profesisonals with appropriate training.

Evidence statement

One moderate quality RCT[100] investigated the effectiveness of an enzymatic debriding agent. Adults were eligible to participate if they had a chronic purulent and/or necrotic leg ulcer, did not have an illness likely to interfere with skin healing and were not taking systemic medication that would influence the study results. Eighty-four participants were randomised (stratified on ulcer size) to four groups receiving treatment with the assigned ointment and a non-stick dressing twice daily for three weeks. Group 1 received the full experimental ointment containing complete proteolytic ointment 1.28 U fibrinolysin/g with 1006 U of desoxyribonuclease/g. The second group received an ointment containing 1.15 U of fibrinolysin/g, the third group received 1027 U of desoxyribonuclease/g ointment and the fourth group received a placebo ointment. After three weeks all groups had achieved a small improvement for amount of purulent exudate, amount of necrotic tissue and an overall wound assessment (all assessed using a Likert scale). There were no significant differences between groups for any of the outcome measures. One participant (group not reported) experienced increased pain and inflammation deemed to be unrelated to the therapy.[100]

A low quality RCT[98] investigated the comparative effectiveness of an enzymatic debriding agent (n=27) to an autolytic debriding product (n=15). Participants were adults with CVI and a VLU of at least 6 week duration who were free from malignancy, arterial occlusion or disease that may inhibit healing. The primary outcome measure was a weekly subjective visual assessment of wound condition that was reported to be insufficient to determine an effect of the treatment over 14 days, leading to an extension of the trial for an additional 7 days. This reduced confidence in the finding that, for the patients who showed a response to treatment, both products produced a statistically significant decrease in slough and necrotic tissue and a significant increase in re-

epithelialised tissue and granulated tissue in the first 14 days (p values ranged from 0.01 to 0.04) No between group comparisons was reported. Neither product was considered to have produced a statistically significant difference in wound condition when the full 21 days of therapy was considered. Patients performed their own dressings on a daily basis, which may have influenced the findings. Withdrawals from the trial were not reported and more than half of the participants in both groups did not respond to the treatment. The ethical approval process for this study was unclear and participants only consented verbally.[98]

In another low quality RCT,[103] the effectiveness of an enzymatic debriding agent, streptokinase-streptodornase, in cleansing ulcers of pus and debris was compared to saline. Participants were adult hospitalised patients without hard necrotic ulcer tissue who were randomised to receive either the enzymatic debriding agent (n=15) or saline (n=16) twice daily for 15 days. Ulcers were evaluated by a blinded observer using a 4 point scale to describe the level of pus and debris present in the ulcer and patient complaints of pain were noted. At day 10 there was significantly more ulcers in the treatment group that had small or no amounts of pus and debris compared to the control group (92% vs. 50%, $p<0.05$); however, patients who withdrew from the treatment group were not considered in the analysis and this is likely to have influenced the significance of the finding. There was no significant difference between group at day 15 and pain levels did not differ between groups. Side effects were not reported. The researchers did not report methods of randomisation, allocation concealment and blinding of patients. Participants were described as having chronic ulcers or wounds, and the origin of the ulcers was not reported.[103]

6.6 Elevation

Oedema associated with venous hypertension contributes to poor healing of VLUs. Elevation of lower limbs to reduce oedema could therefore increase healing.[104]

No systematic reviews or RCTs investigating the effect of elevation on VLU healing were identified in the literature search. Lower level evidence provided some data on the effect of elevation; however the trials were of poor quality. The Expert Working Committee reached consensus that elevation is appropriate to incorporate into a VLU management plan.

There is evidence that the benefits of leg elevation are related to changes in microcirculation in patients with VLUs. (Grade D)

Elevation is recommended to reduce lower limb oedema and promote VLU healing. (EBO)

Practice tips

- To be most effective, legs should be elevated during periods of inactivity, and ideally above the level of the heart, with consideration to the patient's lifestyle and limitations.
- Maintenance of an elevation diary by the patient can increase concordance with an elevation regimen.[105]

Evidence statement

In a small observational trial[105] the relationship between VLU healing and time spent elevating the leg was investigated. Participants (n=29) had VLUs of at least 6 weeks duration and an ABPI above 0.9. At baseline the median ulcer size for participants was 2.8cm^2. Exclusion criteria were vasculitis; renal hepatic or haematological disease; and those taking corticosteroids. Participants wore a validated data logging device that recorded time spent elevating limbs and the angle of elevation for 6 weeks. Ulcers were measured weekly using wound tracings. The median ulcer percentage reduction over 6 weeks for the 26 participants for whom useable data was recorded was 50%. Median elevation time was 352 minutes per 24 hours. The correlation between ulcer healing and elevation time was non-significant (p=0.616). The researchers suggested that lack of correlation may have related to elevation providing limited advantages above the concurrent 4-layer compression bandaging participants wore; or that the intermittent elevation regimen was insufficient to achieve benefit.[105]

Another small prospective trial[104] investigated the effect on microcirculation of the skin of elevation of limbs by participants with VLUs. Participants (n=13) with VLUs of more than 2 years' duration and without concurrent systemic disease were hospitalised throughout the trial. Measurements of transcutaneous oxygen tension ($TcPO_2$) and laser Doppler fluximetry were made at baseline, 4 hours following elevation of limbs at 10° and after 24 hours of continuous elevation. Increase in laser Doppler fluximetry was significant, indicating that continuous elevation leads to changes in skin microcirculation. The trial did not investigate the correlation between skin microcirculatory changes and VLU healing.[104]

6.7 Exercise

The deep veins in the lower extremities are surrounded by calf muscle that has a function in assisting venous blood return. When the calf muscle is relaxed, blood pools in the veins. When the calf muscle contracts there is a pumping action propelling blood back to the heart. This calf muscle pump function is optimised during heel-toe walking. In patients with impaired venous function, calf muscle exercises can improve the calf muscle function and increase the ejection of blood through the veins.[106, 107]

The exercises reported in the literature review included active planter flexion using resistance (4 kg). Exercise programs were implemented under supervision for a minimum of 7 days, with the exercises performed for a minimum of three sets daily of 6 minutes length. Exercise programs were implemented in conjunction with a compression regimen.

The evidence underpinning this recommendation comes from a low quality study conducted in participants with VLU. The study indicated that exercise designed to improve calf muscle strength and mobility has an effect in increasing venous blood flow and calf muscle function. The Expert Working Committee recommends that improving calf muscle function through exercise increases venous blood flow and should be used in the management of VLUs.

There is evidence that exercise improves calf muscle function and promotes venous blood flow. (Grade D)

Exercise is recommended as part of a management plan to promote healing in VLUs. (EBO)

Practice tips

- Exercises should be designed to improve calf muscle function, for example weight bearing foot and ankle exercises and heel-toe walking. Ensure that the patient can perform exercises in a safe manner.
- In one study, exercise leading to an improvement in muscle function consisted of a minimum of 360 planter flexions daily for 7 days.[108]
- Patient concordance with exercise regimen may be greater when performed under supervision.[107]
- Gait analysis is a key factor in patient assessment. Correction of gait may improve calf muscle function.
- Consider referral to a physiotherapist or exercise physiologist with experience in treating patients with venous insufficiency.

Evidence statement

A low quality RCT[108] evaluated the effects of short term supervised calf exercise on calf muscle pump function and venous haemodynamics in limbs with a VLU. Participants with VLUs, impaired calf muscle function (ejection fraction <60%) and full ankle joint movement were randomised to either an exercise therapy group (n=10) or to a non-exercise group (n=11). Exclusion criteria included mixed origin ulcers, ABPI above 1.0, vasculitis, collagen diseases, steroid therapy, immunosuppression, venous outflow obstruction, pregnancy, cancer, congestive cardiac failure and uncontrolled diabetes. The exercise group participated in a supervised program with active planter flexions using standardised 4 kg resistance pedal ergometer for three sets of 6 minutes daily for 7 days. Both groups received concurrent ulcer dressings twice weekly and inelastic (short stretch) bandaging. Ejected venous volume and ejection fraction was measured using air plethysmography. On day eight the exercise group had significantly better ejected venous volume ($p<0.001$) and ejection fraction ($p<0.001$) than the control group. The venous filling index and venous volume did not change ($p>0.5$) in either study group. Calf muscle endurance in the exercise group increased 135% from a median 153 planter flexions at baseline to 360 daily on day 7 ($p=0.001$). This study provided low quality evidence that active exercise in patients with VLUs promotes muscular endurance and the power and efficacy of calf muscle function.[108]

6.8 Nutrition and hydration

Protein and individual amino acids; energy; a range of vitamins including A, C and E; and zinc are all associated with wound healing. Optimal nutrition, particularly calories and protein, are essential for all wound healing.[109]

No SRs or RCTs addressing nutritional interventions met the inclusion criteria for the literature review. The Expert Working Committee recommends that nutrition is important in the overall management of VLUs.

Optimising nutrition and hydration is important to the healing of VLUs. (EBO)

Practice tips

- Nutritional requirements should be based on energy/caloric requirements with additional consideration to the stress response to illness.[109]
- Protein requirements in healthy patients are 0.8 g protein/kg daily. This may need to be increased to 1.5 to 2 g protein/kg daily in patients with heavily exudating ulcers.[109]
- There is no research on the effect of L-arginine supplements in improving venous leg ulcer healing.
- Oral zinc supplements are not effective for improving wound healing (see recommendationon 8.5).
- Patients with heavily exudating VLUs may require an increase in fluid intake[109] if they have no fluid restrictions related to co morbidities, particularly in warmer weather.
- Patients with heavily exudating VLUs may require closer electrolyte and albumin management in warmer climates.

6.9 Skin grafting

When VLUs remain unhealed for extended periods, skin grafting can be used to promote wound closure. Skin grafts can be derived from the patient's own skin (autograft), preserved animal skin (xenograft) or bioengineered skin substitutes (allograft).[110] Bioengineered skin grafts are manufactured skin replacement products not derived from human or animal skin cells.

Autografts replace the dermis and epidermis. Allografts replace the function of the epidermis and/or dermis until the skin repairs itself. Some bioengineered products feature a matrix into which cells used in skin repair are seeded.[111]

There is some evidence that bi-layered bioengineered skin grafts are more effective than standard care in promoting healing in persistent VLUs. (Grade B)

Caution

Skin grafting may cause blood loss, pain, scarring, reduced sensitivity at the graft site or infection. Grafting performed under anaesthetic has increased risks (eg. Allergic reaction to medications).[112] Reporting of adverse events in the trials included in the literature was limited. Most trials found no increase in adverse events such as infection or contact dermatitis. One trial reported squamous cell carcinoma associated with grafting.[110]

Practice tips

- Compression is required after skin grafting to ensure the graft takes and to prevent further leg oedema. This compression may be required for life.

Evidence statement

A Cochrane review[110] investigated the effectiveness of different types of skin grafting in healing VLUs. Seventeen trials compared skin grafts to standard therapy (generally a non-adherent dressing) or other skin graft types. All trials were conducted in participants with hard to heal ulcers (persisting more than 6 months) and were of moderate to low methodological quality.[110]

Autografts compared to hydrocolloid dressings

Two trials investigated effectiveness of split thickness autografts to hydrocolloid dressings, whilst one trial (n=102) found no significant differences between the two treatments the other trial reported a large significant effect for skin grafting. The difference in healing in the control groups was large between the two trials, although both used populations with difficult to heal dressings and conducted a 6 month follow up. The findings were insufficient to make a recommendation on effectiveness of autografts compared to hydrocolloid dressings.[110]

Allografts compared to standard care

Three trials (n=80) compared frozen allografts to standard care (with a non adherent dressing or hydrocolloid dressing). The trials were small and of low methodological quality. Pooled results indicated no effect of allografts above standard therapy. Three trials (n=45) investigated fresh allografts compared to standard care (non-adherent dressings) and pooled results showed no significant differences in healing. However, pooling of the results from trials comparing eith frozen or fresh allografts to standard care (n=125) showed a significant improvement in healing in ulcers treated with grafting (RR 2.00, 95% CI 1.04 to 3.84, p=0.038).[110]

Human skin equivalent compared to standard care

Two trials (n=345) compared bi-layered (dermal thickness) grafting to simple dressings with compression in participants with hard to heal ulcers. Both trials reported superior healing in VLUs treated with the bilayered grafts. (RR 1.51, 95% CI 1.22 to 1.88, p=0.0002). Clinical effect was large, with healing improving by 40 to 60%. Two trials (n=71) compared single thickness grafting using skin replacements to standard therapy. None of the individual trials reported significant results after 12 weeks. Results were not pooled due to differences in treatment regimens, primarily the number of pieces of dermal skin replacements.[110]

Comparison of different graft types

Five trials compared different graft types to each other and none of the trials provided strong evidence for a superior effect of a specific type of graft product.[110]

The review concluded that the strongest evidence suggests that bi-layered tissue engineered skin with compression was more effective in promoting healing in VLUs than a standard dressing under compression for hard to heal ulcers. Healing rate increased by approximately 14%. This may provide benefits to the patient as grafting does not require skin harvesting.[110]

One good quality SR[111] reported the results from nine trials investigating BSSs used to treat VLUs. Most of the trials were also reported in the Cochrane review.[110] Nine trials of moderate and low quality met the review inclusion criteria. Participant and ulcer characteristics were not reported. In all trials the group receiving a BSS was treated with concurrent compression therapy. One moderate quality trial (n=275) investigated Apligraf® compared to Unna's boot. At six months significantly more patients treated with Apligraf had complete ulcer closer (absolute risk difference 0.14; 95% CI 0.03 to 0.26); however the power of the study to measure this effect was not reported. There was no difference in recurrence rates after wound closure. Two blinded trials investigated Dermagraft® compared to compression alone. Neither trial showed a significant difference between treatment and control groups at 12 weeks; however pooled results showed a small significant effect (OR 4.48, 95% CI 1.01 to 19.8, p=0.05). One moderate quality trial investigated OASIS® Wound Matrix (n=120) compared to compression alone. At 12 weeks significantly more patients in the treatment group achieved complete wound healing (absolute risk difference 0.20, 95% CI 0.03 to 0.38). One low quality trial investigated Promogran™ (n=73) compared to compression with petroleum gauze. There was no significant difference in complete wound healing at 12 weeks; however, more participants treated with Promogran reported severe pain. One low quality trial investigated EpiDex® (n=77) compared to compression with split-thickness skin graft. There was no significant difference in healing at 12 weeks or 6 months. Two trials compared cytopreserved cultured allografts to a hydrocolloid. One (n=27) was of low quality, and the second (n=43) was of moderate quality. Neither study showed significant differences in healing between treatment and control groups. One low quality trial (n=22) investigating cultured keratinocyte allografts compared to placebo and compression reported no significant difference in healing after 6 weeks. In trials reporting adverse effects (n=7) such as infection and cellulitis there was no significant difference between treatment and control groups. In one trial nine deaths occurred; however these were not different between groups and no cause was reported. This good quality systematic review concluded that BSS products that had a dermal matrix component showed efficacy above standard therapy for healing of ulcers. However, the trials were not of high quality, patient and ulcer characteristics are unknown and description of the comparative treatments was lacking.[111]

6.10 Pain management

Patients with VLU regularly report moderate to severe pain. Increased pain can increase healing times by decreasing patient concordance with management strategies (eg. compression, dressing attendance and exercise). Adequate pain management is essential to promote quality of life and VLU healing.[35]

Evidence was available for three specific pain management interventions—EMLA® cream, ibuprofen dressing and electrotherapy.

EMLA cream is a topical anaesthetic agent combining lignocaine and prilocaine. It is absorbed through the skin to produce a numbing effect prior to painful procedures including wound debridement and dressing changes. It is also appropriate to use prior to skin grafting.[113]

Ibuprofen impregnated dressings can be used to manage exudating wounds. Although the primary action of the dressing product is moist wound healing and exudate management, the dressing also delivers continuous release of low dose ibuprofen (a non-steroidal anti inflammatory drug) directly to the wound. Presence of exudate stimulates ibuprofen release.[114]

Further information about electrotherapy is available in section 8.2.

The recommendation that EMLA cream is effective in managing pain associated with VLU debridement is underpinned by a good quality SR reporting good quality RCTs that consistently showed a moderate effect in relieving pain. The evidence related to ibuprofen dressings comes from low quality RCTs. Only one trial reported the pain relieving effect of electrotherapy.

There is excellent evidence that EMLA® cream is effective in reducing pain associated with the debridement of VLUs. (Grade A)

There is some evidence that an ibuprofen impregnated dressing reduces pain associated with VLUs. (Grade C)

There is weak evidence that electrotherapy may have an effect in reducing pain from VLUs. (Grade D)

Caution

The Expert Group recommend consulting specific product information, the National Prescribing Service (www.nps.org.au), Australian Therapeutic Guidelines (www.tg.org.au) or New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz) before prescribing medications.

Skin sensitivity may result from topical products used for extended periods.

Side effects from EMLA cream may include local itching, burning sensation, swelling, paleness or redness.[113] However, in the trials reported in the literature, local side effects were not more common in patients treated with EMLA cream compared with placebo cream.[115] The manufacturer reports that rarely, a serious allergic reaction can occur, and when used in large doses there is a risk of methaemoglobinaemia.[113]

No major adverse effects of electrotherapy were reported in the trials included in this review. In one trial participants experienced slight burning under electrode sites.[116] Electrotherapy is contraindicated in patients with electrical implants (eg. pacemakers),

epilepsy, malignancy or who are pregnant. It should be used with caution in patients with impaired circulation.[117]

Practice tips

- If a patient is experiencing moderate to severe pain the ulcer and its management, and the patient's pain management plan should be reviewed.
- Consider the use of topical analgesics such as EMLA cream.
- Apply EMLA cream according to the manufacturer's instructions.
- EMLA cream should be applied 30 mins prior to debriding the VLU.[113]
- EMLA cream should be covered with a dressing (eg gauze) following application. It is also available as a patch that does not require additional dressings.[113]
- Ibuprofen-impregnated dressings maintain their pain relief effect for up to seven days[118] and should be applied according to manufacturer directions.
- Topical anti-inflammatory agents such as ibuprofen may delay wound healing so should not be used for prolonged periods.

Evidence statement

EMLA cream

A good quality meta-analysis[115] investigating the management of chronic VLU pain identified six RCTs for inclusion, all of which investigated the effectiveness of EMLA 5% cream in reducing pain during debridement. All trials were of good methodological quality. The six RCTs were conducted in patients with VLU less than 50 cm^2 in size. Half of the trials excluded patients with diabetes, which may be significant as patients with diabetes will be more likely to have peripheral neuropathy and impaired perception of pain. Two trials only included participants who had previous experience of pain during debridement, which also may affect the perception of whether the debridement event is painful. Five of the six included trials used sharp debridement whilst the sixth included any form of debridement. In one trial the VAS was administered during the procedure, leading to significantly higher pain scores. A limitation of all the trials was a lack of recording of baseline pain assessments prior to the procedure.[115]

A total of 159 participants were treated with EMLA 5 % cream 30 minutes prior to debridement and 158 participants were randomly allocated to receive a placebo cream. The results were pooled in a meta-analysis for the outcome measure of pain on VAS during debridement. Mean difference in pain score using a random effects model favoured the treatment group, with a WMD -20.65 (95% CI -29.11 to -12.19, p<0.000001). This correlates to a mean reduction of 20.65 mm on VAS. Meta-analysis was conducted using a fixed effects model for the results of three trials that reported adverse events. The findings indicated no significant differences between the EMLA 5% cream groups and the control groups for either burning when cream removed (OR 1.72, 95% CI 0.74 to 4.01, p=0.21) or itching when cream removed (OR 1.68, 95% CI 0.64, 4.38, p=0.29).[115]

Ibuprofen foam dressing

One moderate quality trial[119] investigated the effect of a dressing impregnated with slow release ibuprofen in relieving pain from VLUs. Adults aged over 65 years with painful chronic venous leg

ulcers of more than 8 weeks with a baseline pain described as at least moderate on a 5-point verbal rating scale who had an ABPI above 0.8 were eligible following a 2 week run in period in which the ulcer was treated with compression. Patients were ineligible if they had experienced an analgesic-resistant ulcer in the preceding 6 months, had an allergy to NSAIDs, asthma, urticaria, clinical infection, were pregnant or lactating, diagnosed with diabetes, or taken unscheduled analgesia in the 3 days before trial commencement. The participants had ulcers ranging in size, with a minimum length of 1.6cm and maximum area of 50 cm^2. Participants were randomised to receive either a dressing containing 112.5 mg of ibuprofen releasing over 7 days (n=62) or a comparator foam dressing (n=60), with treatment continuing for 47 days. In the last five days of the trial, the ibuprofen dressing group received the control dressing. Outcomes were assessed daily in the first and last 5 days of the trial. Significantly more participants in the ibuprofen dressing group had pain relief in the first five days of the trial (74% vs. 58%, $p<0.05$). Wound pain intensity in the first 5 days was significantly greater for the ibuprofen dressing group (40% reduction vs 30% reduction, $p < 0.003$) and decreased for all patients over time ($p < 0.001$). In the last 5 days of the trial, when the treatment group received the control dressing, this group experienced a significant increase ($p<0.05$) in wound pain but the control group pain intensity remained stable. There was no significant difference in rate of ulcer healing, no serious adverse events and the minor adverse events (primarily skin reactions) occurred at a comparable rate between the groups. This trial provided moderate quality evidence for the effect of an ibuprofen impregnated dressing in reducing pain, with a moderate clinical impact of at least 2 points on a 10 point pain scale.[119]

Electrotherapy

A low quality RCT[120] reported the effectiveness of electrotherapy for reduction of pain and promotion of healing in 39 patients with chronic VLU of average 42 months duration. Details of the trials are reported under electrotherapy. The electrotherapy group had achieved significant reduction in pain by the end of the first treatment month and this remained significant until 4 month follow up ($p=0.01$) and was also significant compared to the sham therapy group ($p=0.049$). However, 59% of participants took concurrent analgesia, and it was unclear if this was equivalent between groups. This trial provided low quality evidence that electrotherapy may be associated in a reduction of pain.[120]

A low quality trial[116] with 35 participants investigated the treatment of VLUs with frequency rhythmic electrical modulation system (FREMS). The trial is reported in more detail under electrotherapy. At 8 week follow up FREMS was associated with a significant decrease in pain scores measured on VAS. However, the groups were non-equivalent at baseline, with the control group having ulcers of significantly longer duration. Participants treated with FREMs experienced slight burning at electrode sites.[116]

6.11 Therapuetic ultrasound

Ultrasound therapy delivers acoustic vibrations at a range of high frequencies in either a continuous or a pulsed manner to the area under treatment. Usually a water or gel based coupling agent is used between the ulcer area and the ultrasound applicator. The benefits of ultrasound are achieved from both thermal effects and non-thermal effects. Thermal effects, generally achieved through continuous ultrasound, are hypothesised to increase blood flow to the area. Non-thermal effects, such as acoustic streaming and cavitation are achieved through pulsed ultrasound.[121, 122] These are variously theorised to provide benefits through enzymatic fibrinolysis, stimulation of

protein synthesis, increasing cell proliferation, stimulating an increase in inflammation and promoting angiogenesis; however, there is insufficient research in this area to determine the validity of these theories.[121] These non-thermal effects are distinguished from the use of ultrasound for debridement.

Trials on the use of ultrasound in treating VLUs generally used pulsed ultrasound at a frequency range of between 1 and 3 MHz at an intensity of 0.5 to 1 W/cm^2, for durations of 5 to 10 minutes. Treatment length varied from between 3 weeks to 12 weeks, with treatment generally applied at a weekly or twice weekly frequency.[121, 123]

The evidence supporting the recommendation on ultrasound therapy comes from a two meta-analyses of results from moderate and low quality studies with small numbers of participants. Results were consistent that there is no effect on total numbers of ulcers healed; however there was a slight effect reported on the percentage of ulcer area that healed in participants treated with various ultrasound regimens.

There is good evidence that therapeutic ultrasound therapy is not related to an improvement in total ulcer healing but may slightly improve the percentage of healed ulcer area when used in combination with compression therapy. (Grade B)

Caution

In trials conducted in patients with VLUs there was no significant adverse events associated with ultrasound therapy. Ultrasound is not recommended for patients with a pacemaker or other implanted electrical devices.[124]

Evidence Statement

A good quality Cochrane review[121] reported on the effectiveness of ultrasound therapy for the treatment of VLUs. The review was of good quality; however the trials included were of a generally low methodological quality and included small numbers of participants.

Ultrasound therapy compared to sham ultrasound

The results of five low and moderate quality trials were pooled using a fixed effect model where the same outcome measures were reported. Two of the trials included participants with VLUs at least 2 cm^2 in size and had persisted for at least 2 to 3 months. Follow up periods used in the trials were between 8 and 12 weeks. In all trials, both groups received either compression or support bandaging, ultrasound treatment regimens investigated were:

a) 3 MHz at 1 W/cm^2 3 times per week for 4 weeks in two trials
b) 1 MHz at 0.5 W/cm^2 3 times per week in the first month, twice weekly in the second month and weekly for the final month
c) 1 MHz at 1.0 W/cm^2 twice per week for 8 weeks

Findings in individual trials varied, with some establishing a significant effect on specific outcome measures at some time periods. In the meta-analysis, there was no statistically significant difference in total number of ulcers healed (RR 1.41; 95% CI 0.83 to 2.39, p=0.20); however, the results favoured

ultrasound therapy for percentage of ulcer area remaining (WMD -4.75%, 95% CI -8.24 to -1.26, p=0.0076). It was unclear how healing was defined in individual trials or how area of the wound was measured. [121]

Ultrasound therapy compared to standard therapy

Three trials compared ultrasound therapy to different standard therapies that consisted of various dressing products, antibiotics, fibrinolyic agents and support bandaging. Participants receiving ultrasound were also treated with the same standard therapies in all trials. Follow up varied from 3 weeks to 12 weeks. One trial used ultrasound at 30 kHz administered in water and the other two used pulsed ultrasound at 0.5 to 1 MHz, 0.5 W/cm². The results of these three trails were pooled using a fixed effects model and showed no statistically significant difference between the groups for number of ulcers totally healed (RR 1.55, 95% CI 1.00 to 2.40). [121]

In trials reporting withdrawals or side effects, allergy and pain were the primary reported conditions and occurrence rates did not differ between ultrasound and control groups.[121]

A low quality SR[123] also investigated the effect of ultrasound therapy. The review was at risk of bias due to the methods used for pooling and the minimal critical appraisal of included studies. Findings from the same studies reported in the Cochrane review[121] were pooled in a meta-analysis and the results concurred that ultrasound compared to sham ultrasound is associated with an improvement in percentage of ulcer area healed but not total number of ulcers healed.[123]

6.12 Education and psychosocial support

6.12.1 Health professional education

Given the complex nature of the assessment and management of leg ulcers, education and training is essential for achieving positive patient outcomes.

The literature suggested that despite having attended previous post-basic education on VLUs, some community nurses benefited from a range of different educational programs that focused on assessment, management, hands-on skills (eg. performing ABPI using Doppler ultrasound and performing compression bandaging) and quality of life issues for VLUs.[44, 125-127] One study provided evidence that improving the knowledge of nurses caring for patients with VLUs was related to improved patient outcomes including a reduction in ulcer recurrence rates.[128] Low level evidence provided support for various programs ranging from highly experiential to didactic lectures.

The literature search identified only one low quality RCT investigating the effectiveness of education interventions. The trial reported a beneficial effect on the knowledge of nursing staff of personalised expert feedback on their ulcer care. A number of non-randomised quasi-experimental trials provided consistent additional support for the effect of education for health professionals.

There is some evidence that health professionals benefit from appropriate education on VLUs and their management. Patient outcomes may be superior when ulcer care is conducted by an appropriately trained health professional. (Grade C)

Evidence statement

One low quality RCT[44] provided evidence that community nurses' knowledge of VLUs improves as a result of education specific to the nurses' requirements. Thirty-eight nurses with patients suffering from VLUs were recruited into the trial after volunteering and attending intensive information sessions. After completing a validated pre-test to determine baseline knowledge on VLU diagnosis, assessment, physiology and care, nurses were randomised (method not reported) to regular a group where participants maintained work conditions (no specific support) or to a second group receiving tele-advice from an expert when required. Nurses receiving the intervention took digital photos of the patients' wounds and received personalised feedback via telephone regarding the most appropriate care. After 12 weeks the participants all completed a post-test to detect changes in knowledge levels. Those in the intervention group had significant improvements from baseline in overall average score ($p=0.022$) and score for both dressing and management of wound care questions ($p=0.05$) but did not improve on questions related to physiology ($p=0.23$) or those classified as most the difficult questions. The control group showed no significant improvement in any category, a significant decrease on scores for most difficult questions ($p=0.006$) and for weighted average score ($p=0.008$). The trial was too small to make inter-group comparisons. Although the study suggested that this form of education may improve nursing knowledge, there was numerous limitations. There was no control for nursing staff completing their own research to improve scores; it was unclear if advice was received from the same expert for all participants; and those who participated were likely to have been highly motivated to perform well. The contribution that improved knowledge may make to the overall care and healing rate of the patient's VLU was not addressed in this trial, although follow on studies were inferred.[44]

Lower level evidence

One quasi-experimental, non-randomised trial[127] conducted in Hong Kong investigated the ability of an ulcer specific education program in improving the knowledge and skills in caring for patients with VLU of 42 enrolled and registered nurses working in community settings and had varying baseline knowledge levels. The education program administered to the nurses included didactic teaching, open discussion, multi-media presentation and skill demonstration. Content of the program included epidemiology, pathology, ulcer assessment and management and QOL issues. Participants demonstrated improvements in knowledge after participating in the program, with identification of ulcer aetiology being an area in which nurses made significant improvement in their knowledge.[127]

Another quasi-experimental, non-randomised trial[125] conducted with 264 community nurses in the UK investigated the effect on knowledge of an education program consisting of an open learning pack, two day study period, a visit to a VLU clinic and multi-media presentations. The 224 nurses who participated in the education program achieved greater improvement on a knowledge questionnaire following the education than did 40 control nurses who were not exposed to targeted education.[125]

However, a second non-randomised quasi-experimental study[126] conducted in the UK to compare the effects of a 4-hour educational program designed to incorporate different learning styles and needs to those of a standardised program found no significant differences between the knowledge improvements of participants. The experimental learning program was designed to address needs identified through participant performance at hands-on and enquiry stations. It consisted of didactic learning, instruction in group and individual settings, discussion groups, case studies and group debate and problem solving. The program was as effective as a regular didactic lecture in improving knowledge of VLUs.[126]

One quasi-experimental study[128] investigated the relationship between a nurse education program and improving patient adherence to treatment and ulcer recurrence. Patients from various district nursing programs were followed for 52 weeks. Nurses working in the districts receiving the experimental education program participated in a 3 hour education session focused on improving patient compliance with therapy. Patients in this group received educational pamphlets describing strategies to prevent VLU recurrence. The control group of nurses received a one hour education session on VLU guidelines and patients received standard care. At 52 weeks, the experimental group patients had a significantly lower rate of VLU recurrence (p=0.004) compared to the patients in the control group, although there was no significant differences between the two groups for time spent wearing compression. The experimental group performed greater leg elevation. The trial suggested that nurse education may be a factor in improving patient adherence to therapy and reduction of VLU recurrence.[128]

Practice tips

- Education in the assessment and management of VLU should be provided to all health professionals caring for patients with VLUs.
- An accredited or endorsed program should be sought as such programs promote sound education and practice advice.

6.12.2 Patient education

Patient concordance with management regimens significantly influences both healing times and prevention of VLU recurrence. Interventions such as compression, elevation and exercise require patient persistence. It is therefore crucial that patients understand the importance of such interventions and how they should be implemented.

The literature search identified only one, small low quality RCT investigating the effect of written education material in improving knowledge of patients with VLUs. The trial showed that written education did not lead to greater improvements in a patient's knowledge beyond that achieved with verbal education from a health professional. The Expert Committee reached consensus that providing patients with VLUs with education about their condition and its management is essential.

There is weak evidence that patients with VLUs benefit from appropriate education on their condition and its management. (Grade D)

Practice tips

- Both verbal and written education leads to improvements in patient knowledge regarding management of their VLU.[129]
- Patient education includes:
    - basic pathophysiology of venous hypertension and VLU
    - compression therapy and the role it plays in managing VLUs and venous hypertension. This includes the potential implications of declining compression therapy.
    - Devices and appliances that may assist in donning and doffing compression garments
    - elevation and exercise
    - nutrition
    - skin care
    - potential adverse effects of any therapies and when to seek assistance
    - managing co morbidities (eg. diabetes)
- Support groups (eg. "leg clubs") provide patients with education and support to manage their ongoing disease, although they are not available in all locations.

Evidence statement

A low quality RCT[129] investigated the effectiveness of written information material in improving the knowledge patients with VLU have regarding their disease and its management. The researchers recruited 20 participants who took a baseline knowledge questionnaire before receiving verbal information from the doctor together with written supportive information (n-10) or no written information (n=10). Patients repeated the questionnaire 4 to 6 weeks later. The result indicated no significant differences between patients who did or did not receive reinforcing written educational material. Participants in both groups had significant improvement in knowledge, particularly regarding exercise and compression for VLUs. The study did not investigate if improved education translated into implementation of appropriate intervention. The study was small, participants had a low level of education (65% had no formal education beyond primary schooling) and confounding issues such as cognitive illness, sensory deficits, non-English speaking backgrounds, emotional status, support from carers, other access to educational material and ability to read were either not discussed or not considered in the trial design. The results that written material is not beneficial should be considered cautiously given the study design, patient selection and small size of the trial.[129]

A moderate quality SR[130] reported on the effectiveness of different programs in improving patient concordance with therapy. The majority of papers compared different types of compression therapy; however, three of the included papers addressed educational and psychosocial interventions. One paper reported on the development of "leg ulcer clubs" focused on social interaction, patient participation, role modeling and interactive education (early detection and prevention). Although methods of assessment were not reported, failure of patients to initaite or continue with recommended therapies reduced from 17% at commencement of the clubs to 5% after 11 months. Of those who failed to concord with recommeded therapy by the end of the trial,

the majority had concurrent diagnosis of dementia. An audit of similar clinics reported only 3 out of 10 patients who had attended a "leg club" failed to implement recommendations reagrding maintenance of dressings. Two studies reported educational interventions to improve concordance with VLU treatments. In one quasi-experiment a program comprising combinations of behavioural, educational and affective strategies was shown to have a positive effect. Participants (n=51) exposed to the educational intervention elevated their legs for more than 12 hours per day, whilst the control group spent less than 10 hours with legs elevated. However, time spent wearing compression bandaging did not change and the groups were not comparable at baseline. In the second trial, education in the form of oral and written information and a quiz achieved 91% concordance with therapy in VLU patients. Both studies were of low quality and confounding factors (eg. patient selection) seem likely to have influenced the results.[130]

6.12.3 Psychosocial support

Chronic disease is reported to have a negative psychosocial impact. The literature reported patients with VLU may be at increased risk of negative psychosocial outcomes including depression, low self esteem, social isolation, fear and anger. Pain, functional limitations, impact of compression bandaging (eg. finding shoes/clothes to cover the bandaging) and the financial burden of ongoing care are contributing factors and may also reduce the patient's concordance with therapy in the long term.[4, 131]

Studies related to psychosocial care investigated the assessment and psychosocial profile of patients with VLU but did not address strategies that are effective in providing psychosocial support. The Expert Working Committee recommends that consideration to the patient's psychosocial status forms part of an holistic management plan.

Psychosocial assessment and support is an essential component in the patient's management. (EBO)

Practice tips

- Include patients in the development of their management plan. This may increase the feasibility of the plan and the patient's concordance with therapy.[131]
- Providing patients with clear information about their own progress (eg. graphs of wound size) may contribute to patient concordance with management.[131]
- Quality of life scales specific to populations with VLU and/or venous disease (eg. the CWIS and CVIQ) include assessment of psychosocial factors.[4]
- Support groups (eg. "Leg clubs") provide patients with education and support to manage their ongoing disease, although they are not available in all locations.

Evidence statement

A low quality SR[4] reported on the life impact of VLUs. Participants in the research included in the review were primarily older females. Findings related to psychosocial impact of VLUs were

conflicting. While some studies reported no differences between patients with VLUs and healthy populations for emotional outcomes such as loneliness, relationships and life satisfaction, other studies reported significantly lower scores on QOL scales for patients with VLUs. Patients with VLU were reported to have lower self esteem and greater fear depression, isolation and anger. Other themes included pain, function limitations and sleep deficits. The review concluded that patients with VLU have a significantly lower QOL compared with healthy populations and assessment with appropriately validated psychosocial tools is desirable.[4]

A moderate quality qualitative SR[131] reported research related to patient concordance with therapy and influencing factors. The research addressed both concordance with management for an active VLU and management to prevent recurrence of VLU. The results showed that concordance with therapy is influenced by various factors including treatment regimens, psychosocial issues, interpersonal relationships and patient-related factors. Data collected from nurses suggested that health professionals primarily focus on patient-related factors (eg. lack of knowledge, poor motivation) as a reason for lack of concordance with treatment; however, data from patients indicated more complex reasons. Pain and discomfort appeared to be a significant factor in patients not wearing compression bandaging and also in lack of participation in exercise. Patient beliefs (eg. believing compression therapy was ineffective or that the ulcer would not heal) were a factor for some patients. Some studies identified lifestyle issues that influenced compliance (eg. affordability of bandages, lifestyle factors impacting upon opportunity to elevate legs). The review questioned the categorisation of some behaviour as "non-compliant", suggesting that the lifestyle advice given to patients was not always appropriate to their situation, leaving patients little option but to ignore the advice. For example, a patient with a history of musculoskeletal problems may have significant activity limitations and be unable to participate in exercise, despite health professionals advising this as part of a treatment regimen. The researchers made recommendations for improving patient concordance with VLU therapy. Developing an effective relationship with the patient and encouraging his or her input into management planning was considered important. Conducting an holistic assessment before recommending therapy was reported as a factor that may increase the relevence of internventions to the patient of lifestyle. Ensuring the patient had a pain management plan, particularly before commencing compression therapy, was considered important. Providing the patient with knowledge (eg. about the validity of therapies, about expectations of pain) may enhance concordance with therapy. Addressing social isolation by being proactive in organising support from family, friends or community groups was proposed in the research. Finally, the reviewers recommended that health professionals make efforts to share the patient's progress (eg. healing rates, reduction in oedema) with the patient to improve motivation.[131]

6.13 Pharmacological management

The Expert Working Committee recommends consulting specific product information, the National Prescribing Service (www.nps.org.au), Australian Therapeutic Guidelines (www.tg.org.au) or New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz) before prescribing medications.

6.13.1 Pentoxifylline

Pentoxifylline is a haemorheologic agent, that increases blood circulation and oxygenation of tissues.[132-134] The medication increases the efficiency of blood flow through an effect in decreasing blood viscosity, platelet aggregation and fibrinogen levels.[132-135]

The evidence underpinning the recommendation that pentoxifylline promotes VLU healing comes from a good quality SR reporting 12 moderate and low quality RCTs that were generally consistent in showing a moderate clinical effect of pentoxifylline compared to placebo.

There is good evidence that pentoxifylline is effective in promoting healing in VLUs. (Grade B)

Caution

Pentoxifylline is not recommended for patients with a history of severe haemorrhage (eg. Retinal haemorrhage, cerebral haemorrhage, active peptic ulcer), acute myocardial infarction or angina. Pentoxifylline is also not recommended for patients with marked impairment of the liver or kidney and care should be taken if prescribing to patient's with mild renal or liver disease. [134] Pentoxifylline has not been tested in children or pregnant or breast feeding women.[133, 134]

Pentoxifylline is related to a higher incidence of gastrointestinal side effects than placebo.[132, 133]

Other common side effects include dizziness and headaches.[133] Pentoxifylline increases the effect and toxicity of theophylline and caffeine, and increases the effect of some anticoagulants (including warfarin). It should be taken with caution in patients taking these medications and concurrent caffeine intake should be minimised.[135]

Practice tips

- Although some of the evidence suggested that pentoxifylline is more effective than compression therapy in healing VLUs,[132] best practice supports the use of compression therapy wherever possible, and if used, pentoxifylline should be concurrent to compression therapy.
- Regularly monitor the blood pressure of hypertensive patients taking pentoxifylline.[134]
- Pentoxifylline should be taken with meals to reduce GIT side effects.[133]
- Pentoxifylline may take up to 8 weeks to show full effects.[133, 134]
- Patients should inform their surgeon or dentist if they are taking pentoxifylline before undergoing major procedures.[133, 135]

Evidence statement

A good quality Cochrane SR[132] included 12 RCTs published up to 2009 that investigated the effectiveness of pentoxifylline 400mg (twice or three times daily) for the treatment of VLUs. Of the trials included in the review, quality ranged from moderate to low.

Results from eleven trials (n=841) comparing pentoxifylline to placebo pooled using a random effects model showed that participants receiving pentoxifylline were more likely to heal than those receiving placebo (RR 1.70, 95% CI 1.30 to 2.24, p=0.00013); however, the trials were heterogeneous. The reviewers conducted a number of sensitivity analyses (eg. published vs. unpublished trials, based on duration, based on primary outcome measure). The only sensitivity analysis without significant heterogeneity was that in which studies that specifically recruited hard-to-heal patients were excluded. In this analysis, participants treated with pentoxifylline were more likely to have ulcer healing than those receiving placebo (RR 1.30; 95% CI 1.10 to 1.54, p=0.0019). This translated to an absolute increase in healing of 21% (95% CI 8% to 34%) and a NNT ranging from 3 (95%CI 2 to 12) to 11 (95%CI 6 to 43) for pentoxifylline compared to placebo.[132]

Pooled results from seven trials comparing pentoxifylline to compression plus placebo using a random effects model showed that participants receiving pentoxifylline were more likely to have ulcer healing than those receiving compression and a placebo (RR 1.56, 95% CI 1.14 to 2.13, p=0.005). Once again, there was significant heterogeneity. When results from the three trials that recruited hard-to-heal patients were combined using a fixed effects model, the results were homogeneous and showed that participants treated with pentoxifylline were more likely to have ulcer healing than those who received compression plus placebo (RR 2.36; 95% CI 1.74 to 3.19, p<0.00001). This translated to an absolute increase in healing of 23% (95% CI 4% to 43%) and a NNT ranging from 3 (95%CI 2 to 8) to 4 (95%CI 2 to 9) for pentoxifylline without concurrent compression therapy.[132]

Nine trials (n-549) reported on side effects. These trials were combined using a fixed effects model and the analysis showed that participants treated with pentoxifylline were significantly more likely to experience side effects than those receiving placebo (RR 1.56; 95% CI 1.10 to 2.22, p=0.014). Gastrointestinal side effects were the most experienced adverse event.[132]

6.13.2 Micronised purified flavanoid fraction

Micronised purified flavanoid fraction (MPFF) consists of diosamin and flavanoids. It is thought to have an effect in reducing venous distension and increasing lymphatic drainage thereby reducing oedema.[136]

Evidence underpinning the recommendation that MPFF may decrease ulcer healing times comes from a moderate quality SR reporting five RCTs that were of low quality and had inconsistent findings.

There is weak evidence that micronised purified flavanoid fraction may decrease the healing time for VLUs. (Grade D)

Caution

The risk of adverse events with MPFF is very low. In one trial GIT side effects were reported in approximately 14% of participants, which was not significantly different from patients taking placebo. There are no known drug intereactions.[136]

Evidence statement

One moderate quality systematic review[137, 138] investigated the effect of micronised purified flavonoid fraction (MPFF) on VLU healing. The SR included five trials. Participants (n=723) had clinical signs of VLU, a previous history of varicose veins or post-thrombotic syndrome. In all trials, VLUs were present for at least three months. Participants across the five included trials had a mean ulcer area of 10.4 cm^2 (range 1 to 108 cm^2); mean ulcer duration of was 19.6 months (range 1 to 237 months); and average ulcer disease duration of average 13.5 years (range 0 to 58 years). Trials compared MPFF 1 g daily as an adjunct therapy to compression bandaging at a minimum of 30 mm Hg at the ankle. Pooled data from four trials for complete healing at six months showed a relative risk reduction (RRR) of 32% (95% CI 3% to 70%) for MPFF. However, there was significant heterogeneity (p=0.014). Exclusion of one trial that had a large proportion of ulcers that were less than $5cm^2$ and of shorter duration created homogeneity and showed a RRR of 45% (95% CI 23% to 71%). A sub group analysis of participants with ulcers more than $5cm^2$ in area (4 trials) showed a RRR of 53% (95% CI 15 to 103%) for complete healing in six months with MPFF. Results from five trials showed a RRR 44% (95% CI 7 to94%; p=0.015) of complete healing in two months for MPFF, but the results for healing at four months were not significant.

The results of this systematic review should be considered within the context of the methodological limitations of the trials included in the analysis. Of the included trials, only two used a placebo control.[137, 138] One of these did not report complete healing at six months so was excluded from the primary analysis leaving open the possibility that the findings are influenced by the placebo effect. In addition, only two of the trials in this review were double blinded, with no blinding in the other three. Once again, the two double blinded trials were those not included in the primary analysis. The issues related to methodological flaws within the included trials, along with potential bias from the involvement of the product manufacturer in providing funding this review, suggest that the outcome should be considered cautiously until further good quality placebo-controlled, blinded RCTs investigating the role of MPFF in ulcer-healing provide further evidence.

7. RECOMMENDATIONS FOR PREVENTING RECURRENCE OF VLUs

7.1 Maintenance of leg care

The risk of VLU recurrence is reduced through the maintenance of practices that promote the health of the legs. (EBO)

Practice tips

- Exercise and regular ambulation helps reduce the signs and symptoms of venous disease.
- Regular mositurising of the lower limbs helps maintain skin intergrity.

- Elevation of the limbs when sitting and avoidance of standing for prolonged periods assists in controlling oedema.
- Support groups (eg "leg clubs") can promote uptake of and concordance with practices that help maintain skin integrity and provide long term psychosocial support.

7.2 Ongoing compression therapy

Compression therapy aims to promote venous return, reduce venous pressure and prevent venous stasis. Continuing compression therapy following healing of a VLU can help reduce the long term effects of venous disease. More information on compression therapy is provided in the recommendation for the treatment of VLU.

The recommendation on prevention of VLU recurrence was based on moderate quality RCTs that were generally consistent.

There is some evidence that compression systems are effective in reducing the risk of recurrence of VLUs. (Grade C)

Caution

Refer to the caution statement in the recommendation for use of compression therapy in the treatment of VLUs.

Practice tips

- There is minimal evidence to suggest that there is a superior compression system to prevent recurrence of VLUs.[45, 139] Moderate and low quality RCTs suggest that medical grade compression hosiery may be more effective than compression bandages in preventing ulcer recurrence (24% vs. 53%, $p<0.05$).[48]
- The Expert Working Committee recommends that after healing has been achieved it is ideal that compression bandaging be maintained to the same degree for 2 to 4 weeks before changing to medical grade compression hosiery.
- Moderate compression may be as effective as a higher compression in preventing ulcer recurrence. The Expert Working Committee's consensus is that compression of 18—40 mmHg will reduce the risk of ulcer recurrence. Patients should be offered the strongest compression that they can tolerate and manage.
- Patient acceptance of higher pressure medical grade compression hosiery may be an issue. In one trial more than 20% of participants wearing high grade medical grade compression hosiery to prevent ulcer recurrence withdrew due to 'stocking related events'[140] and another RCT reported a more moderate grade compression was better tolerated than high grade compression.[139] A patient

survey indicated that patients were less likely to wear medical grade compression hosiery if they were uncomfortable.[141]

- Patients require education about the importance of wearing compression hosiery. Patient beliefs about the benefits of medical grade compression hosiery in preventing ulcers may influence concordance. A survey found participants were more likely to wear stockings if they believed the stockings were worthwhile (OR 21, 95% CI 3.5 to 240, p=0.0002) and if they believed ulcers would be prevented (OR 4.40, 95% CI 1.50 to 13, p=0.004).[141]
- Further practice tips can be found under compression therapy for the treatment of VLUs (recommendation 6.1).

Evidence statement

One good quality Cochrane review[139] reported secondary outcome measures from moderate to low quality RCTs sponsored by product manufacturers. In one trial, 32% of participants who were non-compliant with stocking compression had recurrence of an ulcer within the five year trial period, compared with 19% of participants who wore stockings on a daily basis. In the second trial a post hoc analysis found that the participants who were excluded from the trial due to inability to apply stockings experienced significantly greater recurrence of ulcers compared to those who participated in the trial (RR 2.58, 95% CI 1.33 to 5.01).[139]

A second good quality Cochrane review[45] reported one moderate to low quality RCT (n=233) comparing compression to no compression for preventing recurrence of VLUs. There were no significant differences in likelihood of ulcer recurrence or time to reoccurrence over 12 months (p=0.38) between a four layer bandage system and usual care. The trial was under powered to detect a significant result. In another trial (n=30) there was no cases of recurrence within 6 months in VLUs treated for 12 weeks with single layer elastic bandaging, four layer bandaging or a four component compression with paste bandaging. There was no non-compression comparison group.[45]

One good quality RCT[140] reported re-ulceration as a secondary outcome. Participants who had healed from a VLU were randomised to receive either no compression or below knee compression stockings (35 to 45 mmHG graduated pressure) for up to 12 months. The group wearing stockings had a lower rate of reulceration (22.36% vs. 54.3%, p=not reported). However, 22% of participants in the compression stocking group withdrew from the trial due to undefined stocking-related events.[140]

8. TREATMENTS NOT CURRENTLY RECOMMENDED

The following sections outline treatments that are not recommended by the Expert Working Committee. Reasons for not recommending a treatment are detailed in each section. Reasons include conflicting evidence, evidence that the treatment is not effective and treatments for which the risks outweigh benefits.

8.1 Electromagnetic therapy

Electromagnetic therapy exposes the patient to a magnetic field effect, usually in a pulsed fashion. It includes pulsed short wave diathermy, pulsed electromagnetic field therapy and diapulse.[142, 143] These therapies use different radio frequencies, energy frequencies, pulse lengths and energy powers. Their effect is theorised to be an energy boost to the ulcer through a calculated disruption to the ions, molecules, membranes and cells that can have physiological effects that promote healing. It is purported that electromagnetic therapy increases white cells and fibroblasts within a wound, stimulates osteogenesis and enhances blood flow.[142]

The current research on electromagnetic therapy comes from small studies, many of which have poor methodological quality. However, a number of good quality trials have shown conflicting findings regarding the ability of electromagnetic therapies to promote healing in VLUs. Although there does not appear to be a substantial positive effect from these therapies, there are inconsistencies within the body of evidence.

There is conflicting evidence on the effectiveness of electromagnetic therapies for promoting healing in VLUs. (Grade C)

Caution

No major adverse effects of electromagnetic therapy were reported in the trials included in this review. Manufacturers of devices used to administer electromagnetic therapy do not recommend their use in patients with pacemakers or other implanted devices, diabetes, cancer, epilepsy, cardiac infarction less than 2 months ago, congenital pathology of central nervous system or kidney disease or in pregnant women.[144, 145]

Evidence statement

A good quality Cochrane review[143] investigated electromagnetic therapy for treating VLUs. After a comprehensive literature search only 3 RCTs meeting the well-defined inclusion criteria were identified. The trials were subjected to critical appraisal and reported to be of varying quality. Due to variations in the type of treatments, the outcomes of the studies were not appropriate for pooling in meta-analysis and were reported in a discursive format. All the studies in the review were small and likely to be underpowered. [143]

Two of the RCTs compared PEMT to sham therapy. The first was a moderate quality double-blind RCT included 44 people with VLU. Participants were randomised to receive either electromagnetic

therapy at 75 Hz, 2.7 mT, with an impulse width 1.3ms (n = 22) or sham stimulation (n = 22) for four hours per day for 3 months. The two groups were not comparable with respect to ulcer size at the commencement of the trial. Using data from participants who completed the trial, at 90 days there was significantly greater proportion of people with healed ulcers in the PEMT group compared to those receiving sham therapy (97% vs. 32%, RR 2.11, 95% CI 1.01 to 4.42, p=0.47). When the participants who dropped out of the trial were included in analysis, there were no significant differences (RR 2.0, 95% CI 0.92 to 4.37). In a good quality but small RCT participants were randomised to receive PEMT at 0.06 mV/cm, with a signal of 3.5 ms total width (n=18) or to sham therapy (n=13) for 3 hours for 12 weeks. The groups were comparable at baseline, there was blinded outcome measurement and the researchers conducted ITT analysis for the primary outcome measure. At 8 weeks, participants in the PEMT group had a 47% reduction in the size of ulcers, whilst those in the sham therapy group had a 49% increase in size of ulcers. The third trial was a low quality double blind RCT comparing PEMT with standard topical treatments. Participants (n=19) were randomly assigned one of three groups. The first group received electromagnetic therapy at 600 Hz electric field and 25 mTesla magnetic field. The second received electromagnetic therapy at 600 Hz on the first five days followed by 800 Hz and a 25 mTesla magnetic field for the remainder of the trial. The third group received sham therapy. Therapy was administered for 5 days a week for 30 days along with regular dressings. There was no significant difference between the two groups in the number of ulcers healed (20% vs 22%, RR 0.90, 95% CI 0.16 to 5.13, p=0.91). The review concluded there was no reliable evidence supporting the effectiveness of PEMT in treating VLU.[143]

A second good quality SR[142] reported the results from 6 RCTs investigating PEMT. The review reported that 4 of the RCTs were of strong methodological designs and 2 were low quality studies. Three of the trials were reported in the Cochrane review.[143] Pooling of results was not performed due to heterogeneous treatment regimens. Four of the six trials reported a significant improvement in ulcers exposed to PEMT. There were inconsistencies in the findings between studies regarding the ability of PEMT to heal ulcers within a specific time frame. Studies reportedly included participants with different sized VLUs and the reviewers noted a pattern for smaller VLUs (<15cm^2) having the most significant rates of healing. Although the review concluded that there is strong evidence for a significant effect of PEMT on healing VLUs,[142] there are inconsistencies reported between studies within the review and between this review and a Cochrane review[143] reporting some of the same studies.

A low quality RCT[146] investigating the effectiveness of static electromagnetic therapy for healing VLUs. The intervention of interest, Ulcer Care, was described as containing 4 neodynamic magnets and was used for 12 weeks on the participants randomised to the treatment group (n=16), although the regimen was not reported. The placebo group (n=12) received sham treatment. Similarities between groups at baseline were unclear, but it appeared the intervention group had small ulcers. The intervention group achieved significantly greater healing after 12 weeks on outcome measures of change in ulcer area, change in and ulcer width, perimeter and length. There was no difference between the magnetic and the sham therapies for pain intensity, QOL and overall measures of health. Patients who withdrew or had missing data were not considered in the analysis and were not equivalent between groups. Due to methodological short comings the results of this trial were unconvincing.[146]

8.2 Electrotherapy

Electrotherapy is proposed as a therapy for accelerating natural wound healing processes. The trials reviewed in the literature appraisal used a range of different therapy regimens. One trial specifically investigated high voltage therapy[147] whilst voltage was varied between 100 and 300 V in other trials depending upon patient response. One trial investigated continuous rhythmic application of electrical pulse. Frequency was generally between 100 and 128 Hz. Treatments ranged from 50 to 100 days, with therapy applied on 3 to 6 days per week for periods between 30 and 50 minutes.

Because various cell types respond differently to electrotherapy throughout the wound healing process, there may be a role for application of different current types. In the initial inflammatory stages of wound healing, mast cells are reduced by negative polarity. In proliferative wound stages, fibroblasts migrate to negative polarity.[120] Two trials[120, 147] included in this review used treatment regimens that varied the application of electrotherapy between cathode and anode electrodes at various wound healing stages.

The recommendation on electrotherapy is underpinned by evidence from three low quality RCTs. The findings between the trials were inconsistent regarding the effect of electrotherapy on healing, with two trials reporting no effect and one reporting a slight increase in healing rates, although there was significant methodological inconsistency. The effect of electrotherapy on pain is reported under pain management.

There is weak evidence that electrotherapy offers no benefit over standard care in promoting healing in VLUs. (Grade D)

Caution

No major adverse effects of electrotherapy were reported in the trials included in this review. In one trial participants experienced slight burning under electrode sites.[116] Electrotherapy is contraindicated in patients with electrical implants (eg. pacemakers), epilepsy, malignancy or who are pregnant. It should be used with caution in patients with impaired circulation.[117]

Evidence statement

A low quality RCT[120] reported the effectiveness of electrotherapy for reduction of pain and promotion of healing in 39 patients with chronic VLU of average 42 months duration. Participants were treated for a 3 month run-in period with compression then randomised to receive electrotherapy at a pulse of 128 Hz and average strength of 300 µA or sham electrotherapy. Electrotherapy was applied under compression twice daily for 30 minutes using a treatment cycle of 7 days of negative polarity followed by 3 days of positive polarity. Treatment continued for an average of 100 days (ie 10 cycles). After 4 months the electrotherapy group had achieved a significant reduction in ulcer surface area (p=0.03) but this was not significant compared to the sham treatment group. Equivalence of baseline demographic and ulcer characteristics was also

not reported and there was no discussion of adverse events. This trial provided low quality evidence that electrotherapy does not promote ulcer healing.[120]

A low quality trial[147] investigated the effect of electrotherapy in healing VLUs. Randomisation was by alternate admission to two different hospital wards. Thirty-three participants in one ward were treated with electrotherapy consisting at 100 Hz frequency and approximately 100 V depending on patient response for 50 minutes, 6 days per week for a total of 7 weeks. Participants were treated with negative polarity until pus coverage of the VLU cleared (between 1 and 3 weeks), then treatment was conducted with positive polarity. The second group of participants (n=32) were treated with various different topical dressings for a period of 6 weeks. Both groups received concurrent compression therapy. A third group of 14 participants being treated as outpatients were also recruited and treated with Unna's boot for 5.5 weeks. Baseline comparisons are poorly reported; however the community group had ulcers of shorter duration and smaller in size and the topically-treated group had VLUs with a greater coverage of pus at baseline. At the trial completion all groups had significantly improved VLUs and there was no significant difference between the groups in rate of healing. The group treated with electrotherapy had significantly faster resolution of supporative ulcer area; however this group had less pus at commencement of the trial.[147]

A low quality trial[116] investigated the treatment of VLUs with frequency rhythmic electrical modulation system (FREMS). Participants were 35 patients with primarily VLUs. All participants were treated with a range of dressings and topical treatments but no compression. Conventional analgesics were also prescribed. The intervention group (n=20) received FREMS 5 days per week for 3 weeks for 40 minutes at pulse amplitudes from 0 to 300 V and intensity from 100 to 170 µA. It was unclear if the control participants (n=19) received a placebo/sham treatment. At 8 week follow up FREMS was associated with a significant decrease in ulcer surface area measured using a digital imaging technique and overall ulcer condition using subjective Likert scales. However, the groups were non-equivalent at baseline, with the control group having ulcers of significantly longer duration. Participants treated with FREMs experienced slight burning at electrode sites.[116]

8.3 Low level laser therapy

Low level laser therapy (LLLT) is proposed as an alternative therapy for treating VLUs. Theories regarding the potential effectiveness of LLLT suggest an action in stimulating microcirculation, tissue oxygenation, regeneration of the lymphatic system and stimulation of collagen and elastin production.[148] There is currently little evidence that LLLT has these effects or if it does, they have yet to be shown to promote healing in VLUs more effectively than sham lasers or standard therapies. There is no evidence regarding the effectiveness of infrared light therapy.

The recommendation that LLLT offers no benefits in treating VLUs is underpinned by findings from a good quality SR reporting two good quality RCTs that had consistent findings of no effect.

There is some evidence that low level laser therapy offers no benefit over standard care in promoting healing in VLUs. (Grade C)

Caution

No adverse events were reported for trials investigating LLLT.[148, 149] Participants in trials investigating the use of low level laser therapy (LLLT) for other conditions have not experienced adverse events.[150, 151]

Evidence statement

A good quality Cochrane SR[149] reported two RCTs comparing LLLT to sham laser therapy. One RCT (reported to have adequate methodology) compared helium neon laser used at an energy level of 4 Joules/cm² (n=23) to sham laser therapy (n=23). Participants also received standard treatment of saline cleansing, paste and support bandages and were encouraged to perform exercise. LLLT was conducted twice weekly for 12 weeks. There was no significant difference in proportion of ulcers healed after 12 weeks (LLLT 17%, placebo 13%). The second RCT (also of adequate methodology) investigated a gallium arsenide laser at an energy level of 1.96 Joules/cm². Participants also received standard treatment of saline cleansing, paste and support bandage and an exercise program. Laser (n=21) or sham laser (n=21) was administered twice weekly for 12 weeks. In contrast to the first trial, in this trial there was a large proportion of healing observed in both the LLLT group (62%) and the sham therapy group (52%). Comparison between groups showed no statistically significant difference in proportion of ulcers healed at 12 weeks. The results of these two trials were pooled and no heterogeneity was found. There was no statistically significant difference between treatment with any type of laser compared to sham laser (RR 1.21; 85% CI 0.73 to 2.03, p=0.46).[149]

A moderate quality RCT[148] investigated the effectiveness of LLLT in healing VLUs. Patients with VLUs were eligible for inclusion if they had an ulcer 1–8cm in diameter and between 3 months and 3 years duration that had previously been treated with compression. Exclusion criteria included malignancy, insulin dependent diabetes mellitus and arterial dysfunction. Participants were randomised to LLLT (n=17), placebo laser (n=17) or standard treatment (n=10). The laser therapy consisting of a continuous red light wave of 685nm at a fluence of 200mW producing 4J/cm² administered for 6 to18 minutes depending upon ulcer size, daily for 14 days then alternate days for 14 days. All groups received enzymatic debridement of the ulcer in the first week of therapy and daily (first 2 weeks) then alternate day hydrofiber dressings and compression. At the end of the treatment phase (day 28), there was no significant difference between the three groups for reduction in mean ulcer size measured by wound tracings and planimetry. The placebo laser group achieved a significant reduction in mean ulcer size between commencement and day 28 (median reduction approximately 2cm², p=0.023), as did the control group (mean reduction approximately 5cm², p=0.047). There was no change in the median size of ulcers in the laser group (p= 0.492). At 90 days follow up there remained no significant between group difference and only the placebo laser group had a significant reduction in ulcer size from baseline (p=0.011). Lack of treatment effect may have been due to insufficient laser dosage, the smaller size of the ulcers in the treatment group at baseline (although the difference was not significant between groups), or the lack of ITT analysis.[148]

8.4 Topical phenytoin

The side effect of stimulatory over-epithelialisation in patients treated with phenytoin for epilepsy led to the experimentation with topical phenytoin for wound care.[152] Although

the mechanisms of action of topical phenytoin are not completely understood, it is theorised that it stimulates fibroblast proliferation and the activity of growth factors, reduces collagenase activity and decreases wound exudate.[152, 153]

Topical phenytoin formulations include gel, cream, phenytoin sodium powder and phenytoin powder.[152, 153] The trials included in the evidence base did not report specific regimens.

The recommendation that topical phenytoin is effective for improving VLU healing was underpinned by moderate quality trials reported in narrative summary in a moderate quality SR. The trials consistently showed an effect above placebo for improving wound healing, although the effect size was not reported. However, in vitro studies have shown that topical phenytoin has cytotoxic effects on skin cells[152, 154] and has been associated with malignant conditions. Because of these serious side effects that can also be detrimental to healing, the Expert Working Committee does not recommend topical phenytoin for VLUs until more research is available.

There is some evidence that topical phenytoin is more effective than standard care for promoting healing in VLUs. (Grade C)

Topical phenytoin is not recommended by the Expert Working Committee due to the risk of serious adverse events outweighing the benefits. (EBO)

Caution

Skin sensitivity may result from topical products used for extended periods. Burning sensation,[152] gingivial hyperplasia[154] and hirsuitism[154] have been reported when using topical phenytoin. Topical phenytoin has cytotoxic effects, and in rare cases is associated with lymphoma (including malignant lymphoma), hypersensitivity syndrome, alterations in clotting and cutaneous eruptions. It should not be used in pregnancy due to the risks of foetal damage.[154]

Evidence statement

A moderate quality SR[153] provided a narrative report of three RCTs at moderate risk of bias that reported the use of topical phenytoin for treating VLUs. One good quality RCT compared phenytoin to placebo in 30 patients, reporting on the primary outcome measure of decrease in ulcer size after 13 weeks. At follow up, the ulcers in the phenytoin group had decreased in size compared with deterioration in condition observed in the control group VLUs. Some patients treated with phenytoin experienced ataxia and dizziness. The second RCT was a non-blinded trial comparing phenytoin with honey to honey alone in 50 patients with VLUS. After 4 weeks of treatment there was significantly greater healing in the phenytoin group compared to the group treated with honey alone (22% vs. 0%, $p<0.05$). No adverse events were reported. The third RCT compared phenytoin (n=50) to EUSOL (n=52) in managing VLUs over 4 weeks. In this trial there was a significant increase in healthy granulation in the VLUs in the phenytoin group compared to the control ($p<0.001$). Both VLU surface area ($p<0.01$) and subjectively measured pain levels ($p<0.05$)

improved significantly for the phenytoin group. No adverse events were reported. The reviewers conclude there is moderate evidence to support the use of phenytoin in treating VLUs for 4 to 13 weeks.[153]

8.5 Oral zinc

Zinc is a trace metal that the body requires for the function of some enzymes and hormones. It also has an anti-inflammatory effect. The trials reported in the systematic review underpinning this recommendation tested the effect of zinc in high doses (200 to 220 mg daily) to promote healing.[155]

The recommendation that zinc has no effect in promoting healing of VLUs is underpinned by a good quality meta-analysis of small, moderate quality trials. The trials were consistent in finding no effect for zinc in increasing the total number of VLUs healed in 3 to 10 months. The meta-analysis concurred with these findings.

There is excellent evidence that oral zinc offers no benefit over standard care in improving healing of VLUs. (Grade A)

Caution

Zinc is a safe supplement when taken at recommended daily doses. It should not be taken during pregnancy or lactation.[156] No adverse events were reported in the trials reported in the literature. Product information recommends zinc is taken on a full stomach and the only reported side effect is mild epigastric discomfort which occurs rarely.[156]

Evidence statement

A Cochrane review[155] included four moderate quality RCTs investigating the effect of oral zinc for improving healing of VLUs. All trials were randomised and double blinded, although methods were not always reported within the trials. In two of the trials the groups were not comparable at baseline with respect to the size of ulcers. Intention to treat analysis was not used in one trial. The trials were all small (between 10 and 42 participants) and used a regimen of oral zinc 200 to 220mg, three times daily for the period of the trial, which ranged from 3 to 10 months. Comparison groups were assigned placebos. In all trials, ulcers had persisted beyond 4 weeks, and in two of the trials participation was restricted to people with ulcers of between 10 and 100 cm^2. In two trials baseline measures of serum zinc were conducted; however, it is unclear if group assignment was stratified by baseline serum zinc levels and whether this would influence the findings. Concomitant therapies included a variety of dressing types and in one trial participants also received compression therapy. All trials reported the number of ulcer healed at the trial end point as the primary outcome measure. No individual trials reported a significant effect for oral zinc compared to placebo for healing venous leg ulcers. In one trial a sub-group analysis was conducted to determine if an effect existed in participants with low serum zinc levels (less than 110mcg/100ml) and this analysis also showed no effect above placebo. Pooled results from the 4 RCTs found no significant effect above placebo for oral zinc in the treatment of venous leg ulcers (RR 1.22; 95% CI

0.88 to 1.68, p=0.24). The results should be considered cautiously due to the methodological flaws in these trials and the low number of participants in individual trials, which likely meant these studies were underpowered to measure an effect. The unclear contribution of serum zinc levels of participants at baseline and the restriction to ulcers of at least 4 weeks duration may also have influenced findings.[155]

8.6 Horse chestnut seed extract

Horse chestnut (*Aescin hippocastanum L.)* is a traditional herbal remedy. The seeds of the horse chestnut contain a mixture of chemical saponins called aescin, which is claimed to promote blood circulation. Although the mechanisms of its action are not fully understood, it has an enzyme inhibiting action and potential prevention of leukocyte activation.[157, 158]

Good quality systematic reviews have shown a role for HCSE in the reductions of signs and symptoms of CVI including leg volume and circumference, leg pain, oedema and leg heaviness. These reviews did not investigate the prevention or healing of VLUs as a specific outcome measure.[157, 158]

The recommendation that HCSE is not effective at promoting healing of VLUs is based on one good quality RCT conducted in an Australian population that found no effect above placebo for wound healing rate, reduction in wound surface area or total healing over 12 weeks.

There is good evidence that horse chestnut seed extract is not more effective than standard care in promoting healing in VLUs. (Grade B)

Caution

Adverse events associated with horse chestnut seed extract (HCSE) include gastrointestinal signs and symptoms (diarrhoea and vomiting), enlarged pupils and visual disturbance, dizziness, flushing, fatigue, headaches, an d pruritus.[157-159] A systematic review of trials investigating the use of HCSE in patients with CVI reported the adverse event rate to vary between 1% and 36% of participants.[157] Horse chestnut seed extract may increase the risk of bleeding therefore it is not recommended for patients with bleeding disorders or taking anticoagulants.[159]

Evidence statement

A good quality, double blind RCT[160] investigated the effectiveness of horse chestnut see extract (HCSE) for healing VLUs. Participants were recruited from an Australian ulcer clinic and randomised to receive either 375 mg daily HCSE (n=27) or a daily placebo (n=27) for 12 weeks or until the VLU healed. Participants had a mean age of 77 years, a mean ABPI of 1.05 and had ulcers of at least 4 weeks duration that were between 1 cm and 20 cms in diameter. The participants were treated with either a low adherent dressing, absorbent dressing or zing impregnated past bandage with either high, moderate or low pressure compression. Selection of concurrent dressing was

considered in the final analysis. Ulcers were assessed at baseline and every 4 weeks using a validated digital photography method and computerized planimetry. At 12 weeks both groups showed a significant improvement in wound surface area. However, there were no between group differences for percentage of ulcers healed at 12 weeks, rate of wound healing, wound surface area or ulcer recurrence. The HCSE group had a reduction in frequency of dressing changes over the trial period compared to an increase in dressing changes for the placebo group (p=0.009); however, the researchers did not report how the decision to change a dressing was made. The HCSE group had a significantly greater number of adverse events (p=0.014), reported to be primarily gastrointestinal symptoms lasting less than 24 hours. Although the trial had insufficient participants to meet the a-priori power calculation requirements, it was a well conducted trial that provided good evidence for a lack of effect of HCSE 375 mg daily in improving the healing of VLUs over 12 weeks.[160]

9. INTERVENTIONS WITH INSUFFICIENT INFORMATION

There is insufficient evidence to make a recommendation on the effectiveness of the following therapies in the management or prevention of VLUs: (EBO)

- **balneotherapy**
- **aspirin**
- **hyperbaric oxygen**
- **topical negative pressure therapy**
- **topical paw-paw derived products**

Balneotherapy is a spa treatment that combines mineral water spas with aqua-exercises aimed at improving calf muscle pump function. Only one trial investigating balneotherapy met the inclusion criteria for the literature review. The trial, which investigated balneotherapy in patients with CVI, reported a non-significant increase in the occurrence of VLUs after 12 months. The intervention was not related to any serious adverse events.[161]

Aspirin has an anti-platelet effect through its inhibition of the production of thromboxane. In one report it was hypothesised that aspirin may promote the healing of VLUs through reducing thrombocytosis. A small, low quality trial that reported a significant reduction in ulcer surface area and increase in ulcer healing compared to placebo. No adverse events were experienced.[162]

Hyperbaric oxygen therapy (HBOT) is a therapy in which the patient is exposed to oxygen at pressures greater than the normal atmosphere. It is reported that this achieves increased arterial oxygenation that improves fibroblast activity, regulates the inflammatory response and has antibacterial effects.[163] Only one small, low quality trial

was identified in the literature and this trial reported no long term benefits for healing VLUs. Adverse events included aural barotrauma.[163]

Topical negative pressure therapy is reported to stimulate cell growth, local blood perfusion and granulation formation by applying suction to the wound. The suction is also reported to remove wound exudate and reduce localised oedema.[164] One small low quality trial reported that therapy was effective in reducing healing times for chronic legl ulcers.[165]

Topical paw paw derived products are marketed as salves to help clean wounds and promote comfort. There was no identified research on their use in treating VLUs.

Evidence statement

Balneotherapy

One low quality, single blinded RCT[161] investigated the effectiveness of balneotherapy in treating CVI. Although not the primary outcome measure of the trial, of interest to this systematic review was the occurrence of VLUs at 12 months. Other outcome measures include change in skin pigmentation, quality of life and subjective assessment of CVI symptoms. Participants, who continued to receive their regular treatment throughout the trial, were randomised to receive either balneotherapy (n=29) or waiting list for therapy (n=30). The therapy was conducted over 3 weeks, with participants receiving 4 sessions daily on 6 days per week. It consisted of massage and a variety of exercises conducted in heated mineral waters. The treatment group also received three 90 minute interactive educational sessions providing information on CVI and its management, with an emphasis on compression therapy. After 12 months the treatment group had no significant difference in occurrence of VLU compared to the control group (1 vs. 5, p=ns). The treatment group had significant improvement in skin pigmentation (effect size 0.77, p<0.01) and in measures of QOL (effect size 0.82, p<0.01); however, these results may have been due to the education sessions, the experience of a 3 week retreat, the increased interaction with care staff or concurrent therapies (eg. uptake of compression following education). This study provided evidence that balneotherapy in conjunction with exercise may improve symptoms and QOL for people with CVI, but does not reduce the risk of VLU over 12 months.[161]

Aspirin

One low quality trial[162] reported on the effectiveness of aspirin for treating VLUs. Twenty participants (average age less than 65 years) with ulcers larger than 2cm^2 and of durations exceeding 10 years, an ABPI above 0.9 and not already taking aspirin, anticoagulants or NSAIDS were recruited from a dermatological outpatient clinic. At baseline the groups were reported to be equivalent with respect to biochemical and hematological indices and lower limb characteristics (eg. erythema, eczema, dermatoliposclerosis) but methods of measurement were not reported. It was unclear if the groups were equivalent with respect to ulcer size and duration at baseline. Participants were randomised to receive either enteric-coated aspirin 300mg daily or a placebo for 4 months. Wound healing rate was measured using duplicate tracings and wound planimetry to determine wound surface area. At 4 months the intervention group had a significantly greater number of totally healed ulcers (38% vs. 0%, p<0.007) and a significantly greater number of ulcers assessed as having reduced in size (52% vs. 26%, p<0.007). More ulcers in the placebo group had increased in size at the completion of the trial (26% vs. 10%, p<0.004). No adverse events were experienced

during the trial. The trial provided low quality evidence that daily aspirin 300 mg may contribute to healing of VLUs.[162]

Hyperbaric oxygen therapy

A moderate quality SR[163] reported on the effectiveness of HBOT in the treatment of any sort of ulcer. One of the included RCTs investigated the effect of HBOT in healing VLUs. The trial was of low methodological quality, with no blinding or ITT analysis. Participants with an ABPI of above 0.8 VLUs of at least one year duration were randomised to receive either HBOT (n=8) or sham air therapy (n=8) in conjunction with usual wound care (not described). Participants underwent HBOT or sham therapy 30 times for a period of 90 minutes in each session at an atmospheric absolute of 2.5, Immediately following the therapy course participants in the HBOT group had significantly greater mean wound reduction (WMD 33%, 95% CI 18.97 to 47.03, p= not reported). At 18 weeks follow up there was no significant difference between the groups in mean wound reduction and the chance of healing was not significantly different between groups (RR 1.33, 95% CI 0.89 to 1.99, p=ns). Five participants withdrew from the trial for unreported reasons and were not included in the final analysis. Although this study did not report on adverse events, the review reported adverse events from other included RCTs. Two trials reported that no participants experienced an adverse event and another trial reported two cases of aural barotrauma in participants treated with HBOT.[163]

Topical negative pressure therapy

One low quality non-blinded RCT[165] reported the effectiveness of vacuum assisted closure in patients with a leg ulcer (not all ulcer were of venous origin) that had been treated with a split thickness skin graft. Following grafting, participants (n=45) were randomly assigned to receive vacuum assisted closure (VAC) or treatment of the ulcer with normal saline soaked gauze. Ulcers treated with VAC following grafting were faster to heal (29 days vs. 45 days, p=0.0001). This small trial provided some low quality evidence that topical negative wond pressure may increase healing in ulcers following skin grafting.[165]

10. EMERGING TREATMENTS

10.1 Protein-derived topical treatments

Protein-derived topical products are biological agents that contain proteins. Two products were identified in the literature—Xelma® and a tissue plasminogen activator. Xelma is described as an extracellular matrix that provides a framework within the wound onto which cells can attach during healing.[166] Tissue plasminogen activator is a topical product containing proteins that assist in the breakdown of blood clots.[167]

Moderate and low quality trials that had inconsistent findings provided weak evidence that protein-derived topical treatments are no more effective than standard care (Grade D) and they are currently not used within Australia and New Zealand.

Evidence statement

A moderate quality, single blind RCT[168] investigated the effectiveness of a cutaneous wound extracellular matrix protein equivalent 30 mg amelogenins/ml solution (Xelma®) in promoting

healing in VLUs. Participants, who were recruited from 20 international settings, were randomised to receive either the experimental dressing or an alginate dressing. Patients were eligible for inclusion in the trial if they had an ABPI of at least 0.8, an ulcer of between 5 and 25 cm^2 that had persisted for at least 6 months, and who had been treated with compression therapy for at least one month without an improvement in ulcer condition prior to admission into the trail. Patients with uncontrolled diabetes, wound infection, heavy exudates, arterial disease or illness that may inhibit healing were excluded from the trial. Participants were randomised to receive either Xelma (n=62) or a placebo aqueous solution (n=61) applied weekly as a 0.5mm coating to the ulcer under a secondary dressing and compression for 12 weeks or until complete healing. After 12 weeks there was no significant difference between groups in the rate of ulcer healing in either the intention to treat (ITT) or per protocol analysis, in a sub-analysis of participants with ulcers with ulcers of greater than $10cm^2$ or in participants with ulcers of a duration longer than 12 months. Adverse events, which included small numbers of infection, pain and maceration, were not different between groups. Healing rates were reported to vary widely between the settings. This moderate quality trial provided evidence that an extracellular matrix protein dressing is not superior to an aqueous solution for treating hard to heal VLUs.[168]

A second trial investigated the same product. This low quality RCT[169, 170] investigated Xelma used in conjunction with compression compared to compression alone for the management of VLUs. Participants were adults with an ABPI of at least 0.8 and an ulcer between $8cm^2$ and $36cm^2$ that was at least 6 months old. Patients with uncontrolled diabetes, severe immobility, an underlying disease state that would impact upon healing, hypersensitivity to dressings or who were taking corticosteroids were ineligible. Patients with highly exudating ulcers, clinical signs of infection or an ulcer that had achieved more than 50% improvement in condition in the one month run-in period in which patients received compression were also excluded. The treatment group (n=42) had wounds cleansed with saline, treated with the experimental product and secondary dressing applied underneath compression weekly for 12 weeks. The regimen for the control group was not reported; however they received high grade compression only. Condition of ulcers was visually assessed weekly and wound tracings and photography were used to calculate percentage reduction in ulcer size. After 12 weeks the treatment group achieved a significantly greater mean percentage change in ulcer size than the control group (between group difference -22.04%, SD -43.05 to -1.01%, p=0.03). More ulcers in the treatment group were rated as improved (47.5% vs 19.5%, p=0.01) and rated as having a reduction in exudate (p=0.01) compared to the contro.l group. The treatment group also had a significant reduction in wound pain, with a mean difference of -1.59 (-2.84 to -0.34, p=0.01) on an eleven point VAS, although this is likely to be a negligible clinical impact. There was no difference between groups in viable tissue, wound odour or calf circumference measurements, and no difference in adverse events. The trial quality was limited due to the lack of reporting on methods of randomisation, allocation concealment, blinding, baseline comparability and the treatment received by the control group. More than 20% of patients withdrew from the trial; however the reasons for this were not reported. The trial provided low quality evidence that Xelma used weekly for 12 weeks is effective for treatment for VLUs.[169, 170]

A low quality trial[167] investigated the effectiveness of tissue plasminogen activator (tPA), a protein involved in the breakdown of blood clots, for healing VLUs. Twelve participants with VLUs and no history or evidence of bleeding were recruited to the trial. Participants were randomised one of four groups receiving a topical treatment: tPA with 1% sodium hyaluronate vehicle at a dose of 250 µg, tPA dose 500 µg, tPA dose 1000 µg or a placebo. The topical treatment was applied directly to the wound and the ulcer was covered with a non adherent dressing under compression. Treatment continued for 4 weeks, with final follow up at 6 weeks. At 6 weeks healing

rate, measured in cm^2 per week, was greater in those treated with tPA, with a greater response in those treated with higher doses. There were no significant differences in fibrinogen levels, prothombin time, complete blood count, differential platelet count or partial thromboplastin time. Adverse events at the ulcer site were not reported. This very small trial provided low quality evidence of an effect of tPA in healing VLUs; however, the size of the trial prevents confident recommendation of this therapy.[167]

10.2 Growth factor treatments

Growth factors are naturally occurring proteins or hormones that stimulate cell growth. Keratinocyte growth factor stimulates epithelialisation.[171] Granulocyte-macrophage colony-stimulating factor (GM-CSF) reportedly stimulates neutrophils, macrophages and keratinocytes, all of which promote wound healing.[172, 173] Protein-derived growth factors are reported to play a role in blood vessel formation in the wound base.

The evidence on growth factors is conflicting. Whilst some trials reported significant improvements in healing, others found no effect above standard care for growth factor preparations. Further research is required on these emerging treatments.

Evidence statement

Granulocyte-macrophage colony-stimulating factor

A good quality RCT[173] investigated the dose-relationship of recombinant human granulocyte macrophage colony-stimulating factor (rhuGM-CSF) for treating VLUs. Patients eligible for inclusion were adults with VLUs of at least 3 months duration with an ABPI above 0.8 and without diabetes, clinical infection or complex disease. The mean ulcer size of participants was $4.7cm^2$ to $6.1cm^2$. Participants received intra-ulcer administration of rhuGM-CSF 200 µg (n=21), rhuGM-CSF 400 µg (n=19) or placebo (saline; n=21). Treatment was administered through four injections (totaling 5 ml) subcutaneously at peri-wound sites weekly for 4 weeks. Prior to administration ulcers were debrided, cleansed and povidone iodine. A gauze dressing and compression bandaging was applied. Wounds were cleansed every second day. At 12 to 14 weeks follow up significantly more wounds treated with rhuGM-CSF had achieved complete healing (rhuGM-CSF 200 µg 57%; rhuGM-CSF 400 µg 61%; placebo 19%; both treatment group compared with placebo $p<0.05$). More ulcers in both treatment groups had also achieved 50% healing at 12 to 14 weeks. However, more ulcers in the treatment groups compared with the placebo group had positive bacterial culture swabs and more adverse events (38% rhuGM-CSF 200 µg; 26% rhuGM-CSF 400 µg; 9% placebo) including lumbar pain and malaise. This trial provided evidence that rhuGM-CSF is effective for healing smaller ulcers; however, the adverse events may detract from the feasibility of the treatment for some patients.[173]

A good quality trial[174] investigated the effect of intravenous iloprost in the healing of VLUs. Participants had active VLUs between 10 and 30 cm^2 that had persisted for less than 18 months and had no signs of clinical infection. Exclusion criteria included vasculitis, arterial disease, recent venous surgery, malignant blood disorders and use of anticoagulants. Patients were randomised to receive Intravenous iloprost (n=43) at titrated in doses up to 2 ng/kg/minute over 6 hours daily for 5 days followed by 2 rest days repeated weekly for 3 weeks or a placebo saline infusion (n=45) on the same regimen. All patients received local therapy consisting of debridement, topical

antiseptics, compression bandaging and leg elevation during infusion therapy. Ulcer healing was evaluated using a computerised measure and planimetry. The analysis showed significantly better healing (p=not reported) for VLUs in participants treated with iloprost. The treatment group ulcers were 100% healed after 90 days compared to the placebo group, in which 50% of ulcers were totally healed after 105 days and 84% were healed at the final 150 day evaluation. Two participants in the treatment group withdrew due to myocardial infarction (relationship to treatment was not reported). The small trial provided some evidence that 6 hourly infusions of iloprost may improve healing of VLUs. Concordance with the regimen may be an issue; however only approximately 10% of participants withdrew from the trial due to failure to complete follow ups.[174]

In a small, low quality trial[172] participants were randomised to receive 400 µg GM-CSF (n=16) or placebo (n=9) injected into the peri-lesional area of their VLUs. Participants were adults with ulcers of at least 6 weeks duration (average greater than one year) with a surface area between 1 and 30cm^2 (average 10cm^2). Patients with diabetes, clinical infection, neoplasms or complex co morbidities were excluded. Ulcers were treated with povidone iodine ointment, and a simple dressing that was changed every second day. After the first month of the trial, blinding was broken and because the treatment was deemed to be ineffective, recruiting for the trial ceased. Analysis of wound tracing results comparing baseline to day 8 showed the treatment group had a significant reduction from baseline in ulcer size ($p<0.01$) and the placebo group had a slight increase in ulcer size. By 8 weeks about half the ulcers in the treatment group had healed. The only reported adverse event occurring more frequently in the treatment group compared to placebo was wound itching. This trial provided low quality evidence and was too small to provide any indication of the effectiveness of this therapy.[172]

Keratinocyte growth factor

A moderate to good quality trial[171] investigated repifermin, a keratinocyte growth factor, applied topically for the treatment of VLUs. Participants were adults with CVI with ulcers up to 30cm^2 and between 3 and 36 months duration. Patents with clinical infection, arterial disease, vasculitis, cellulitis, dermatologic disease, malignancies, other chronic illness or taking vasoactive medication were ineligible to enroll. Participants were randomised to one of three groups. The first received 20 µg/cm^2 of repifermen (n=31), the second received 60 µg/cm^2 of repifermen (n=32) and the third received a topical placebo (n=31). Treatment and placebo were sprayed from approximately 30 cm away onto the wound starting from the perimeter and moving inward. After administration the wound was covered with a non-adherent dressing and compression. Treatment was administered twice weekly for 12 weeks. At 12 weeks follow up more participants in the treatment groups had achieved 75% healing of their ulcer compared with the placebo group (p=0.0007). Ulcers classified as 100% healed were not significantly different between the group. Treatment effect appeared greater for wounds less than 15cm^2 or less than 18mth duration. Adverse events including pruritus, rash, leg pain and reopening of leg ulcer did not occur more frequently than in the placebo group. This trial provided moderate to good quality evidence that repifermin may contribute to healing in smaller ulcers of less duration; however further evidence is required on its usefulness in promoting VLU healing.[171]

Protein-derived growth factor

A moderate quality RCT[175] compared autologous platelet lysate to a topical placebo for the treatment of VLUs. Participants were eligible for inclusion if they had diagnosed venous disease

and comorbidities and/or exclusion criteria were not reported. Participants had ulcers with a mean size of 2cm^2 that had persisted for a mean duration of 3 months. Participants were randomised to receive either platelet lysate (n=46) or placebo (n=42) applied topically twice per week. Topical treatment was applied via a soaked piece of gauze cut to fit the ulcer delivering 150 µl per cm^2 of solution. All participants received the same concurrent compression bandaging. Ulcers were assessed weekly using wound tracings, photography and planimetry until they healed or for 9 months. Participants who did not display response to treatment after 3 months were withdrawn from the trials but were included in the analysis. The results showed no significant differences in the healing rates between the two groups. Adverse events were primarily allergic responses to the concurrent bandaging.[175]

Adverse events

Protein derived growth factor increases the risk of cancer mortality.

10.3 Intravenous prostaglandins

Although the mechanisms are unclear, prostaglandins are reported to be an anti-inflammatory and have an effect in reducing the action of neutrophils. This is described as leading to increases in microcirculation and transcutaneous oxygen pressure.[176] In trials included in the literature, prostaglandin E1 was administered intravenously daily for between 20 and 120 days. Intravenous infusion was administered over 6 hours.[176, 177]

The evidence that intravenous prostaglandin E1 is effective in improving healing in hard to heal ulcers was provided by a good quality and a low quality RCT which both showed a moderate effect of treatment when used daily for at least 20 days (Grade B). Although there is good evidence for its effect in conjunction with compression for improving VLUs this therapy is currently not used in Australia or New Zealand.

Evidence statement

A good quality, double blind RCT[177] investigated the effect on VLU healing of intravenous prostaglandin E1. The researchers recruited 87 participants who had CVI and at least one VLU that was of less than one year duration and between 5 and 30cm^2. Participants were ineligible if they had ulcers of other origins, diabetes, neuropathy, vasculitis, clinical infection, recent venous surgery, vasoactive medication or blood disorders. The treatment group (n=43) received 60mg intravenous prostaglandin daily for 20 days and the control group (n=44) received an intravenous placebo. Both groups were treated with compression and VLUs received topical antibacterials. The protocol required participants to be hospitalized for 6 hours daily throughout the treatment phase. Ulcers were assessed every 20 days using wound tracings and planimetry. At the final measurement (day 120), the participants treated with prostaglandin E1 had achieved significantly better outcomes. One hundred percent of ulcers treated with prostaglandin E1 had healed by day 120 compared with 84% of the control group ($p<0.05$). Healing occurred more rapidly in the treatment group, with 85% of VLUs healed after 80 days compared with 50% in the placebo group. The incidence of adverse events, including changes hypotension, headache, ad GIT effects, were greater in the prostaglandin E1 group (11% vs 5%) and one participant withdrew from the treatment group due to GIT side effects. The trial provided good evidence for a positive effect

above placebo of intravenous prostaglandin E1 in ulcer healing; however, the time consuming regimen and high rate of side effects may reduce its feasibility for patients.[177]

A low quality trial[176] investigated the use of intravenous prostaglandin E1 on a daily basis for 6 weeks for healing VLUs. Participants with VLUs of at least 4 months duration and at least 0.5cm in diameter who did not have cardiac or renal disease, thrombocytosis, recent myocardial infarction and were not taking vasoactive medications were eligible for inclusion. Patients underwent a 14 day wash-out period and were randomised to receive either 60 µg prostaglandin E1 (n=22) or placebo (n=22) by intravenous infusion over 3 hours daily. Treatment continued for 6 weeks or until ulcers healed and was concurrent with compression, diuretic therapy for oedema and elevation. Ulcers were assessed using a Likert scale scoring system that included diameter, depth, wound edges and surface area. At the conclusion of therapy participants treated with prostaglandin E1 for whom there was complete data (n=20) had achieved a 70.4% improvement in ulcer scores compared with 23.8% improvement in the placebo group. Improvement in ulcer diameter was significantly greater in the prostaglandin E1 group ($p<0.001$). Forty percent of the treatment group had completely healed ulcers and 85% had resolution of oedema compared with 9.1% and 35% for the placebo group. No adverse events occurred. This trial was low quality, baseline comparability of the groups was not established and withdrawals were not described.[176]

Adverse events

In trials conducted in patients with VLUs, adverse events occurred more frequently than placebo and included headache, hypotension and GIT effects.[177]

REFERENCES

1. Baker S & Stacey M. 1994. Epidemiology of chronic leg ulcers in Australia. Australia and New Zealand Journal of Surgery. **64**(4): p. 258-61.
2. London N & Donnelly R. 2000. Abc of arterial and venous disease. Ulcerated lower limb. British Medical Journal. **320**(7249): p. 1589-91.
3. Nelzen O, Bergqvist D & Lindhagen A. 1997. Long-term prognosis for patients with cronic leg ulcers: a prospective cohort study. European Journal of Vascular and Endovascular Surgery. **13**(5): p. 500-8.
4. Persoon A, Heinen M, van der Vleuten C, de Rooij M, van de Kerkhof P & van Achterberg T. 2004. Leg ulcers: a review of their impact on daily life. Journal of Clinical Nursing. **13**(3): p. 341-54.
5. Walker N, Rodgers A, Norton R & al. e. 2002. The occurrence of leg ulcers in Auckland, New Zealand: results of a population-based study. New Zealand Medical Journal. **115**: p. 159-62.
6. Walker N, Vandal A, Holden J & al.. e. 2002. Does capture-recapture analysis provide more reliable estimates of the incidence and prevalence of leg ulcers in the community. Australia and New Zealand Journal of Public Health. **26**: p. 451-5.
7. Australian Institute of Health and Welfare, 2009. Aboriginal and Torres Strait Islander Health Performance Framework 2008 report: detailed analyses. AIHW: Canberra.
8. Minister of Health and Minister of Pacific Island Affairs, 2010. `Ala Mo`ui: Pathways to Pacific health and well-being 2010-2014. Ministry of Health.: Wellington.
9. Ministry of Health and University of Otago, 2006. Decades of Disparity III: ethnic and socio-economic inequalities in mortality, New Zealand, 1981-1999. Ministry of Health: Wellington.
10. Australian Beureau of Statistics (ABS) & Australian Institute of Health and Welfare (AIHW), 2008. Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples ABS and AIHW: Canberra.
11. Council of Australian Governments' Meeting, 10 February 2006. http://www.coag.gov.au/coag_meeting_outcomes/2006-02-10/index.cfm.
12. Productivity Commission, 2005. Economic implications of an ageing Australia: Productivity Commission research report. Productivity Commission,: Canberra.
13. Ministry of Health, 2004 Population Ageing and Health Expenditure: New Zealand 2002-2051. Ministry of Health: Wellington.
14. Palfreyman S, Nelson E, Lochiel R & Michaels J. 2006. Dressing for healing venous leg ulcers. Cochrane Database of Systematic Reviews. **3**.
15. de Araujo T, Valencia I, Federman D & Kirsner R. 2003. Managing the patient with venous ulcers. Annals of Internal Medincine. **138**(4): p. 326-34.
16. Nelzen O, Bergqvist D & Lindhagen A. 1991. A leg ulcer etiology: A cross-sectional population study. Journal of Vascular Surgery. **14**(4): p. 557-64.
17. Carville K & Lewin G. 1998. Caring in the community: a wound prevalence survey. Primary Intention. **6**(2): p. 54-62.
18. Carville K & Smith J. 2004. A report on the effectiveness of comprehensive wound assessment and documentation in the community. Primary Intention. **12**(1): p. 41-4.
19. Vowden K & Vowden P. 2006. Preventing venous ulcer recurrence: a review. International Wound Journal. **3**(1): p. 11-21.
20. Grindlay A & MacLellan D. 1997. Inpatient management of leg ulcers: A costly option? Primary Intention. **5**(1): p. 24-6.
21. Carville K, 1997. Time and cost to healing one year post audit. Silver Chain: Silver Chain Report (unpublished), Osborne Park, WA.
22. Carville K, 2000-2001. Department of Veterans' Affairs Clients: One year post audit time and cost to wound healing. Silver Chain: Silver Chain Report (unpublished), Osborne Park, WA.
23. Rural Health Education Foundation (RHEF). Wound Management: A holistic approach and practical skills update. 2010 [cited September 2010]; http://www.rhef.com.au/programs/program-1/?program_id=60.

24. New Zealand Guidelines Group, The Royal New Zealand College of General Practitioners & The College of Nurses Aotearoa, 1999. Care of people with chronic leg ulcers: an evidence based guideline: Auckland.
25. Registered Nurses Association of Ontario, 2004. Assessment and management of venous leg ulcers. RNAO: Toronto.
26. The Royal College of Nursing (UK), 2006. Clinical practice guidelines: The nursing management of patients with venous leg ulcers - Recommendations. RCN: London.
27. The Royal College of Nursing (UK), 2006. Implementation guide: The nursing management of patients with venous leg ulcers. RCN: London.
28. Coleman K, Norris S, Weston A, Grimmer K, Hillier S, Merlin T, Middleton P, Tooher R & Salisbury J, 2005. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: pilot program 2005 - 2007. NHMRC: Canberra.
29. Scottish Intercollegiate Guidelines Network, 2001-2009. Critical apprasisal: notes and checklists, in http://www.sign.ac.uk/methodology/checklists.html, SIGN, Editor.
30. Benigni J, Sadoun S, Allaert F & Vin F. 2003. Efficacy of Class 1 elastic compression stockings in the early stages of chronic venous disease, A comparative study. International Angiology. **22**(4): p. 383-92.
31. Martinez M, Bonfill X, Moreno R, Vargas E & Capella D. 2005. Phlebotonics for venous insufficiency. Cochrane Database of Systematic Reviews. **Issue 3**.
32. Australian Wound Management Association Inc. 2010. Standards for wound management 2nd ed: AWMA
33. Registered Nurses Association of Ontario (RNAO), 2007 Assessment and management of venous leg ulcers: guideline supplement. RNAO: Toronto.
34. Scottish Intercollegiate Guidelines Network (SIGN), 2010. Management of chronic venous leg ulcers. A national clinical guideline. SIGN: Edinburgh.
35. Royal College of Nursing Centre for Evidence Based Nursing, 2006. Clinical practice guidelines: The nursing management of patients with venous leg ulcers. Recommendations. RCN: London.
36. Carville K. 2005. Wound Care Manual WA, Australia: Silver Chain Nursing Association.
37. Bianchi J, Douglas W, Dawe R, Lucke T, Loney M, McEvoy M & Urcelay M. 2000. Pulse oximetry: a new tool to assess patients with leg ulcers. Journal of Wound Care. **9**(3): p. 109-12.
38. Al-Qaisi M, Nott D, King D & Kaddoura S. 2009. Ankle Brachial Pressure Index (ABPI): An update for practitioners. **5**: p. 833 - 841.
39. Dugdale D & Medline Plus. Duplex ultrasound. 2010 [cited 2010 October]; http://www.nlm.nih.gov/medlineplus/ency/article/003433.htm.
40. Dodds S. ABC of Vascular Disease: Photoplethysmography (PPG). 2001 [cited 2010 October]; http://www.simondodds.com/Venous/Investigations/Photoplethysmography.htm.
41. Australian Wound Management Association Inc, 2010. Diabetic foot guidelines. Australian Wound Management Association Inc, .
42. Kantor J & Margolis D. 2000. A multicenter study of percentage change in venous leg ulcer area as a prognostic index of healing at 24 weeks. Br J Dermatologic Surgery. **142**: p. 960-4.
43. Moffat C, Leg Ulcers, in Vascular disease Nursing and Management. , Murry S, Editor. 2001, Whurr Publishers.: London. p. 200 – 237.
44. Ameen J, Coll A & Peters M. 2005. Impact of tele-advice on community nurses' knowledge of venous leg ulcer care. Journal of Advanced Nursing. **50**(6): p. 583-94.
45. O'Meara S, Cullum N & Nelson E. 2009. Compression for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.
46. World Union of Wound Healing Societies (WUWHS). 2008. Principles of best practice. Compression in venous leg ulcers. A consensus document London: MEP Ltd
47. Feben K. 2003 How effective is training in compression bandaging techniques? British Journal of Community Nursing. **8**(2): p. 80-4.
48. O'Meara S, Tierney J, Cullum N, Bland J, Franks P, Mole T & Scriven M. 2009. Four layer bandage compared with short stretch bandage for venous leg ulcers: systematic review and meta-analysis of randomised controlled trials with data from individual patients. BMJ. **338**: p. 1344
49. Palfreyman S, Lochiel R & Michaels J. 1998. A systematic review of compression therapy for venous leg ulcers. Vascular Medicine. **3**(4): p. 301-313.

50. Amsler F, Willenberg T & Blättler W. 2009. In search of optimal compression therapy for venous leg ulcers: a meta-analysis of studies comparing divers bandages with specifically designed stockings. Journal of Vascular Surgery. **50**(3): p. 668-74.
51. Moffatt C, Edwards L, Collier M, Treadwell T, Miller M, Shafer L, Sibbald G, Brassard A, McIntosh A, Reyzelman A, Price P, Kraus S, Walters S & Harding K. 2008. A randomised controlled 8-week crossover clinical evaluation of the 3M Coban 2 Layer Compression System versus Profore to evaluate the product performance in patients with venous leg ulcers. International Wound Journal. **5**(2): p. 267-79.
52. Rowland J. 2000 Intermittent pump versus compression bandages in the treatment of venous leg ulcers. Australian & New Zealand Journal of Surgery. **70**(2): p. 110-3.
53. Pagan A. 2008. Healing a chronic venous ulceration using the Southland Snail, an innovative pressure device. Wound Practice and Research. **16**(4): p. 181-185.
54. Meaume S, Ourabah Z, Cartier H, Granel-Brocard F, Combemale P, Bressieux J & Bohbot S. 2005. Evaluation of a lipidocolloid wound dressing in the local management of leg ulcers. Journal of Wound Care. **14**(7): p. 329-34.
55. Norkus A, Dargis V, Thomsen J, Harding K, Ivins N, Serra N, Torres de Castro O, Galindo A, Andersen K, Roed-Petersen J, Gottrup F, Blanco J, de Mena M, Hauschild A, Moll I, Svensson A & Carter K. 2005. Use of a hydrocapillary dressing in the management of highly exuding ulcers: a comparative study. Journal of Wound Care. **14**(9): p. 429-32.
56. Rainey J. 1993. A comparison of two dressings in the treatment of heavily exuding leg ulcers. Journal of Wound Care. **2**(4): p. 199-200.
57. Schulze H, Lane C, Charles H, Ballard K, Hampton S & Moll I. 2001. Evaluating a superabsorbent hydropolymer dressing for exuding venous leg ulcers. Journal of Wound Care. **10**(1): p. 511-8.
58. Alvarez O, Patel M, Booker J & Markowitz L. 2004. Effectiveness of a biocellulose wound dressing for the treatment of chronic venous leg ulcers: results of a single center randomized study involving 24 patients. . Wounds: A Compendium of Clinical Research and Practice. **16**(7): p. 224-33.
59. Borges EL, Caliri MHL & Haas VJ. 2007. Systematic review of topic treatment for venous ulcers. Revista Latino-Americana de Enfermagem. **15**(6): p. 1163-70.
60. Bouza C, Munoz A & Amate JM. 2005. Efficacy of modern dressings in the treatment of leg ulcers: A systematic review Wound Repair and Regeneration. **13**(3): p. 218-229.
61. O'Donnell TF & Lau J. 2006. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. Journal of Vascular Surgery. **44**(5): p. 1118-25.
62. Palfreyman S, Nelson EA & Michaels JA. 2007. Dressings for venous leg ulcers: systematic review and meta-analysis. BMJ. **335**(7613): p. 244-256.
63. Franks P, Moody M, Moffatt C, Hiskett G, Gatto P, Davies C, Furlong W, Barrow E & Thomas H. 2007. Wound Healing Nursing Research Group. Randomized trial of two foam dressings in the management of chronic venous ulceration. . Wound Repair & Regeneration. **15**(2): p. 197-202.
64. Vanscheidt W, Sibbald R & Eager C. 2004. Comparing a foam composite to a hydrocellular foam dressing in the management of venous leg ulcers: a controlled clinical study. . Ostomy Wound Management. **50**(11): p. 42-55.
65. Schmutz J, Meaume S, Fays S, Ourabah Z, Guillot B, Thirion V, Collier M, Barrett S, Smith J, Bohbot S & Dompmartin A. 2008. Evaluation of the nano-oligosaccharide factor lipido-colloid matrix in the local management of venous leg ulcers: results of a randomised, controlled trial. International Wound Journal. **5**(2): p. 172-82.
66. Bradley M, Cullum N, Nelson E, Petticrew M, Sheldon T & Torgerson D. 1999. Systematic reviews of wound care management: (2) dressings and topical agents used in the healing of chronic wounds. Health Technology Assessment. **3**(17 II): p. iii-126.
67. Smeets R, Ulrich D, Unglaub F, Woltje M & Pallua N. 2008 Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. International Wound Journal. **5**(2): p. 195-203.
68. Duncan G, Andrews S & McCulloch W. 2002. Issues in clinical practice: Dressings 2. Primary Intention. **10**(2): p. 83-86.
69. Eagle M. 1999. Paste-impregnated bandages. Journal of Wound Care. **8**(6): p. 300-301.
70. Rowe S, Hilmi S & Wood F. 2007. The use of ichthammol glycerin in burn wound care: a literature review. Primary Intention. **15**(1): p. 29-32.

71. Beckert S, Warnecke J, Zelenkov aH, Kovnerystyy O, Stege H, Cholcha W, Konigsrainer A & Coerper S. 2006. Efficacy of topical pale sulfonated shale oil in the treatment of venous leg ulcers: a randomized, controlled, multicenter study. Journal of Vascular Surgery. **43**(1): p. 94-100.
72. Rivera-Arce E, Chavez-Soto M, Herrera-Arellano A, Arzate S, Aguero J, Feria-Romero I, Cruz-Guzman A & Lozoya X. 2007 Therapeutic effectiveness of a Mimosa tenuiflora cortex extract in venous leg ulceration treatment. . Journal of Ethnopharmacology. **109**(3): p. 523-8.
73. Nicolaides A. 2000. Investigation of chronic venous insufficiency: A consensus statement (France, March 5-9, 1997). Circulation. **102**(20): p. E126-63.
74. Draper R. Varicose eczema. 2009 [cited 2010 September]; http://www.patient.co.uk/doctor/Varicose-Eczema.htm.
75. Cameron J, Hoffman D, Wilson J & Cherry G. 2005. Comparison of two peri-wound skin protectants in venous leg ulcers: a randomised controlled trial. Journal of Wound Care. **14**(5): p. 233-6.
76. Neander K & Hesse F. 2003. The protective effects of a new preparation on wound edges. Journal of Wound Care. **12**(10): p. 369-71.
77. O'Meara S, Al-Kurdi D & Ovington L. 2010. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.
78. MedlinePlus. Iodine. 2010 [cited 2010 August]; http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-iodine.html#Safety.
79. Smith & Nephew. Cadexomer Iodine Dressings. 2010 [cited 2010 August]; http://wound.smith-nephew.com/au/Standard.asp?NodeId=3821.
80. Chambers H, Dumville J & Cullum N. 2007. Silver treatments for leg ulcers: A systematic review. Wound Repair and Regeneration. **15**(2): p. 165-173.
81. Templeton S. 2005. Management of chronic wounds: the role of silver-containing dressings. Primary Intention. **13**(4): p. 170-179.
82. Vermeulen H, van Hattem J, Storm-Versloot M & Ubbink D. 2007. Topical silver for treating infected wounds. Cochrane Database of Systematic Reviews **Issue 1**.
83. White R & Cutting K. 2006. Exploring the Effects of Silver in Wound Management - What is Optimal? Wounds. **18**(11): p. 307-314.
84. O'Meara S, Cullum N, Majid M & Sheldon T. 2001 Systematic review of antimicrobial agents used for chronic wounds British Journal of Surgery. **88**(1): p. 4-21.
85. Dimakakos E, Katsenis K, Kalemikerakis J, Arkadopoulos N, Mylonas S, Arapoglou V & et al. 2009. Infected venous leg ulcers: management with silver-releasing foam dressing. Wounds: A Compendium of Clinical Research and Practice. **21**(1): p. 4-8.
86. Jull A, Rodgers A & Walker N. 2008. Honey as a topical treatment for wounds Cochrane Database of Systematic Reviews. **Issue 4**.
87. Gethin G & Cowman S. 2009. Manuka honey vs. hydrogel--a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. Journal of Clinical Nursing. **18**(3): p. 466-74.
88. Jull A, Walker N, Parag V, Molan P, Rodgers A & on behalf of the Honey as Adjuvant Leg Ulcer Therapy trial collaborators. 2008. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. British Journal of Surgery. **95**(2): p. 175-82.
89. Haller G, Faltin-Traub E, Faltin D & Kern C. 2002. Oxygen embolism after hydrogen peroxide irrigation of a vulvar abscess. Br J Anaesth. **88**: p. 597-9
90. Henley N, A. D, Kaehr D & Clements B. 2004. Air Embolism associated with irrigation of external fixator pin sites with hydrogen peroxide. The Journal of Bone and Joint Surgery. **86**: p. 821-822.
91. Sleigh J & Linter S. 1985. Hazards of hydrogen peroxide. British Medical Journal. **291**(6510): p. 1706.
92. Brennan S & Leaper D. 1985. The effect of antiseptics on the healing wound: a study using the rabbit ear chamber. British Journal of Surgery. **72**(10): p. 780-782.
93. Lineaweaver W, Howard R, Soucy D, McMorris S, Freeman J, Crain C, Robertson J & T. R. 1985. Topical antimicrobial toxicity. Archives of Surgery. **120**(3): p. 267-270.
94. Ward R & Saffle J. 1995. Topical agents in bum and wound care. Physical Therapy. **75**: p. 526-5381.
95. F H Faulding & Co Limited. 1998 Betadine Povidone-Iodine Product Monograph. Fourth edition. Adelaide: F H Faulding & Co Limited
96. Australian Wound Management Association Inc, 2009. Position Document of the Australian Wound Management Association: Bacterial impact on wound healing: From contamination to

infection. Australian Wound Management Association Inc.: http://www.awma.com.au/publications/2009/bacterial_impact_position_document_V_1_0.pdf.
97. NSW Health. NSW Health factshhet: Antibiotic use. 2005 [cited 2010 August]; http://www.health.nsw.gov.au/factsheets/general/antibiotic_use.html.
98. Konig M, Vanscheidt W, Augustin M & Kapp H. 2005. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. Journal of Wound Care. **14**(7): p. 320-3.
99. Enoch S & Harding K. 2003. Wound Bed Preparation: Wound Debridement Wounds (available: http://www.medscape.com/viewarticle/459733_6). **15**(7).
100. Falabella A, Carson P, Eaglstein W & Falanga V. 1998. The safety and efficacy of a proteolytic ointment in the treatment of chronic ulcers of the lower extremity. Journal of the American Academy of Dermatology. **39**(5 Pt 1): p. 737-40.
101. Shi L & Carson D. 2009. Collagenase Santyl Ointment: A Selective Agent for Wound Debridement. Journal of Wound, Ostomy and Continence Nursing. **36**(6S): p. S12-S16.
102. Ramundo J & Gray M. 2009. Collagenase for Enzymatic Debridement: A Systematic Review. Journal of Wound, Ostomy and Continence Nursing. **36**(6S): p. S4-S11.
103. Forsling E. 1988. Comparison of saline and streptokinase-streptodornase in the treatment of leg ulcers. European Journal of Clinical Pharmacology. **33**(6): p. 637-8.
104. Barnes M, Mani R, Barret D & White J. 1992. Changes in skin microcirculation at periulcerous sites in patients with chronic venous ulcers during leg elevation. Phlebology. **7**: p. 36-39.
105. Dix F, Reilly B, David M, Simon D, Dowding E, Ivers L, Bhowmick A & McCollum C. 2005. Effect of leg elevation on healing, venous velocity and ambulatory venous pressure in venous ulceration. Phlebology. **20**(2): p. 87-94.
106. Coghlan D. 2004 Chronic venous insufficiency ASUM Ultrasound Bulletin. **7**(4): p. 14-21.
107. Padberg F, Johnston M & Sisto S. 2004. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. Journal of vascular surgery. **39**(1): p. 79-87.
108. Kan Y & Delis K. 2001. Hemodynamic effects of supervised calf muscle exercise in patients with venous leg ulceration: a prospective controlled study. Archives of Surgery. **136**(12): p. 1364-9.
109. Dolynchuk K, Keast D, Campbell K, Houghton P, Orsted H, Sibbald G & Atkinson A. 2000. Best practices for the prevention and treatment of pressure ulcers. Ostomy/Wound Management. **46**(11): p. 38-52.
110. Jones J & Nelson E. 2007. Skin grafting for venous leg ulcers. Cochrane Database of Systematic Reviews. **2:CD001737**.
111. Barber C, Watt A, Pham C, Humphreys K, Penington A, Mutimer K, Edwards M & Maddern G. 2008 Influence of bioengineered skin substitutes on diabetic foot ulcer and venous leg ulcer outcomes. Journal of Wound Care. **17**(12): p. 517-27
112. Fitzgibbons R & Zieve D. Skin graft. 2008 [cited 2010 October]; http://www.drugs.com/enc/skin-graft.html.
113. AstraZeneca Pty Ltd, 2010. EMLA cream, Lignocaine and prilocaine. Eutectic Mixture of Local Anaesthetics. Consumer Medicine Information. AstraZeneca Pty Ltd: NSW.
114. Coloplast. Biatain Ibu Foam Dressing. 2008 [cited 2010 September]; www.biatain.coloplast.com.
115. Briggs M & Nelson E. 2003. Topical agents or dressings for pain in venous leg ulcers. . Cochrane Database of Systematic Reviews. **Issue 1**.
116. Jankovic A & Binic I. 2008. Frequency rhythmic electrical modulation system in the treatment of chronic painful leg ulcers. Archives of Dermatological Research. **300**(7): p. 377-83.
117. Watson T. Electrical therapy on the web: an educational resource: contraindications. 2010 [cited 2010 September]; http://www.electrotherapy.org/modalities/contragrid.htm.
118. World Wide Wounds. Product News: New pain-reducing wound dressing from Coloplast. 2006 [cited 2010; http://www.worldwidewounds.com/News/Product-News.html.
119. Gottrup F, Jorgensen B, Karlsmark T, Sibbald R, Rimdeika R, Harding K, Price P, Venning V, Vowden P, Junger M, Wortmann S, Sulcaite R, Vilkevicius G, Ahokas T, Ettler K & Arenbergerova M. 2008. Reducing wound pain in venous leg ulcers with Biatain Ibu: a randomized, controlled double-blind clinical investigation on the performance and safety. Wound Repair & Regeneration. **16**(5): p. 615-25.

120. Junger M, Arnold A, Zuder D, Stahl H & Heising S. 2008. Local therapy and treatment costs of chronic, venous leg ulcers with electrical stimulation (Dermapulse): a prospective, placebo controlled, double blind trial. Wound Repair & Regeneration. **16**(4): p. 480-7.
121. Al-Kurdi D, Bell-Syer SE & Flemming K. 2008. Therapeutic ultrasound for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.
122. Robinson V, Brosseau L, Peterson J & et al. 2006. Therapeutic ultrasound for osteoarthritis of the knee. Cochrane Database of Systematic Reviews. **Issue 3**.
123. Johannsen F, Gam A & Karlsmark T. 1998. Ultrasound therapy in chronic leg ulceration: a meta-analysis. Wound Repair and Regeneration. **6**(2): p. 121-126.
124. Batavia M. 2004. Contraindications for superficial heat and therapeutic ultrasound: Do sources agree? Arch Phys Med Rehabil. **85**: p. 1006-12.
125. Jones J & Nelson E. 1997 Evaluation of an education package in leg ulcer management. Journal of Wound Care. **6**(7): p. 342-3.
126. Seeley M & Harding K. 2008. The effects of education and training on clinical practice in wound healing. International Wound Journal. **5**(5): p. 660-4.
127. Wong I. 2003. Assessing the value of a leg ulcer education programme in Hong Kong. Journal of Wound Care. **12**(1): p. 17-9.
128. Brooks J, Ersser S, Lloyd A & Ryan T. 2004 Nurse-led education sets out to improve patient concordance and prevent recurrence of leg ulcers. Journal of Wound Care. **11**(3): p. 111-6.
129. Clarke Moloney M, Moore A, Adelola O, Burke P, McGee H & Grace P. 2005. Information leaflets for venous leg ulcer patients: are they effective? Journal of Wound Care. **14**(2): p. 75-7.
130. Van Hecke A, Grypdonck M & Defloor T. 2008 Interventions to enhance patient compliance with leg ulcer treatment: a review of the literature. Journal of Clinical Nursing. **17**(1): p. 29-39.
131. Van Hecke A, Grypdonck M & Defloor T. 2009. A review of why patients with leg ulcers do not adhere to treatment. Journal of Clinical Nursing. . **18**(3): p. 337-49.
132. Jull A, Arroll B, Parag V & Waters J. 2007. Pentoxifylline for treating venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 3**.
133. Medline Plus, 2008. Pentoxifylline, in http://www.nlm.nih.gov/medlineplus/druginfo/meds/a685027.html, U.S. National Library of Medicine and National Institutes of Health, Editor.
134. Sanofi-Aventis New Zealand Limited, 2010. Data Sheet - Trental, in http://www.medsafe.govt.nz/, Health M-NZGMo, Editor.
135. Wishart D, accessed 28 July 2010. Drugbank drug card for Pentoxifylline, in http://www.drugbank.ca/drugs/DB00806 Wishart D, Editor.
136. Katsenis K. 2005. Micronized Purified Flavonoid Fraction (MPFF): A Review of its Pharmacological Effects, Therapeutic Efficacy and Benefits in the Management of Chronic Venous Insufficiency. Current Vascular Pharmacology. **3**: p. 1-9.
137. Coleridge-Smith P. 2005. Daflon 500 mg and venous leg ulcer: New results from a meta-analysis. Angiology. **56**(1): p. S33-S39.
138. Coleridge-Smith P, Lok C & Ramelet A. 2005. Venous Leg Ulcer: A Meta-analysis of Adjunctive Therapy with Micronized Purified Flavonoid Fraction. Eur J Vasc Endovasc Surg. **30**: p. 198-208.
139. Nelson A, Bell-Syer S & Cullum NA. 2000 Compression for preventing recurrence of venous ulcers. Cochrane Database of Systematic Reviews. **Issue 4**.
140. Vandongen Y & Stacey M. 2000. Graduated compression elastic stockings reduce lipodermatosclerosis and ulcer recurrence. Phlebology. **15**(1): p. 33-37.
141. Jull A, Mitchell N, Arroll J, Jones M, Waters J, Latta A, Walker N & Arroll B. 2004. Factors influencing concordance with compression stockings after venous leg ulcer healing. Journal of Wound Care. **13**(3): p. 90-2.
142. McGaughey H, Dhamija S, Oliver L, Porter-Armstrong A & McDonough S. 2009. Pulsed electromagnetic energy in management of chronic wounds: a systematic review. Physical Therapy Reviews. **14**(2): p. 132-46.
143. Ravaghi H, Flemming K, Cullum N & Olyaee Manesh A. 2006. Electromagnetic therapy for treating venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 2**.
144. Dbaly J. 2005. Pulsed electromagnetic field therapy: The best option for many patients. . Swiss Medical Tribune.
145. Energy Medicine Developments, 2004. The EnerMed therapy. EMD.

146. Eccles N & Hollinworth H. 2005. A pilot study to determine whether a static magnetic device can promote chronic leg ulcer healing. Journal of Wound Care. **14**(2): p. 64-7.
147. Franek A, Polak A & Kucharzewski M. 2000. Modern application of high voltage stimulation for enhanced healing of venous crural ulceration. . Medical Engineering & Physics. **22**(9): p. 647-55.
148. Kopera D, Kokol R, Berger C & Haas J. 2005. Does the use of low-level laser influence wound healing in chronic venous leg ulcers? Journal of Wound Care. **14**(8): p. 391-4.
149. Flemming K & Cullum N. 1999. Laser therapy for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.
150. Di Domenica F, Sarzi-Puttini P, Cazzola M, Atzeni F, Cappadonia C, Caserta A, Galletti R, Volontè L & Mele G. 2005. Physical and rehabilitative approaches in osteoarthritis. Seminars in Arthritis and Rheumatism: p. 62-9.
151. Tascioglu F, Armagan O, Tabak Y, Corapci I & Oner C. 2004. Low power laser treatment in patients with knee osteoarthritis. Swiss Medical Weekly. **134**(17-18): p. 254-8.
152. Bhatia A & Prakash S. 2004. Topical phenytoin for wound healing. Dermatology Online Journal. **10**(1): p. 5.
153. Shaw J, Hughes C, Lagan K & Bell P. 2007. The clinical effect of topical phenytoin on wound healing: A systematic review. British Journal of Dermatology. **157**(5): p. 997-1004.
154. Scheinfeld N. 2003. Phenytoin in cutaneous medicine: Its uses, mechanisms and side effects. Dermatology Online Journal. **9**(3): p. 6.
155. Wilkinson E & Hawke C. 1998 Oral zinc for arterial and venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 4**.
156. New Zealand Medicines and Medical Devices Safety Authority. Medsafe: Zincaps. 2010 [cited 2010 September].
157. Pittler M & Ernst E. 2006. Horse chestnut seed extract for chronic venous insufficiency. . Cochrane Database of Systematic Reviews. **Issue 1**.
158. Siebert U, Brach M, Sroczynski G & Uberla K. 2002. Efficacy, routine effectiveness, and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency: a meta-analysis of randomized controlled trials and large observational studies. International Angiology. **21**(4): p. 305-315.
159. Guillaume M & Padioleau F. 1994. Venotonic effect, vascular protection, anti-inflammatory and free radical scavenging properties of horse chestnut extract. . Arzneim-Forsch Drug Res. **44**: p. 25-35.
160. Leach M, Pincombe J & Foster G. 2006 Clinical efficacy of horsechestnut seed extract in the treatment of venous ulceration. Journal of Wound Care. . **15**(4): p. 159-67.
161. Carpentier P & Satger B. 2009. Randomized trial of balneotherapy associated with patient education in patients with advanced chronic venous insufficiency. Journal of Vascular Surgery. **49**(1): p. 163-70.
162. Layton A, Ibbotson S, Davies J & Goodfield M. 1994. Randomised trial of oral aspirin for chronic venous leg ulcers. Lancet. **344**(8916): p. 164-5.
163. Roeckl-Wiedmann I, Bennett M & Kranke P. 2005. Systematic review of hyperbaric oxygen in the management of chronic wounds. British Journal of Surgery. **92**(1): p. 24-32.
164. KCI Medical. For Positive Healing Outcomes in the Treatment of Chronic Leg Ulcers consider V.A.C.® Therapy. 2010 [cited 2010 October]; http://www.help2heal.eu/uk/vlu/vactherapyclinicalbenefits.html.
165. Vuerstaek J, Vainas T, Wuite J, Nelemans P, Neumann M & Veraart J. 2006. State-of-the-art treatment of chronic leg ulcers: A randomized controlled trial comparing vacuum-assisted closure (V.A.C.) with modern wound dressings. J Vasc Surg **44**(5): p. 1029-37.
166. Mölnlycke Health Care. Xelma What is the extracellular matrix? 2009 [cited 2010 October]; http://www.xelma.com/en/What-is-Xelma/What-is-the-extracellular-matrix/.
167. Falanga V, Carson P, Greenberg A, Hasan A, Nichols E & McPherson J. 1996 Topically applied recombinant tissue plasminogen activator for the treatment of venous ulcers. Preliminary report. Dermatologic Surgery. **22**(7): p. 643-4.
168. Vowden P, Romanelli M, Peter R, Bostrom A, Josefsson A & Stege H. 2006. The effect of amelogenins (Xelma) on hard-to-heal venous leg ulcers. Wound Repair & Regeneration. **14**(3): p. 240-6.
169. Romanelli M, Kaha E, Stege H, Wnorowski J, Vowden P, Majamaa H & Lazaro J. 2008. Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers: follow-up data. Journal of Wound Care. **17**(1): p. 17-8, 20-3.

170. Vowden P, Romanelli M & Price P. 2007. Effect of amelogenin extracellular matrix protein and compression on hard-to-heal venous leg ulcers. Journal of Wound Care. **16**(5): p. 189-95.
171. Robson M, Phillips T, Falanga V, Odenheimer D, Parish L, Jensen J & Steed D. 2001. Randomized trial of topically applied repifermin (recombinant human keratinocyte growth factor-2) to accelerate wound healing in venous ulcers. Wound Repair & Regeneration. **9**(5): p. 347-52.
172. da Costa R, F. RJ, Aniceto C & Mendes M. 1997. Double-blind randomized placebo-controlled trial of the use of granulocyte-macrophage colony-stimulating factor in chronic leg ulcers. American Journal of Surgery. **173**(3): p. 165-8.
173. da Costa R, F. RJ, Aniceto C & Mendes M. 1999. Randomized, double-blind, placebo-controlled, dose- ranging study of granulocyte-macrophage colony stimulating factor in patients with chronic venous leg ulcers. Wound Repair & Regeneration. **7**(1): p. 17-25.
174. Ferrara F, Meli F, Raimondi F, Amato C, Bonura F, Mule G, Novo G & Novo S. 2007. The treatment of venous leg ulcers: a new therapeutic use of iloprost. Annals of Surgery. **246**(5): p. 860-5.
175. Stacey M, Mata S, Trengove N & Mather C. 2000 Randomised double-blind placebo controlled trial of topical autologous platelet lysate in venous ulcer healing. European Journal of Vascular & Endovascular Surgery. **20**(3): p. 296-301.
176. Rudofsky G. 1989. Intravenous prostaglandin E1 in the treatment of venous ulcers--a double-blind, placebo-controlled trial. Vasa - Supplementum. **28**(3): p. 9-43.
177. Milio G, Mina C, Cospite V, Almasio P & Novo S. 2005. Efficacy of the treatment with prostaglandin E-1 in venous ulcers of the lower limbs. Journal of Vascular Surgery. **42**(2): p. 304-8.

APPENDIX ONE EXPERT WORKING COMMITTEE

1. Membership of the Expert Working Committee

The Expert Working Committee who has overseen the development of the guideline and supporting documents comprised of a vascular surgeon, geriatrician, nurse practitioners, registered nurses, three consumer representatives, a medical research consultant and a National Health and Medical Research Council (NHMRC) advisor. The Expert Working Committee comprised:

Committee member	Qualifications	Representation
Donna Angel	RN; BN; NP; PGraddip (Clin Spec); MSc (Nur); MRCNA	Nurse practitioner (wound management)
Judith Barker, Vice Chair	RN; NP; STN; BHlthSc (Nurs); MN(NP)	Nurse practitioner (wound management)
Debbie Blanchfield	RN; Masters of Wound Care	Clinical nurse consultant
Keryln Carville	RN; STN (Cred); PhD	A/Professor
Roy Cochrane		Consumer representative
Michelle Gibb	RN; NP Wound Care MNrsgSc(NP),	Nurse practitioner
Emily Haesler	BN, PGradDipAdvNsg	Methodologist and researcher
Cathy Hammond	RN, MN	Clinical nurse specialist: wound care
David Hardman, Chair	MBBS (Hons); LLB (Hons); GradcertHE; FRACS; FACLM	Vascular surgeon; A/Professor
Susan Hillier	BappSc(Physiotherapy); PhD	NHMRC GAR consultant
Suzanne Kapp	BN; PGDip (AdvNsg); MNSci	Clinical nurse consultant
Deane Larkman	BSci(Hons); GradDip CompStud; MInfTech	Consumer representative
Judith Manning	RN; MA; BEd.	Clinical nurse (wound management)
Bill McGuiness	RN; DipT; BN; MNS; PhD; A/Professor; AWMA President	AWMA President; A/Professor
Robyn Rayner	RN; BSc (Nursing); Postgrad Health Admin; Master of Wound Care	Clinical nurse (wound management)
Jan Rice	RN; MRCNA; AMWA Cert. Plastic & Reconstructive Surgery; FAWMA	Clinical nurse educator
Pip Rutherford	RGON; BN; GradDip CaseManage; GradCert Wound Care; MN	Nurse Practitioner
Juliet Scott	BAppSci (Prim Hlth); Grad Cert; Grad Dip DN	Clinical nurse consultant

Jill Sparks	RN; MWoundManage	Clinical nurse consultant
Sue Templeton	RN; BN; MNSc(NP)	Nurse practitioner (wound management)
Carolina Weller	BN; MEd(Research); GradCertHlthEd	PhD scholar
Peter Wilkins		Consumer representative
Michael Woodward	MB; BS; FRACP	Past AWMA President; A/Professor

2. Conflicts of Interest

Members of the Expert Working Committee completed an AWMA declaration of conflict of interest and confidentiality statement (Appendix Four) annually throughout the project. Conflicts of interest were raised at every meeting. Although the majority of Expert Working Committee members had no conflicts of interest to declare those who did made their conflicts of interest known and refrained from participating in discussion where these conflicts were relevant. Full details are attached within the AWMA declaration of conflict of interest and confidentiality statement. The following conflicts of interest were declared:

Member	Declared conflicts of interest
Donna Angel	No conflicts to declare
Judith Barker, Vice Chair	No conflicts to declare
Debbie Blanchfield	Presentations for Convatec, Astra Zenica and Australian Pharmacy Association
Keryln Carville	No conflicts to declare
Roy Cochrane	No conflicts to declare
Michelle Gibb	No conflicts to declare
Emily Haesler	No conflicts to declare
Cathy Hammond	No conflicts to declare
David Hardman, Chair	No conflicts to declare
Susan Hillier	No conflicts to declare
Suzanne Kapp	No conflicts to declare
Deane Larkman	No conflicts to declare

Judith Manning	No conflicts to declare
Bill McGuiness	No conflicts to declare
Robyn Rayner	No conflicts to declare
Jan Rice	No conflicts to declare
Pip Rutherford	No conflicts to declare
Juliet Scott	No conflicts to declare
Jill Sparks	No conflicts to declare
Sue Templeton	Sponsorship from manufacturers/distributors of wound management products to: • attend educational programs; • prepare and deliver unrestricted education material at conferences; • provide editorial comment of a general nature for promotional wound management material.
Carolina Weller	No conflicts to declare
Peter Wilkins	No conflicts to declare
Michael Woodward	Membership of scientific advisory committee and advisor to Phoenix Eagle Paid presenter for Coloplast, 3M and Nestle

APPENDIX TWO PROCESS REPORT

This report outlines the process used for the development of the evidence-based *Australian and New Zealand clinical practice guideline for the prevention and management of venous leg ulcers*

The project consisted of the following phases:

- formation of a multi-disciplinary Expert Working Committee (see Appendix One);
- development of a scoping document providing an overview of the objectives and process for the development of the guidelines that received NHMRC approval;
- systematic literature searches to identify evidence;
- retrieval of papers, selection of relevant material and appraisal of the evidence;
- development of evidence statements summarising the findings in the evidence;
- synthesis of evidence statements into graded clinical recommendations;
- peer review and appraisal through a public consultation process; and
- response to feedback and completion of final guideline.

1 Identification, appraisal and synthesis of new evidence

Search strategy

A search was conducted for papers on the diagnosis and management of VLUs. The search was performed in Medline, Embase, CINAHL, the Cochrane library including CENTRAL Cochrane Controlled Trial Register, The WHO International Clinical Trials Registry Platform Search Portal, the Australian Wound Management journal and reference lists of included articles for English language publications from January 1985 to September 2009.

The database search of MEDLINE, EMBASE and CINAHL combined search terms describing venous ulceration. The initial search was not restricted by terms describing interventions for venous ulceration; however searches were conducted using filters for systematic reviews and randomised controlled trials to limit the identified evidence to that of a high level. An additional search was conducted to identify lower level research related to assessment of VLUs in order to inform the body of evidence. The search strategies below were applied to the MEDLINE database and adapted to apply to the other databases.

Search strategy for systematic reviews

1	exp review/
2	(medline or medlars or embase or pubmed).ti,ab,sh.
3	(scisearch or psychlit or psyclit).ti,ab,sh.
4	(psycinfo or psychinfo).ti,ab,sh.
5	cinahl.ti,ab,sh.
6	((hand adj2 search$) or (manual$ adj search$)).tw.
7	((electronic adj database$) or (bibliographic adj database$)).tw.
8	((pooled adj analys$) or pooling).tw.
9	(peto or dersimonian or (fixed adj effect) or mantel haenszel).tw.
10	RETRACTED ARTICLE/
11	6 or 3 or 7 or 9 or 2 or 8 or 4 or 10 or 5
12	11 and 1
13	exp meta analysis/
14	meta?analys$.tw,sh.
15	(systematic$ adj5 review$).tw,sh.
16	(systematic$ adj5 overview$).tw,sh.
17	(quantitativ$ adj5 review$).tw,sh.
18	(quantitativ$ adj5 overview$).tw,sh.
19	(methodologic$ adj5 review$).tw,sh.
20	(methodologic$ adj5 overview$).tw,sh.
21	((integrative adj5 research adj5 review$) or (research adj5 integration)).tw.
22	(quantitativ$ adj5 synthesi$).tw,sh.
23	21 or 17 or 20 or 15 or 14 or 22 or 18 or 13 or 16 or 19
24	23 or 12
25	limit 24 to (human and english language and yr="1988-Current")
26	exp Leg Ulcer/
27	Varicose Ulcer/
28	Venous Insufficiency/
29	Venous ulceration.mp.
30	Varicose eczema.mp.
31	27 or 28 or 30 or 26 or 29
32	25 and 31

Search strategy randomised controlled trials

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	randomised.ab.
5	randomised controlled trial.pt.
6	placebo.ab.
7	drug therapy.fs.
8	random*.ab.
9	trial.ab.
10	groups.ab.
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	limit 11 to (english language and humans and yr="1985 -Current")
13	Leg Ulcer/
14	Varicose Ulcer/
15	Venous Insufficiency/
16	Venous ulceration.mp.
17	Varicose eczema.mp.
18	16 or 13 or 17 or 15 or 14
19	18 and 12

Although the initial search was designed to identify research conducted in all populations, additional searches were made to identify literature relevant to Aboriginal and Torres Strait Islander populations. These searches combined terms to describe venous leg ulcers with terms to describe Indigenous populations. No papers that met the review inclusion criteria were identified in this search.

Inclusion/exclusion criteria

Types of studies

Studies that provide Level I evidence or Level II evidence on the National Health and Medical Research Council (NHMRC) Levels of evidence scale[28] (see Table one) were considered for inclusion. For intervention studies, RCTs (or systematic reviews of RCTs) that compared a single or combination intervention to placebo, sham-intervention, no treatment or another active intervention were included. For questions related to aetiology, diagnosis and assessment of leg ulcers, there was limited level I or II evidence available, therefore the search was expanded to include relevant level III and level IV research, as well as expert opinion and consensus guidelines. Randomised controlled trials that were reported in systematic reviews that were included were not subjected to individual critical appraisal to prevent replication of data.

Table one – NHMRC levels of evidence[28]

Level	Intervention	Prognosis	Diagnosis
I	Evidence obtained from a systematic review of all relevant randomised, controlled trials	A systematic review of level II studies	A systematic review of level II studies
II	Evidence obtained from at least one properly designed, randomised, controlled trial	A prospective cohort study	A study of test accuracy with independent blinded comparison with a valid reference standard, among consecutive patients with a defined clinical presentation
III –1	Evidence obtained from well-designed, pseudo-randomised, controlled trials (alternate allocation or some other method)	All or none	A study of test accuracy with independent blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation
III –2	Evidence obtained from comparative studies with concurrent controls and	Analysis of prognostic factors amongst persons in a single	A comparison with reference standard that does not meet the criteria

	allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	arm of a randomised controlled trial	for Level II or Level III-1 evidence
III –3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group	A retrospective cohort study	Diagnostic case–control evidence
IV	Evidence obtained from case series, either post-test or pre-test and post-test	Case series, or cohort study of persons at different stages of disease	Study of diagnostic yield (no reference standard)

Types of participants

The review included research conducted in participants with VLUs and participants at risk of developing VLUs.

Types of interventions

Evidence defined as falling within, but not limited to, the following categories was considered for inclusion:

- Interventions: compression therapy, nutrition, education, health professional training and competency, exercise, elevation, pharmacological management, complementary and/or alternative treatments, environmental barriers, wound management products, specialised leg ulcer clinics, hyperbaric oxygen, foot pump, leg clubs
- Diagnosis and assessment: Doppler studies – measurements of ankle brachial pressure index (ABPI), palpation of lower limb pulses, assessment tools, health professional education and competency, specialised leg ulcer clinics

Types of outcomes

Outcome measures of interest included:

- Outcomes assessing wound response to the intervention: time to complete wound healing, changes in ulcer size, proportion of ulcers healed in trial period, prevention of recurrence (e.g. number of new ulcers developed in trial period)
- Other outcomes related to the intervention: quality of life and global assessments, functional outcomes, venous ulcer specific quality of life, pain, compliance with therapy
- Adverse events

Critical appraisal

All studies included in the literature review were critically appraised by at least one reviewer. For SRs, one primary reviewer appraised all the retrieved research and 100% of the papers were appraised by a second reviewer. There was a high level of consensus between reviewers for this stage of the critical appraisal. Due to the volume of evidence and the high consensus in appraisal of SRs, the NHMRC allowed that only 30% of the additional research (RCTs) be double reviewed. As much research as possible was reviewed by the same primary reviewer to maintain consistency in appraisal of the literature and when minor discrepancies occurred, a third reviewer assessed the evidence.

Critical appraisal tools developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/checklists.html) were used to appraise the research. Randomised controlled trials were also appraised using the Jadad scale. Studies were classified as being of high, moderate or low quality based on how well they covered the key criteria on the appropriate SIGN appraisal tool.

Methodological quality of RCTs was assessed against key criteria on the SIGN assessment tool including:

- defined appropriate criteria to select studies for inclusion
- thorough and transparent search strategy
- validity of included studies is appraised and reproducible
- results similar from study to study or discrepancies can be explained
- appropriate strategies are used for pooling and analysing results
- potential conflicts of interest are clearly reported

Methodological quality of SRs was assessed against key criteria on the SIGN assessment tool including:

- appropriate randomisation and allocation concealment methods
- study groups similar at baseline regarding prognostic indicators
- blinding of subjects, therapists/researchers and assessors of the outcomes
- relevant outcomes were measured in a standard, valid and reliable manner
- all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”
- potential conflicts of interest are clearly reported

Data extraction

The primary reviewer systematically extracted the data from all studies using a data extraction tool that combined NHMRC data extraction[28] suggestions with information collected using the SIGN checklist tools. A second reviewer checked data extraction for 100% of systematic review papers and 30% of the additional research. Data from included studies was presented in evidence summary statements.

Special Populations

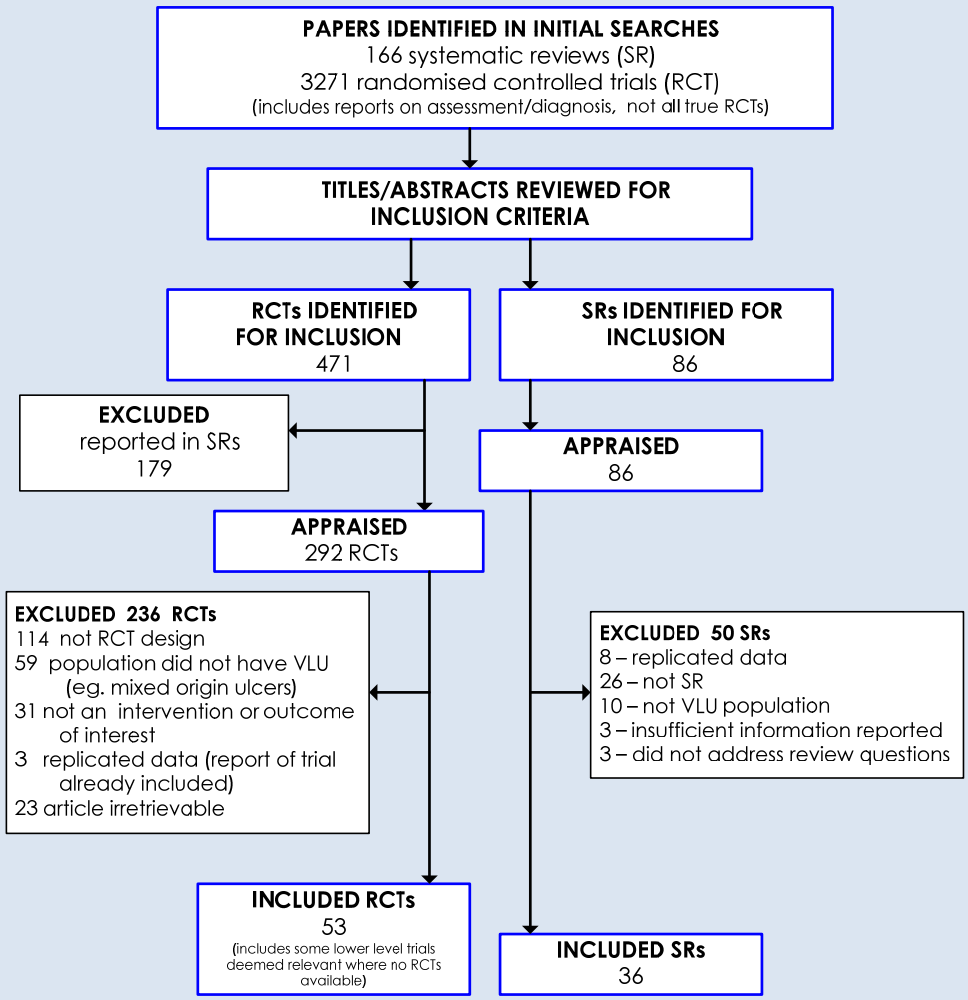
The search strategy was designed to retrieve all available evidence meeting the inclusion criteria, including research specific to special populations including Aboriginal and Torres Strait Islander people; New Zealand Maori people; rural and remote communities; and people from culturally and linguistically diverse backgrounds.

An additional search that sought to specifically identify research conducted in Indigenous populations did not identify any papers meeting the review criteria.

Identified research

Over 3,000 relevant papers were identified in the initial searches. Papers were initially selected for inclusion based on the title and/or the abstract by one reviewer and overseen by the Expert Working Committee. As shown in Figure one, a total of 553 papers were identified for retrieval, of which 86 were systematic reviews. Papers that were reported in the included RCTs were not retrieved for independent appraisal to prevent replication of data. Research subsequently excluded following initial identification as being relevant for retrieval is presented in Appendix Three.

Figure 1 – Review process



2 Development and grading of the recommendations

The Expert Working Committee used the best available evidence together with their expert opinion to develop recommendations relevant to health care practice within Australia and New Zealand.

The evidence was summarised into evidence statements. A body of evidence assessment matrix developed by the NHMRC[28] (Table two) was used to assess the volume and consistency of evidence supporting each recommendation; as well as the clinical impact, generalisability and applicability of the recommendation.

Table two - Body of evidence assessment matrix[28]

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	Several level I or level II studies with low risk of bias	One or two level II studies with low risk of bias or a SR of multiple level III studies with low risk of bias	Level III studies with low risk of bias or level II studies with moderate risk of bias	Level IV studies or level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistencies may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalis-ability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence different to the target population for the guideline but it is clinically sensible to apply this evidence to the target population (e.g. results in adults that are clinically sensible to apply to children)	Population/s studied in the body of evidence different to the target population for the guideline and hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Each recommendation was given a final grading (Table three) representing its overall strength. The grades reflect the confidence and trust health professionals can have when implementing recommendations in clinical practice. The overall grade of each recommendation was reached through consensus of the Expert Working Committee and is based on a summation of the grading of individual components represented in the body of evidence assessment matrix. In reaching an overall grade, recommendations were not graded Aor B unless the volume and consistency of evidence components were both graded either A or B.

Expert based opinion recommendations were developed through group discussion and email. The topics are those that were raised by members of the Expert Working Committee as being significant to the assessment and management of VLUs. In most instances they cover topics for which there is no high level evidence available, often because RCT designs are inappropriate for evaluation of the intervention. Discussion continued until consensus was reached.

Table one: Recommendation grades[28]	
Evidence based research	
A	Excellent evidence - body of evidence can be trusted to guide practice
B	Good evidence - body of evidence can be trusted to guide practice in most situations
C	Some evidence - body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Weak evidence - body of evidence is weak and recommendation must be applied with caution
Expert based opinion	
EBO	Consensus evidence – there was insufficient evidence to make a graded recommendation due to insufficient or no evidence from systematic reviews or RCTs or the literature search not locating research addressing the field. The EBO recommendations are supported by all members of the Expert Working Committee.

3 Consultation phase

Draft versions of *Australian and New Zealand clinical practice guideline for the management of venous leg ulcers* and *Grading of the Australian and New Zealand recommendations for the prevention and management of venous leg ulcers* were presented for public feedback via the AWMA and NZWCS websites. The public consultation period was advertised in major national newspapers and known stakeholders were sent invitations to review the material. Feedback was collated and addressed by the Expert Working Committee and made available to the NHMRC.

The Expert Working Committee extends its thanks to respondents who provided feedback during the consultation phase of the project.

4 Dissemination

Final versions of *Australian and New Zealand clinical practice guideline for the prevention and management of venous leg ulcers* and *Grading of the Australian and New Zealand recommendations for the prevention and management of venous leg*

ulcers will be publicly available to on the NHMRC website and New Zealand Guidelines Group website.

The AWMA and NZWCS intend to develop and distribute appropriate resources related to the guidelines to its members and the public via the AWMA website and the NZWCS website. Resources are likely to include material such as a clinical pathway for venous ulcers to support the implementation of the guideline in various clinical settings and by various health professionals.

APPENDIX THREE EXCLUDED STUDIES

Reasons for exclusion of SRs	
1	replicated data
2	not a SR
3	population did not have VLUs
4	insufficient information in review to assess or report
5	not an outcome of interest, does not primarily address review interests

Excluded systematic reviews	Reason
Amsler F & Blattler W. 2008. Compression Therapy for Occupational Leg Symptoms and Chronic Venous Disorders - a Meta-analysis of Randomised Controlled Trials. European Journal of Vascular and Endovascular Surgery. 35(3): 366-372	3
Anand S, Dean C, Nettleton R & Praburaj D. 2003. Health-related quality of life tools for venous-ulcerated patients. British Journal of Nursing. 12(1):48-59.	2
Berliner E, Ozbilgin B & Zarin D. 2003. A systematic review of pneumatic compression for treatment of chronic venous insufficiency and venous ulcers. Journal of Vascular Surgery. 37(3):539-44.	4
Briggs M & Flemming K. 2007. Living with leg ulceration: a synthesis of qualitative research. Journal of Advanced Nursing. 59(4):319-28.	5
Castonguay G; Short-stretch or four-layer compression bandages: an overview of the literature. Ostomy Wound Management, 2008 Mar; 54 (3): 50-5	2
Ciapponi A, Laffaire E, Roque M Calcium dobesilate for chronic venous insufficiency: a systematic review Angiology 2004 55(2):147-154	3
Coleridge-Smith P. 2009. Leg ulcer treatment. Journal of Vascular Surgery. 49(3): 804-808.	2
Crowe T & Brockbank C. 2009. Nutrition therapy in the prevention and treatment of pressure ulcers. Wound Practice and Research. 17(2)	2
Curran M & Plosker G. 2002. Bilayered bioengineered skin substitute (Apligraf): a review of its use in the treatment of venous leg ulcers and diabetic foot ulcers. Biodrugs. 16(6):439-55.	2
Duncan G & Brooks M. 2009 Chronic wound pain: a literature review. Wound Practice and Research. 17(3)	3
Duprez D. 1993. Ultrasound diagnostics of lower limb venous diseases. International Angiology. 12(3 suppl 1): 45.	2
Ernst E. 1995. Ultrasound for cutaneous wound healing. Phlebology. 10(1): 2-4.	2
Flemming L, Cullum N & Nelson E. 1999. A systematic review of laser therapy for venous leg ulcers. Journal of Wound Care. 8(3):111-4	1
Fletcher A, Cullum N & Sheldon T. 1997. A systematic review of compression treatment for venous leg ulcers. British Medical Journal. 315(7108):576-580.	1
Franks P & Morgan P. 2003. Health-related quality of life with chronic leg ulceration. Expert Review of Pharmacoeconomics and Outcomes Research. 3(5):611-622).	2
Gray M. 2003. Does oral supplementation with vitamins A or E promote healing of chronic wounds Journal of Wound Ostomy and Continence Nursing. 30(6): 290-294.	2
Gregor S. Maegele M. Sauerland S. Krahn J.F. Peinemann F. Lange S.Negative pressure wound therapy: A vacuum of evidence?. Archives of Surgery. 143(2)(pp 189-196), 2008.	3
Heinen M, van Achterberg T, op Reimer W, van de Kerkhof P & de Laat E. 2004. Venous leg ulcer patients: a review of the literature on lifestyle and pain-related interventions. Journal of	4

Excluded systematic reviews	Reason
Clinical Nursing. 13(3):355-66.	
Herber O, Schnepp W & Rieger M. 2007. A systematic review on the impact of leg ulceration on patients' quality of life. Health and Quality of Life Outcomes. 5	5
Howell-Jones R, Wilson M, Hill K, Howard A, Price P & Thomas D. 2005. A review of the microbiology, antibiotic usage and resistance in chronic skin wounds. Journal of Antimicrobial Chemotherapy. 55(2):143-149.	2
Jull A, Waters J & Arroll B. 2002. Pentoxifylline for treatment of venous leg ulcers: A systematic review. Lancet. 359(9317):1550-1554.	1
Khan M & Davies C. 2006. Advances in the management of leg ulcers - The potential role of growth factors. International Wound Journal. 3(2):113-120.	2
Kranke P, Bennett M, Debus S, Roeckl-Wiedmann I & Schnabel Alexander. 2004. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database of Systematic Reviews. Issue 1.	1
Lazarides M & Giannoukas A. 2007. The role of hemodynamic measurements in the management of venous and ischemic ulcers. International Journal of Lower Extremity Wounds. 6(4):254-261.	2
Machet L, Couhe C, Perrinaud A, Hoarau C, Lorette G & Vaillant L. 2004. A high prevalence of sensitization still persists in leg ulcer patients: a retrospective series of 106 patients tested between 2001 and 2002 and a meta-analysis of 1975-2003 data. British Journal of Dermatology. 150(5):929-35.	2
McCann M. 2008. Toe bandaging for lymphoedema and venous ulceration. British Journal of Nursing. 17(7):428, 430-3	2
Nelson E Cullum N & Jones J. 2005. Venous leg ulcers. American Family Physician. 71(7):1365-1366.	2
Nemeth K, Graham I & Harrison M. 2003. The measurement of leg ulcer pain: identification and appraisal of pain assessment tools. Advances in Skin & Wound Care, 16(5):260-7.	4
O'Sullivan-Drombolis D & Houghton P. 2009. Pneumatic compression in the treatment of chronic ulcers. Physical Therapy Reviews. 14(2): 81-92.	2
Palfreyman S, Nelson E, Lochiel R & Michaels J. 2006. Dressings for healing venous leg ulcers. Cochrane Database of Systematic Reviews. Issue 3.	1
Pascarella L. 2007. Essentials of daflon 500 mg: From early valve protection to long-term benefits in the management of chronic venous disease. Current Pharmaceutical Design. 13(4):431-444.	2
Pavlova L, Nikolovska S & Matevska-Cifrevska V. 2000. Evaluation of healing rate and predicting of healing of venous leg ulcers. Acta Dermatovenerologica Croatica. 8(2):73-76.	2
Peters J. 1998. A review of the factors influencing non recurrence of venous leg ulcers. Journal of Clinical Nursing. 7(1):3-9.	2
Pittler M & Ernst E. 1998. Horse-chestnut seed extract for chronic venous insufficiency. A criteria-based systematic review. Archives of Dermatology. 134(11):1356-60.	3
Pittler M & Ernst E. 2006. Horse chestnut seed extract for chronic venous insufficiency. Cochrane Database of Systematic Reviews. Issue 1.	3
Poynard T & Valterio C. 1994. Meta-analysis of hydroxyethylrutosides in the treatment of chronic venous insufficiency. Vasa – Journal of Vascular Diseases. 23(3):244-250.	1
Ramundo J & Gray M. 2008. Enzymatic wound debridement. Journal of Wound, Ostomy & Continence Nursing. 35(3):273-80.	2
Robson M, Cooper D, Aslam R, Gould L, Harding K, Margolis D, Ochs D, Serena T, Snyder R, Steed D, Thomas D & Wiersma-Bryant L. 2006. Guidelines for the treatment of venous ulcers Wound Repair and Regeneration. 14(6):649-662.	2

Excluded systematic reviews	Reason
Romanelli M, Dini V, Vowden P& Agren M. 2008. Amelogenin, an extracellular matrix protein, in the treatment of venous leg ulcers and other hard-to-heal wounds: experimental and clinical evidence. Clinical Interventions In Aging. 3(2):263-72.	**2**
Sadat U, Chang G, Noorani A, Walsh S, Hayes P & Varty K. 2008. Efficacy of TNP on lower limb wounds: a meta-analysis. Journal of Wound Care. 17(1):45-48.	**3**
Saliba Jr. O, Giannini M & Rollo H. 2007. Noninvasive diagnostic methods to evaluate venous insufficiency of the lower limbs. Jornal Vascular Brasileiro. 6(3).	**2**
Savel'ev V, Pokrovskii A, Sapelkin S, Bogachev V, Bogdanets L & Zolotukhin I. 2006. Micronized diosmin (Detralex) for vein-related trophic ulcers: European experience. Angiology & Vascular Surgery. 12(3):53-60.	**1**
Shephard D. 2003. Daflon 500 mg at the very heart of chronic venous insufficiency: Results from the meta-analysis presented at the UIP Congress, San Diego, 2003. Phlebolymphology. (41):172-176.	**2**
Siebert U, Brach M, Sroczynski G & Uberla K. 2002. Efficacy, routine effectiveness, and safety of horsechestnut seed extract in the treatment of chronic venous insufficiency: a meta-analysis of randomized controlled trials and large observational studies. International Angiology. 21(4):305-315	**3**
Smellie W, Shaw N, Bowlees R, Taylor A, Howell-Jones R & McNulty C. 2007. Best practice in primary care pathology: Review 9. Journal of Clinical Pathology. 60(9):966-974.	**2**
Thorne E. 1998. Community leg ulcer clinics and the effectiveness of care. Journal of Wound Care. 7(2): 94-99	**2**
Thurlby K & Griffiths P. 2002. Community leg ulcer clinics vs home visits: which is more effective? British Journal of Community Nursing. 7(5):260-4.	**5**
Vermeulen H, van Hattem J, Storm-Versloot M & Ubbink D. 2007. Topical silver for treating infected wounds. Cochrane Database of Systematic Reviews. Issue 1.	**3**
Vikatmaa P, Juutilainen V, Kuukasjarvi P & Malmivaara A. 2008. Negative Pressure Wound Therapy: a Systematic Review on Effectiveness and Safety. European Journal of Vascular and Endovascular Surgery. 36(4):438-448.	**3**
Wilkinson E & Hawke C. 1998. Does oral zinc aid the healing of chronic leg ulcers? A systematic literature review. Archives of Dermatology. 134(12):1556-60.	**1**

Reasons for exclusion of RCTs	
1	in an included SR
2	not a population of interest, including trials in ulcers of mixed aetiology where results are not reported separately
3	not an RCT (including abstract reports only and trials in which participants randomised more than once)
4	not an intervention or outcome of interest, does not primarily address review interests
5	insufficient information reported in paper to report in review or full article not in English
6	replicated data
7	unable to retrieve

Excluded RCTs	Reason
Abu-Own A, Scurr J &Coleridge Smith P. 1994. Effect of leg elevation on the skin microcirculation in chronic venous insufficiency. Journal of Vascular Surgery. 20(5):705-10.	3
Agrifoglio G, Domanin M, Baggio E, Cao P, Alberti A, Borin F, Todini A, Becchi G & Caserini M. 2000. EMLA anaesthetic cream for sharp debridement of venous leg ulcers: A double-masked, placebo-controlled study. Phlebology. 15(2) : 81-83	1
Alinovi A, Bassissi P & Pini M. 1986. Systemic administration of Antibiotics in the management of venous ulcers. A randomized clinical trial. Journal of the American Academy of Dermatology. 15(2 Pt 1):186-91.	1
Ambrosch A, Lobmann R, Pott A & Preissler J. 2008. Interleukin-6 concentrations in wound fluids rather than serological markers are useful in assessing bacterial triggers of ulcer inflammation. International Wound Journal. 5(1):99-106.	3
Andersen , Franken C, Gad P, Larsen A, Larsen J, van Neer P & et al. 2002. A randomized, controlled study to compare the effectiveness of two foam dressings in the management of lower leg ulcers. Ostomy/Wound Management.48(8): 34-41.	1
Andriessen A, Polignano R & Abel M. 2009, Monitoring the microcirculation to evaluate dressing performance in patients with venous leg ulcers. Journal of Wound Care. 18(4):145-50.	5
Andriessen A, Polignano R & Abel M. 2009.Development and implementation of a clinical pathway to improve venous leg ulcer treatment. Wounds: A Compendium of Clinical Research & Practice (WOUNDS), May; 21(5): 127-33.	7
Annells M, O'Neill J & Flowers C. 2008. Compression bandaging for venous leg ulcers: the essentialness of a willing patient. Journal of Clinical Nursing. 17(3): 350-9 .	3
Arcangeli P. 2000. Pycnogenol in chronic venous insufficiency. Fitoterapia. 71(3):236-44.	2
Arcelus J, Caprini J, Sehgal L & Reyna JJ. 2001. Home use of impulse compression of the foot and compression stockings in the treatment of chronic venous insufficiency. Journal of Vascular Surgery. 34(5):805-11.	3
Arceo A, Berber A & Trevino C. 2002. Clinical evaluation of the efficacy and safety of calcium dobesilate in patients with chronic venous insufficiency of the lower limbs. Angiology. 53(5):539-44.	2
Armstrong S & Ruckley C. 1997. Use of a fibrous dressing in exuding leg ulcers. Journal of Wound Care. 6(7):322-4.	4
Arosio E, Ferrari G, Santoro L, Gianese F & Coccheri S. 2001. Mesoglycan Venous Insufficiency Group. A placebo-controlled, double-blind study of mesoglycan in the treatment of chronic venous ulcers. European Journal of Vascular & Endovascular Surgery. 22(4):365-72.	7
Arsecularatne Y, Walton J, Hofman D & Cherry G. 2003. A comparison of light reflection rheography and duplex scanning in the diagnosis of chronic venous insufficiency. Wounds: A Compendium of Clinical Research & Practice. 15(8): 246-9.	3
Arseculeratne M & Cherry G. 2003.Sensory testing in patients with chronic venous leg ulcers. Nursing times. 99(31): 55-6.	3

Excluded RCTs	Reason
Arseculeratne YM. Cherry GW. Sensory testing in patients with chronic venous leg ulcers using a 10 g Owen Mumford monofilament. Journal of Wound Care. 12(6):215-7, 2003 Jun.	4
Asbeutah AM; Riha AZ; Cameron JD; McGrath BP Quantitative assessment of chronic venous insufficiency using duplex ultrasound and air plethysmography.Journal for Vascular Ultrasound 2006 Mar; 30(1):23-30, 45-6	3
Aschwanden M. Jeanneret C. Koller MT. Thalhammer C. Bucher HC. Jaeger KA. Effect of prolonged treatment with compression stockings to prevent post-thrombotic sequelae: a randomized controlled trial. Journal of Vascular Surgery. 47(5):1015-21, 2008 May.	4
Ashford R Lagan K Brown N Howell C Nolan C Brady D Walsh M. Low intensity laser therapy for chronic venous leg ulcers. Nursing standard. 1999. 14(3): 66-70, 72	1
Atillasoy E. The safety and efficacy of Graftskin (APLIGRAF) in the treatment of venous leg ulcers: a multicenter, randomized, controlled clinical trial. Wounds: A Compendium of Clinical Research and Practice. 2000. 12 vol 5 Suppl A: 20A-6A (18 ref	3
Backhouse CM. Blair SD. Savage AP. Walton J. McCollum CN. Controlled trial of occlusive dressings in healing chronic venous ulcers. British Journal of Surgery. 74(7):626-7, 1987 Jul. Exclude – in an included SR	1
Ballard K McGregor F Baxter H An evaluation of the Parema four-layer bandage system. British journal of nursing. 2000. 9(16) : 1089-94	3
Banerjee AK Levy DW Rawlinson D. Leg ulcers - a comparative study of Synthaderm and conventional dressings. Care of the Elderly. 1990. 2(3): 123-5	1
Banks V. Bale S. Harding K. Harding EF. Evaluation of a new polyurethane foam dressing. Journal of Wound Care. 6(6):266-9, 1997 Jun.	2
Barbarino C. Pentoxifylline in the treatment of venous leg ulcers. Current Medical Research & Opinion. 12(9):547-51, 1992.	1
Basu S. Ramchuran Panray T. Bali Singh T. Gulati AK. Shukla VK.A prospective, descriptive study to identify the microbiological profile of chronic wounds in outpatients. Ostomy Wound Management. 55(1):14-20, 2009 Jan.	2
Bays RA. Healy DA. Atnip RG. Neumyer M. Thiele BL. Validation of air plethysmography, photoplethysmography, and duplex ultrasonography in the evaluation of severe venous stasis. Journal of Vascular Surgery. 20(5):721-7, 1994 Nov.	3
Beitner H. Treatment of chronic leg ulcers with topical application of benzoyl peroxide lotion. Current Therapeutic Research. 1985. 38(4) : 657-60	1
Belcaro G Cesarone MR de Sanctis MT Incandela L Laurora G Février B Wargon C De Gregoris P. Laser Doppler and transcutaneous oximetry: modern investigations to assess drug efficacy in chronic venous insufficiency. International journal of microcirculation, clinical and experimental / sponsored by the European Society for Microcirculation. 1995. 15 Suppl 1: 45-9	3
Belcaro G. Cesarone MR. Dugall M. Efficacy of topical treatment with aescin + essential phospholipids gel in a microcirculatory model of venous insufficiency. Angiology. 55 Suppl 1:S15-8, 2004 May-Jun.	2
Belcaro G. Cesarone MR. Dugall M. Microcirculatory efficacy of topical treatment with aescin + essential phospholipids gel in venous insufficiency and hypertension: new clinical observations. Angiology. 55 Suppl 1:S1-5, 2004 May-Jun.	3
Belcaro G. Cesarone MR. Errichi BM. Di Renzo A. Errichi S. Ricci A. Gizzi G. Dugall M. Cacchio M. Ruffini I. Fano F. Vinciguerra G. Grossi MG. Improvement of microcirculation and healing of venous hypertension and ulcers with Crystacide: evaluation with a microcirculatory model, including free radicals, laser doppler flux, and PO2/PCO2 measurements. Angiology. 58(3):323-8, 2007 Jun-Jul.	1
Belcaro G. Cesarone MR. Errichi BM. Ledda A. Di Renzo A. Stuard S. Dugall M. Pellegrini L. Rohdewald P. Ippolito E. Ricci A. Cacchio M. Ruffini I. Fano F. Hosoi M. Venous ulcers: microcirculatory improvement and faster healing with local use of Pycnogenol. Angiology. 56(6):699-705, 2005 Nov-Dec.	3
Belcaro G. Cesarone MR. Nicolaides AN. De Sanctis MT. Incandela L. Geroulakos G. Treatment of venous ulcers with pentoxifylline: a 6-month randomized, double-blind, placebo controlled trial. Angiology. 53 Suppl 1:S45-7, 2002 Jan-Feb. .	1

Excluded RCTs	Reason
Belcaro G. Cesarone MR. Nicolaides AN. Geroulakos G. Di Renzo A. Milani M. Ricci A. Brandolini R. Dugall M. Ruffini I. Cornelli U. Griffin M. Improvement of microcirculation and healing of venous hypertension and ulcers with Crystacide. Evaluation of free radicals, laser Doppler flux and PO2. A prospective-randomized-controlled study. Angiology. 54(3):325-30, 2003 May-Jun.	1
Belcaro G. Rosaria Cesarone M. Ledda A. Cacchio M. Ruffini I. Ricci A. Ippolito E. Di Renzo A. Dugall M. Corsi M. Marino Santarelli AR. Grossi MG. O-(beta-hydroxyethyl)-rutosides systemic and local treatment in chronic venous disease and microangiopathy: an independent prospective comparative study. Angiology. 59 Suppl 1:7S-13S, 2008 Feb-Mar.	2
Beltramino R. Penenory A. Buceta AM. An open-label, randomised multicentre study comparing the efficacy and safety of CYCLO 3 FORT versus hydroxyethyl rutoside in chronic venous lymphatic insufficiency. International Angiology. 18(4):337-42, 1999 Dec.	2
Beltramino R. Penenory A. Buceta AM. An open-label, randomized multicenter study comparing the efficacy and safety of Cyclo 3 Fort versus hydroxyethyl rutoside in chronic venous lymphatic insufficiency. Angiology. 51(7):535-44, 2000 Jul.	2
Berard A. Kurz X. Zuccarelli F. Ducros JJ. Abenhaim L. Reliability study of the Leg-O-Meter, an improved tape measure device, in patients with chronic venous insufficiency of the leg. VEINES Group.(Venous Insufficiency Epidemiologic and Economic Study). Angiology. 49(3):169-73, 1998 Mar.	3
Bielanski TE Piotrowski ZH. Horse-chestnut seed extract for chronic venous insufficiency. The Journal of family practice. 1999. 48(3) : 171-2	3
Bihari I Mester AR The biostimulative effect of low level laser therapy of long-standing crural ulcers using helium neon laser, helium neon plus infrared lasers, and noncoherent light: Preliminary report of a randomized double blind comparative study. LASER THER. 1989. 1(2): 97-98	1
Biland L. Hurlimann F. Goor W. Korner WF. Kundig A. Madar G. Widmer LK. Ziegler WJ. Treatment of venous ulcers. A multi-center randomized double-blind study. Vasa. 14(4):383-9, 1985.	2
Bishop JB. Phillips LG. Mustoe TA. VanderZee AJ. Wiersema L. Roach DE. Heggers JP. Hill DP Jr. Taylor EL. Robson MC. A prospective randomized evaluator-blinded trial of two potential wound healing agents for the treatment of venous stasis ulcers. Journal of Vascular Surgery. 16(2):251-7, 1992 Aug.	1
Blair SD Backhouse CM Wright DD Riddle E McCollum CN. Do dressings influence the healing of chronic venous ulcers? Phlebology. 1988. 3: 129-34	1
Blair SD Gawne S Topical 1 trial participants. Prospective randomized trial of ICX-PRO (cultured fibroblasts) in healing chronic leg ulcers. Phlebology. 2006. 21(3): 142	3
Blair SD. Wright DD. Backhouse CM. Riddle E. McCollum CN. Sustained compression and healing of chronic venous ulcers. BMJ. 297(6657):1159-61, 1988 Nov 5. [erratum appears in BMJ 1988 Dec 10;297(6662):1500].	1
Blecken SR. Villavicencio JL. Kao TC. Comparison of elastic versus nonelastic compression in bilateral venous ulcers: a randomized trial. Journal of Vascular Surgery. 42(6):1150-5, 2005 Dec.	1
Boccalon H. Causse C. Yubero L. Comparative efficacy of a single daily dose of two capsules Cyclo 3 Fort in the morning versus a repeated dose of one capsule morning and noon. A one-month study. International Angiology. 17(3):155-60, 1998 Sep.	2
Boisseau MR. Taccoen A. Garreau C. Vergnes C. Roudaut MF. Garreau-Gomez B. Fibrinolysis and hemorheology in chronic venous insufficiency: a double blind study of troxerutin efficiency. Journal of Cardiovascular Surgery. 36(4):369-74, 1995 Aug.	2
Bowszyc J. Bowszyc-Dmochowska M. Kazmierowski M. Ben-Amer HM. Garbowska T. Harding E. Comparison of two dressings in the treatment of venous leg ulcers. Journal of Wound Care. 4(3):106-10, 1995 Mar. Exclude – in an included SR	1
Brandrup F. Menne T. Agren MS. Stromberg HE. Holst R. Frisen M. A randomized trial of two occlusive dressings in the treatment of leg ulcers. Acta Dermato-Venereologica. 70(3):231-5, 1990.	1
Brooks J. Ersser SJ. Lloyd A. Ryan TJ. Nurse-led education sets out to improve patient concordance and prevent recurrence of leg ulcers. Journal of Wound Care. 13(3):111-6, 2004 Mar	3

Excluded RCTs	Reason
Brown A Bums E Chalmers L Corcoran F Dale J Douglas S Finnie A Forster T Fowkes G Gibson B Gillies T Hill E Lee R MacGuire C Morley S O'Hare J Prescott R Ruckley V Young C. Effect of a national community intervention programme on healing rates of chronic leg ulcer: Randomised controlled trial. Phlebology. 2002. 17(2): 47-53	**7**
Brown JR. Brown AM. Office diagnosis of lower extremity venous insufficiency and treatment with the use of nonprescription support hose. Journal of the American Osteopathic Association. 92(4):459-68, 471, 1992 Apr.	**3**
Bulstrode CJ Goode AW Scott PJ. A prospective controlled trial of topical irrigation in the treatment of delayed cutaneous healing in human leg ulcers. Clinical science. 1988. 75(6): 637-40	**1**
Bulstrode CJ. Goode AW. Scott PJ. A prospective controlled trial of topical irrigation in the treatment of delayed cutaneous healing in human leg ulcers. Clinical Science. 75(6):637-40, 1988 Dec.	**1**
Burdge J, Cope F, Abbruzzese B, Wille J. Long-term healing of venous stasis ulcers treated with serum-free cultured epidermal autografts. Proceedings of the Eleventh Annual Meeting and Educational Symposium of the Wound Healing Society. 16–18 May 2001, Albuquerque, New Mexico:146.	**1**
Burke PE. Randomized clinical trial and economic analysis of four-layer compression bandaging for venous ulcers. British Journal of Surgery. 90(7):794-8, 2003 Jul [see comment]. Comment in: Br J Surg. 2003 Oct;90(10):1307;	**1**
Callam MJ Harper DR Dale JJ Brown D Gibson B Prescott RJ Ruckley CV Lothian and Forth Valley leg ulcer healing trial. Part 1: Elastic versus non-elastic bandaging in the treatment of chronic leg ulceration PHLEBOLOGY 1992. 7(4): 136-141	**1**
Callam MJ. Harper DR. Dale JJ. Ruckley CV. Prescott RJ. A controlled trial of weekly ultrasound therapy in chronic leg ulceration. Lancet. 2(8552):204-6, 1987 Jul 25.	**1**
Canedo-Dorantes L Garcia-Cantu R Barrera R Mendez-Ramirez I Navarro VH Serrano G. Healing of chronic arterial and venous leg ulcers with systemic electromagnetic fields. Archives of Medical Research. 2002. 33(3): 281-289	**3**
Casley-Smith JR. A double-blind trial of calcium dobesilate in chronic venous insufficiency. Angiology. 39(10):853-7, 1988 Oct.	**1**
Casoni P Laser treatment in chronic leg ulcers. Phlebolymphology. 2006. 14(2): 113	**3**
Cesarone MR. Belcaro G. Ippolito E. Ricci A. Ruffini M. Dugall M. Microcirculatory efficacy of topical treatment with aescin + essential phospholipids gel on transcutaneous PO2 in venous insufficiency. Angiology. 55 Suppl 1:S7-10, 2004 May-Jun.	**3**
Cesarone MR. Belcaro G. Pellegrini L. Ledda A. Vinciguerra G. Ricci A. Di Renzo A. Ruffini I. Gizzi G. Ippolito E. Fano F. Dugall M. Acerbi G. Cornelli U. Hosoi M. Cacchio M. Venoruton vs Daflon: evaluation of effects on quality of life in chronic venous insufficiency. Angiology. 57(2):131-8, 2006 Mar-Apr.	**2**
Cesarone MR. Belcaro G. Rohdewald P. Pellegrini L. Ledda A. Vinciguerra G. Ricci A. Gizzi G. Ippolito E. Fano F. Dugall M. Acerbi G. Cacchio M. Di Renzo A. Hosoi M. Stuard S. Corsi M. Comparison of Pycnogenol and Daflon in treating chronic venous insufficiency: a prospective, controlled study. Clinical & Applied Thrombosis/Hemostasis. 12(2):205-12, 2006 Apr.	**2**
Cesarone MR. Belcaro G. Rohdewald P. Pellegrini L. Ledda A. Vinciguerra G. Ricci A. Gizzi G. Ippolito E. Fano F. Dugall M. Acerbi G. Cacchio M. Di Renzo A. Hosoi M. Stuard S. Corsi M. Rapid relief of signs/symptoms in chronic venous microangiopathy with pycnogenol: a prospective, controlled study.[erratum appears in Angiology. 2008 Jun-Jul;59(3):385]. Angiology. 57(5):569-76, 2006 Oct-Nov.	**2**
Charles H, Venous leg ulcer pain and its characteristics. Journal of tissue viability 2002 12 (4): 154-8	**7**
Charles H. Callicot C. Mathurin D. Ballard K. Hart J. Randomised, comparative study of three primary dressings for the treatment of venous ulcers. British Journal of Community Nursing. 7(6 Suppl):48-54, 2002 Jun.	**1**
Charles H. Compression healing of venous ulcers. Nursing Times 1992. 88(3): 52	**1**
Clancy JM, Shehade SA, Blight AE, Young KE, Levick PL. Treatment of leg ulcers with cultured epithelial grafts. *Journal of the American Academy of Dermatology* 1988;**18**(6):1356–7.	**3**

Excluded RCTs	Reason
Clarke-Moloney M. O'Brien JF. Grace PA. Burke PE. Health-related quality of life during four-layer compression bandaging for venous ulcer disease: a randomised controlled trial. Irish Journal of Medical Science. 174(2):21-5, 2005 Apr-Jun.	1
Coleridge Smith P. Sarin S. Hasty J. Scurr JH. Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial. Surgery. 108(5):871-5, 1990 Nov.	1
Coleridge Smith PD Sarin SA Wilson LAA Scurr JH. Intermittent pneumatic compression improves venous ulcer healing.Phlebologie. 1989 p. 1146-8	1
Coleridge-Smith PD Sarin S Wilson LA Scurr JH. Improved venous ulcer healing using intermittent pneumatic compression. Phlébologie. 1988 41(4) : 788-789	1
Colgan MP. Dormandy JA. Jones PW. Schraibman IG. Shanik DG. Young RA. Oxpentifylline treatment of venous ulcers of the leg. BMJ. 300(6730):972-5, 1990 Apr 14	1
Colletta V. Dioguardi D. Di Lonardo A. Maggio G. Torasso F. A trial to assess the efficacy and tolerability of Hyalofill-F in non-healing venous leg ulcers. Journal of Wound Care. 12(9):357-60, 2003 Oct.	1
Collier J. A moist, odour-free environment. A multicentred trial of a foamed gel and a hydrocolloid dressing. Professional Nurse. 7(12):804, 806, 808, 1992 Sep.	4
Cordts PR. Hanrahan LM. Rodriguez AA. Woodson J. LaMorte WW. Menzoian JO. A prospective, randomized trial of Unna's boot versus Duoderm CGF hydroactive dressing plus compression in the management of venous leg ulcers. Journal of Vascular Surgery. 15(3):480-6, 1992 Mar. [see comment]. Comment in: J Vasc Surg. 1992 Sep;16(3):500-1.	1
Cospite M. Dominici A. Double blind study of the pharmacodynamic and clinical activities of 5682 SE in venous insufficiency. Advantages of the new micronized form. International Angiology. 8(4 Suppl):61-5, 1989 Oct-Dec.	2
Coull A Tolson D McIntosh J. Class-3c compression bandaging for venous ulcers: comparison of spiral and figure-of-eight techniques. Journal of Advanced Nursing. 2006. 54(3): 274-83	2
Courtenay M. Church JC. Ryan TJ. Larva therapy in wound management. Journal of the Royal Society of Medicine. 93(2):72-4, 2000 Feb. [see comment].Comment in: J R Soc Med. 2000 Jul;93(7):394; PMID: 10928035	2
Criado E. Farber MA. Marston WA. Daniel PF. Burnham CB. Keagy BA. The role of air plethysmography in the diagnosis of chronic venous insufficiency. Journal of Vascular Surgery. 27(4):660-70, 1998 Apr.	3
Dale JJ. Ruckley CV. Harper DR. Gibson B. Nelson EA. Prescott RJ. Randomised, double blind placebo controlled trial of pentoxifylline in the treatment of venous leg ulcers. BMJ. 319(7214):875-8, 1999 Oct 2.[see comment][erratum appears in BMJ 2000 Jan 1;320(7226):30]. Comment in: BMJ. 2000 Feb 12;320(7232):446-7; PMID: 10669458.	1
Danielsen L Madsen SM and Hendriksen L Venous leg ulcer healing - a randomized prospective study of long-stretch versus short-stretch compression bandages. Phlebology. 1998. 13: 59-63	1
Danielsen L. Cherry GW. Harding K. Rollman O. Cadexomer iodine in ulcers colonised by Pseudomonas aeruginosa. Journal of Wound Care. 6(4):169-72, 1997 Apr.	3
Danielsen L. Madsen M. Henriksen L. Sindrup J. Petersen L. Subbandage pressure measurements comparing a long-stretch with a short-stretch compression bandage. Acta Dermato-Venereologica. 78(3):201-4, 1998 May.	1
Danielsson G Jungbeck C Peterson K Norgren L A randomised controlled trial of micronised purified flavonoid fraction vs placebo in patients with chronic venous disease. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery. 2002. 23(1): 73-6	2
Davis LB. McCulloch JM. Neal MB. The effectiveness of Unna Boot and semipermeable film vs. Unna Boot alone in the healing of venous ulcers. A pilot report. Ostomy Wound Management. 38(1):19-21, 1992 Jan-Feb. .	1
De Sanctis MT. Belcaro G. Cesarone MR. Ippolito E. Nicolaides AN. Incandela L. Geroulakos G. Treatment of venous ulcers with pentoxifylline: a 12-month, double-blind, placebo controlled trial. Microcirculation and healing. Angiology. 53 Suppl 1:S49-51, 2002 Jan-Feb	1

Excluded RCTs	Reason
De Sanctis MT. Incandela L. Belcaro G. Cesarone MR. Topical treatment of venous microangiopathy in patients with venous ulceration with Essaven gel--a placebo-controlled, randomized study. Angiology. 52 Suppl 3:S29-34, 2001 Dec.	4
DePalma RG Kowallek D Spence RK Caprini JA Nehler MR Jensen J Goldman MP Bundens WP. Comparison of costs and healing rates of two forms of compression in treating venous ulcers. Vascular Surgery 1999. 33(6) : 683-690	1
Dickson S. Gallagher J. McIntyre L. Suter A. Tan J. An open study to assess the safety and efficacy of Aesculus hippocastanum tablets (Aesculaforce 50mg) in the treatment of chronic venous insufficiency. Journal of Herbal Pharmacotherapy. 4(2):19-32, 2004.	3
Diehm C. Trampisch HJ. Lange S. Schmidt C. Comparison of leg compression stocking and oral horse-chestnut seed extract therapy in patients with chronic venous insufficiency. Lancet. 347(8997):292-4, 1996 Feb 3.	1
Diehm C. Vollbrecht D. Amendt K. Comberg HU. Medical edema protection--clinical benefit in patients with chronic deep vein incompetence. A placebo controlled double blind study. Vasa. 21(2):188-92, 1992.	1
Dmochowska M Prokop J Bielecka S Urasinska K Krolicki A Nagaj E et al A randomized, controlled, parallel group clinical trial of a polyurethane foam dressing versus a calcium alginate dressing in the treatment of moderately to heavily exuding venous leg ulcers. Wounds: A Compendium of Clinical Research and Practice. 1999. 11(1): 21-8	3
Domínguez C Brautigam I González E González JA Nazco J Valiente R Boada J. Therapeutic effects of hidrosmin on chronic venous insufficiency of the lower limbs. Current medical research and opinion. 1992. 12(10): 623-30	1
Dominguez C. Brautigam I. Gonzalez E. Gonzalez JA. Nazco J. Valiente R. Boada J. Therapeutic effects of hidrosmin on chronic venous insufficiency of the lower limbs. Current Medical Research & Opinion. 12(10):623-30, 1992.	2
Duby T Hofman D Cameron J Dobloff Brown D Cherry G Ryan T. A randomized trial in the treatment of venous leg ulcers comparing short stretch bandages, four layer bandage system, and a long stretch-paste bandage system. Wounds: A Compendium of Clinical Research and Practice. 1993. 5(6): 276-9	1
Dumville JC. Worthy G. Bland JM. Cullum N. Dowson C. Iglesias C. Mitchell JL. Nelson EA. Soares MO. Torgerson DJ. VenUS II team. Larval therapy for leg ulcers (VenUS II): randomised controlled trial. BMJ. 338:b773, 2009.	2
Duran V. Matic M. Jovanovc M. Mimica N. Gajinov Z. Poljacki M. Boza P. Results of the clinical examination of an ointment with marigold (Calendula officinalis) extract in the treatment of venous leg ulcers. International Journal of Tissue Reactions. 27(3):101-6, 2005.	3
Edwards H. Courtney M. Finlayson K. Lewis C. Lindsay E. Dumble J. Improved healing rates for chronic venous leg ulcers: pilot study results from a randomized controlled trial of a community nursing intervention. International Journal of Nursing Practice. 11(4):169-76, 2005 Aug.	4
Edwards H. Courtney M. Finlayson K. Lindsay E. Lewis C. Shuter P. Chang A. Chronic venous leg ulcers: effect of a community nursing intervention on pain and healing. Nursing Standard. 19(52):47-54, 2005 Sep 7-13.	4
Enander Malmros I. Nilsen T. Lillieborg S. Plasma concentrations and analgesic effect of EMLA (lidocaine/prilocaine) cream for the cleansing of leg ulcers. Acta Dermato-Venereologica. 70(3):227-30, 1990. . Exclude – in an included SR	1
Eriksson G. Comparison of two occlusive bandages in the treatment of venous leg ulcers. British Journal of Dermatology. 114(2):227-30, 1986 Feb.	1
Eriksson SV. Lundeberg T. Malm M. A placebo controlled trial of ultrasound therapy in chronic leg ulceration. Scandinavian Journal of Rehabilitation Medicine. 23(4):211-3, 1991.	1
Etris MB. Pribble J. LaBrecque J. Evaluation of two wound measurement methods in a multi-center, controlled study. Ostomy Wound Management. 40(7):44-8, 1994 Sep.	7
Falanga V, Sabolinski M. A bilayered living skin construct (APLIGRAF) accelerates complete closure of hard-to-heal venous ulcers. *Wound Repair and Regeneration* 1999;**7**:201–7.	1
Falanga V. Eaglstein WH. Bucalo B. Katz MH. Harris B. Carson P. Topical use of human recombinant epidermal growth factor (h-EGF) in venous ulcers. Journal of Dermatologic Surgery & Oncology. 18(7):604-6, 1992 Jul.	7

Excluded RCTs	Reason
Falanga V. Fujitani RM. Diaz C. Hunter G. Jorizzo J. Lawrence PF. Lee BY. Menzoian JO. Tretbar LL. Holloway GA. Hoballah J. Seabrook GR. McMillan DE. Wolf W. Systemic treatment of venous leg ulcers with high doses of pentoxifylline: efficacy in a randomized, placebo-controlled trial. Wound Repair & Regeneration. 7(4):208-13, 1999 Jul-Aug.	1
Falanga V. Saap LJ. Ozonoff A. Wound bed score and its correlation with healing of chronic wounds. Dermatologic Therapy. 19(6):383-90, 2006 Nov-Dec.	4
Fays S. Schmutz JL. Vin F. Thirion V. Sigal-Grinberg M. Ingen-Housz-Oro S. Esteve E. Sauvadet A. Bohbot S. Leg ulcers and the Urgocell Non-Adhesive wound dressing. British Journal of Nursing. 14(11):S15-20, 2005 Jun 9-22.	3
Finnie A. The Scottish Leg Ulcer Project. Journal of tissue viability. 1999. 9(3) : 85-7	5
Flota-Cervera F Flota-Ruiz C Treviño C Berber A. Randomized, double blind, placebo-controlled clinical trial to evaluate the lymphagogue effect and clinical efficacy of calcium dobesilate in chronic venous disease. Angiology. 2008 59(3): 352-6	2
Franek A. Chmielewska D. Brzezinska-Wcislo L. Slezak A. Blaszczak E. Application of various power densities of ultrasound in the treatment of leg ulcers. Journal of Dermatological Treatment. 15(6):379-86, 2004 Dec.	1
Franks PJ. Moody M. Moffatt CJ. Martin R. Blewett R. Seymour E. Hildreth A. Hourican C. Collins J. Heron A. Wound Healing Nursing Research Group. Randomized trial of cohesive short-stretch versus four-layer bandaging in the management of venous ulceration. Wound Repair & Regeneration. 12(2):157-62, 2004 Mar-Apr.	1
Franks PJ. Oldroyd MI. Dickson D. Sharp EJ. Moffatt CJ. Risk factors for leg ulcer recurrence: a randomized trial of two types of compression stocking. Age & Ageing. 24(6):490-4, 1995 Nov.	1
Freak L Simon D Edwards AT Herrick SE Ferguson M McCollum CN. The use of topical human growth hormone on chronic venous ulcers. Journal of Wound Care. 1994. 3(2): 68-70	7
Freak L Simon D Edwards AT McCollum CN. Comparative study of three primary dressings in the healing of chronic venous ulcers. British Journal of Surgery. 1992. 79(11): 1235	1
French L. Community nurse use of Doppler ultrasound in leg ulcer assessment. British Journal of Community Nursing, 2005 Sep; 10(9): S6-13	4
Friedman SJ; Su WP Management of leg ulcers with hydrocolloid occlusive dressing. Archives of dermatology 1984. 120 (10): 1329-36	3
Fullana JM. Cros F. Becker F. Ouchene A. Partsch H. The venous return simulator: an effective tool for investigating the effects of external compression on the venous hemodynamics--first results after thigh compression. Vasa. 34(1):19-23, 2005 Feb.	7
Gaitini D. Torem S. Pery M. Kaftori JK. Image-directed Doppler ultrasound in the diagnosis of lower-limb venous insufficiency. Journal of Clinical Ultrasound. 22(5):291-7, 1994 Jun.	3
Gamborg Nielsen P. Munk Madsen S. Stromberg L. Treatment of chronic leg ulcers with a hydrocolloid dressing. Acta Dermato-Venereologica. Supplementum. 152:1-12, 1989.	4
Gardon-Mollard C Junger M Partsch H Zuccarelli F Taupin V. Efficacy of a tubular compression orthosis compared to a short-stretch bandage in the treatment of venous ulcers. Phlebology. 2003. 18(3): 152	1
Geroulakos G. Nicolaides AN. Controlled studies of Daflon 500 mg in chronic venous insufficiency. Angiology. 45(6 Pt 2):549-53, 1994 Jun.	2
Gethin G,Cowman S. Bacteriological changes in sloughly venous leg ulcers treated with manuka honey or hydrogel: an RCT. Journal of Wound Care. 2008. 17(6): 241-7	1
Gethin G. Cowman S. Manuka honey vs. hydrogel--a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers. Journal of Clinical Nursing. 18(3):466-74, 2009 Feb	1
Ghauri AS Taylor MC Deacon JE Whyman MR Earnshaw JJ Heather BP Poskitt KR. Influence of a specialized leg ulcer service on management and outcome. British Journal of Surgery. 2000. 87(8):1048-1056	3

Excluded RCTs	Reason
Ghauri ASK Currie IC Grabs AJ Whyman MR Farndon JR Poskitt KR Improving the diagnosis of chronic leg ulcers: a one-stop vascular assessment clinic in a community service. Phlebology. 1998. 13(4): 148-152	7
Glinski W Chodynicka B Roszkiewicz J Bogdanowski T Lecewicz-Torun B Kaszuba A Bowszyc J Nowak A Wnorowski J Wasik F Glinska-Ferenz M Blaszczyk M Strzyga P Pachocki R The beneficial augmentative effect of micronised purified flavonoid fraction (MPFF) on the healing of leg ulcers: Anopen, multicentre, controlled, randomised study. Phlebology. 1999. 14(4): 151-157	1
Gohel MS. Barwell JR. Heather BP. Earnshaw JJ. Mitchell DC. Whyman MR. Poskitt KR. The predictive value of haemodynamic assessment in chronic venous leg ulceration. European Journal of Vascular & Endovascular Surgery. 33(6):742-6, 2007 Jun.	3
Gottrup F, Jørgensen B, Karlsmark T, Sibbald RG, Rimdeika R, Harding K, Price P, Venning V, Vowden P, Ju¨ nger M, Wortmann S, Sulcaite R, Vilkevicius G, Ahokas T-L, Ettler K, Arenbergerova M. Lower pain with Biatain–Ibu: a randomised, controlled, double-blind clinical investigation on painful venous leg ulcers. Int Wound J 2007;4 (Suppl. 1):24–34.	6
Gould DJ Campbell S Harding EF Short stretch vs long stretch bandages in the management of chronic venous leg ulcers. Phlebology. 1993. 8 (1): 43	1
Gould DJ Campbell S Newton H Duffelen P Griffin M Harding EF. Setopress vs Elastocrepe in chronic venous ulceration.. British journal of nursing. 1998 7(2) : 66-70, 72-3	1
Greguric S Budimcic D Soldo BA Tudoric M Baricevic B Cajkovac V Dobric I. Hydrocolloid dressing versus a conventional dressing using magnesium sulphate paste in the management of venous leg ulcers. ACTA DERMATOVENEROL CROAT. 1994 2 (2): 65-71	1
Guarnera G. DE Rosa A. Camerini R. Thymosin beta-4 and venous ulcers: clinical remarks on a European prospective, randomized study on safety, tolerability, and enhancement on healing. Annals of the New York Academy of Sciences. 1112:407-12, 2007 Sep.	5
Guerrini S. Lualdi P. Biffignandi P. Treatment of venous leg ulcers with 5% amikacin gel: phase IV trial. International Journal of Clinical Pharmacology Research. 19(1):35-8, 1999.	3
Guilhou JJ. Dereure O. Marzin L. Ouvry P. Zuccarelli F. Debure C. Van Landuyt H. Gillet-Terver MN. Guillot B. Levesque H. Mignot J. Pillion G. Fevrier B. Dubeaux D. Efficacy of Daflon 500 mg in venous leg ulcer healing: a double-blind, randomized, controlled versus placebo trial in 107 patients. Angiology. 48(1):77-85, 1997 Jan.	1
Guilhou JJ. Fevrier F. Debure C. Dubeaux D. Gillet-Terver MN. Guillot B. Levesque H. Marzin L. Mignot J. Ouvry P. Pillion G. Van Landuyt H. Zuccarelli F. Nicolaides AN. Benefit of a 2-month treatment with a micronized, purified flavonoidic fraction on venous ulcer healing. A randomized, double-blind, controlled versus placebo trial. International Journal of Microcirculation: Clinical & Experimental. 17 Suppl 1:21-6, 1997.	1
Guillot B. Dandurand M. Guilhou JJ. Skin perfusion pressure in leg ulcers assessed by photoplethysmography. International Angiology. 7(2 Suppl):33-4, 1988 Apr-Jun.	3
Guillot B. Guilhou JJ. de Champvallins M. Mallet C. Moccatti D. Pointel JP. A long term treatment with a venotropic drug. Results on efficacy and safety of Daflon 500 mg in chronic venous insufficiency. International Angiology. 8(4 Suppl):67-71, 1989 Oct-Dec.	2
Guillot B. Techniques used to evaluate the cutaneous microcirculation: application of photoplethysmography to the assessment of a phlebotropic agent in the treatment of leg ulcers. Angiology. 45(6 Pt 2):542-8, 1994 Jun.	4
Gupta AK. Filonenko N. Salansky N. Sauder DN. The use of low energy photon therapy (LEPT) in venous leg ulcers: a double-blind, placebo-controlled study. Dermatologic Surgery. 24(12):1383-6, 1998 Dec.	7
Guzman-Gardearzabal E. Leyva-Bohorquez G. Salas-Colin S. Paz-Janeiro JL. Alvarado-Ruiz R. Garcia-Salazar R. Treatment of chronic ulcers in the lower extremities with topical becaplermin gel .01%: a multicenter open-label study. Advances in Therapy. 17(4):184-9, 2000 Jul-Aug.	3
Halter G, Kapfer X, Liewald F, Bischoff M. Vacuum-sealed mesh graft transplantation in chronic cutaneous ulcers of the lower leg. *VASA* 2003;**32**:155–8.	3

Excluded RCTs	Reason
Hammarlund C. Sundberg T. Hyperbaric oxygen reduced size of chronic leg ulcers: a randomized double-blind study. Plastic & Reconstructive Surgery. 93(4):829-33; discussion 834, 1994 Apr.	1
Handfield-Jones SE. Grattan CE. Simpson RA. Kennedy CT. Comparison of a hydrocolloid dressing and paraffin gauze in the treatment of venous ulcers. British Journal of Dermatology. 118(3):425-7, 1988 Mar.	1
Hanft JR Serena T Snyder R. A study to evaluate the clinical effectiveness of a Collagen-ORC Antimicrobial Matrix in venous leg ulcers. Wound Repair and Regeneration. 2006. 14(2)p. A64	3
Hansson C. Holm J. Lillieborg S. Syren A. Repeated treatment with lidocaine/prilocaine cream (EMLA) as a topical anaesthetic for the cleansing of venous leg ulcers. A controlled study. Acta Dermato-Venereologica. 73(3):231-3, 1993 Jun. .	1
Hansson C. The effects of cadexomer iodine paste in the treatment of venous leg ulcers compared with hydrocolloid dressing and paraffin gauze dressing. Cadexomer Iodine Study Group. International Journal of Dermatology. 37(5):390-6, 1998 May.	1
Harcup JW. Saul PA. A study of the effect of cadexomer iodine in the treatment of venous leg ulcers. British Journal of Clinical Practice. 40(9):360-4, 1986 Sep.	1
Harley J Harcourt D Hutchinson B McLean M Long M. A comparative trial of long stretch compression bandaging versus multi-layer compression bandaging in the treatment of chronic venous ulcers. Primary Intention. 2004. 12(1): 6-13	1
Harper DR Ruckley CV Dale JJ Callam M Allan P Brown D et al. Prevention of recurrence of chronic leg ulcer: a randomized trial of different degrees of compression. Phlebologie. 1992 p. 902-3	3
Harvey SG. Gibson JR. Burke CA. L-cysteine, glycine and dl-threonine in the treatment of hypostatic leg ulceration: a placebo-controlled study. Pharmatherapeutica. 4(4):227-30, 1985.	2
Heinen MM. Bartholomew LK. Wensing M. van de Kerkhof P. van Achterberg T. Supporting adherence and healthy lifestyles in leg ulcer patients: systematic development of the Lively Legs program for dermatology outpatient clinics. Patient Education & Counseling. 61(2):279-91, 2006 May.	3
Hendricks WM. Swallow RT. Management of stasis leg ulcers with Unna's boots versus elastic support stockings. Journal of the American Academy of Dermatology. 12(1 Pt 1):90-8, 1985 Jan.	1
Herouy Y. Hellstern MO. Vanscheidt W. Schopf E. Norgauer J. Factor XIII-mediated inhibition of fibrinolysis and venous leg ulcers. Lancet. 355(9219):1970-1, 2000 Jun 3.	5
Hillstrom L. Iodosorb compared to standard treatment in chronic venous leg ulcers--a multicenter study. Acta Chirurgica Scandinavica - Supplementum. 544:53-6, 1988.	1
Hillstrom L. Iodosorb compared to standard treatment in chronic venous leg ulcers--a multicenter study. Acta Chirurgica Scandinavica - Supplementum. 544:53-6, 1988.	1
Hoffmann MJ. Knudson PE. Silver-Thorn MB. device for noninvasive assessment of vascular impairment risk in the lower extremity. IEEE Transactions on Biomedical Engineering. 55(12):2786-91, 2008 Dec.	3
Hofman D. Moore K. Cooper R. Eagle M. Cooper S. Use of topical corticosteroids on chronic leg ulcers. Journal of Wound Care. 16(5):227-30, 2007 May.	3
Hofman D. Ryan TJ. Arnold F. Cherry GW. Lindholm C. Bjellerup M. Glynn C. Pain in venous leg ulcers. Journal of Wound Care. 6(5):222-4, 1997 May.	3
Holloway GA Jr. Johansen KH. Barnes RW. Pierce GE. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. Western Journal of Medicine. 151(1):35-8, 1989 Jul.	1
Holloway GA Jr. Johansen KH. Barnes RW. Pierce GE. Multicenter trial of cadexomer iodine to treat venous stasis ulcer. Western Journal of Medicine. 151(1):35-8, 1989 Jul.	1
Holm J Andren B Grafford K Pain control in the surgical debridement of leg ulcers by the use of a topical lidocaine - prilocaine cream, EMLA (R). ACTA DERM-VENEREOL. 1990. 70 (2): 132-136	1

Excluded RCTs	Reason
Holst RG. Kristofferson A. Lidocaine-prilocaine cream (EMLA Cream) as a topical anaesthetic for the cleansing of leg ulcers. The effect of length of application time. European Journal of Dermatology. 8(4):245-7, 1998 Jun. .	1
Houghton PE. Kincaid CB. Lovell M. Campbell KE. Keast DH. Woodbury MG. Harris KA. Effect of electrical stimulation on chronic leg ulcer size and appearance. Physical Therapy. 83(1):17-28, 2003 Jan.	7
Huber L. Role of Klion ointment in the treatment of crural ulcer. Therapia Hungarica. 39(3):148-50, 1991.	3
Huovinen S. Kotilainen P. Jarvinen H. Malanin K. Sarna S. Helander I. Huovinen P. Comparison of ciprofloxacin or trimethoprim therapy for venous leg ulcers: results of a pilot study. Journal of the American Academy of Dermatology. 31(2 Pt 1):279-81, 1994 Aug.	1
Iafrati MD. Welch H. O'Donnell TF. Belkin M. Umphrey S. McLaughlin R. Correlation of venous noninvasive tests with the Society for Vascular Surgery/International Society for Cardiovascular Surgery clinical classification of chronic venous insufficiency. Journal of Vascular Surgery. 19(6):1001-7, 1994 Jun	3
Ieran M. Zaffuto S. Bagnacani M. Annovi M. Moratti A. Cadossi R. Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in humans: a double-blind study. Journal of Orthopaedic Research. 8(2):276-82, 1990 Mar.	1
Iglesias C. Nelson EA. Cullum NA. Torgerson DJ. VenUS Team. VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers. Health Technology Assessment (Winchester, England). 8(29):iii, 1-105, 2004 Jul [see comment]. Comment in: Evid Based Nurs. 2005 Jan;8(1):26; PMID: 15688500	1
Ihme N. Kiesewetter H. Jung F. Hoffmann KH. Birk A. Muller A. Grutzner KI. Leg oedema protection from a buckwheat herb tea in patients with chronic venous insufficiency: a single-centre, randomised, double-blind, placebo-controlled clinical trial. European Journal of Clinical Pharmacology. 50(6):443-7, 1996.	1
Incandela L. Belcaro G. Cesarone MR. De Sanctis MT. Griffin M. Changes in microcirculation in venous ulcers with Essaven gel--a pilot, cross-over, placebo-controlled, randomized study. Angiology. 52 Suppl 3:S23-7, 2001 Dec.	4
Incandela L. Belcaro G. Cesarone MR. De Sanctis MT. Griffin M. Microangiopathy and venous ulceration: topical treatment with Essaven gel--a placebo-controlled, randomized study.Angiology. 52 Suppl 3:S17-21, 2001 Dec.	4
Ippolito E. De Luca S. Sommaruga S. Grassellino V. Nappi G. Experimental-clinical study on the effects of hydromassage with Thermae Oasis's salsobromoiodine water in chronic venous stasis disease of the lower extremities. Minerva Cardioangiologica. 56(4):401-8, 2008 Aug.	3
Jaccard Y. Singer E. Degischer S. Imfeld S. Aschwanden M. Thalhammer C. Labs KH. Jager KA. Effect of silver-threads-containing compression stockings on the cutaneous microcirculation: a double-blind, randomized cross-over study. Clinical Hemorheology & Microcirculation. 36(1):65-73, 2007.	2
Jankicevic J. Vesic S. Vukicevic J. Gajic M. Adamic M. Pavlovic MD. Contact sensitivity in patients with venous leg ulcers in Serbia: comparison with contact dermatitis patients and relationship to ulcer duration. Contact Dermatitis. 58(1):32-6, 2008 Jan.	3
Jankunas V, Bagdonas R, Samsanavicius D, Rimdeika R. An analysis of the effectiveness of skin grafting to treat chronic venous leg ulcers. *Wounds: A Compendium of Clinical Research and Practice* 2007;**19**(5):128–37.	1
Janssen MC. Claassen JA. van Asten WN. Wollersheim H. de Rooij MJ. Thien T. Validation of the supine venous pump function test: a new non-invasive tool in the assessment of deep venous insufficiency. Clinical Science. 91(4):483-8, 1996 Oct.	3
Jantet G. RELIEF study: first consolidated European data. Reflux assEssment and quaLity of llfe improvement with micronized Flavonoids. Angiology. 51(1):31-7, 2000 Jan.	2
Jaschke E. Zabernigg A. Gattringer C. Recombinant human granulocyte-macrophage colony-stimulating factor applied locally in low doses enhances healing and prevents recurrence of chronic venous ulcers. International Journal of Dermatology. 38(5):380-6, 1999 May.	3
Jeran M Zaffuto S Moratti A Bagnacani M Cadossi R. PEMF stimulation of skin ulcers of venous origin in humans: preliminary report of a double blind study. Journal of Bioelectricity. 1987. 6(2): 181-8	1

Excluded RCTs	Reason
Johns BA. EMLA cream for the debridement of venous leg ulcers. Journal of Family Practice. 48(5):332, 1999 May.	6
Johnson CR,Repper J. A double-blind, placebo controlled study of lidocaine/prilocaine cream (EMLA (R) 5%) used as topical analgesic for cleansing and re-dressing of leg ulcers. Astra Zeneca. 1992	1
Johnson M. Miller R. Measuring healing in leg ulcers: practice considerations. Applied Nursing Research. 9(4):204-8, 1996 Nov.	3
Jones JE. Nelson EA. Evaluation of an education package in leg ulcer management. Journal of Wound Care. 6(7):342-3, 1997 Jul.	3
Jones W. Ivins N. Price P. Evaluating the effectiveness of Tegapore wound-contact material. Nursing Times. 100(4):66-9, 2004 Jan 27-Feb 2.	3
Jorgensen B. Friis GJ. Gottrup F. Pain and quality of life for patients with venous leg ulcers: proof of concept of the efficacy of Biatain-Ibu, a new pain reducing wound dressing. Wound Repair & Regeneration. 14(3):233-9, 2006 May-Jun.	3
Jorgensen B. Price P. Andersen KE. Gottrup F. Bech-Thomsen N. Scanlon E. Kirsner R. Rheinen H. Roed-Petersen J. Romanelli M. Jemec G. Leaper DJ. Neumann MH. Veraart J. Coerper S. Agerslev RH. Bendz SH. Larsen JR. Sibbald RG. The silver-releasing foam dressing, Contreet Foam, promotes faster healing of critically colonised venous leg ulcers: a randomised, controlled trial. International Wound Journal. 2(1):64-73, 2005 Mar.	1
Jull A. Walker N. Parag V. Molan P. Rodgers A. Honey as Adjuvant Leg Ulcer Therapy trial collaborators. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. British Journal of Surgery. 95(2):175-82, 2008 Feb	1
Jull AB; Mitchell N; Arroll J; Jones M; Waters J; Latta A; Walker N; Arroll B. Factors influencing concordance with compression stockings after venous leg ulcer healing. Journal of Wound Care (J WOUND CARE), 2004 Mar; 13(3): 90-2	3
Junger M. Wollina U. Kohnen R. Rabe E. Efficacy and tolerability of an ulcer compression stocking for therapy of chronic venous ulcer compared with a below-knee compression bandage: results from a prospective, randomized, multicentre trial. Current Medical Research & Opinion. 20(10):1613-23, 2004 Oct.	1
Kakkos SK. Griffin M. Geroulakos G. Nicolaides AN. The efficacy of a new portable sequential compression device (SCD Express) in preventing venous stasis. Journal of Vascular Surgery. 42(2):296-303, 2005 Aug.	3
Kakkos SK. Szendro G. Griffin M. Sabetai MM. Nicolaides AN. Improved hemodynamic effectiveness and associated clinical correlations of a new intermittent pneumatic compression system in patients with chronic venous insufficiency. Journal of Vascular Surgery. 34(5):915-22, 2001 Nov.	3
Kalodiki E. Ellis M. Kakkos SK. Williams A. Davies AH. Geroulakos G. Immediate hemodynamic effect of the additional use of the SCD EXPRESS Compression System in patients with venous ulcers treated with the four-layer compression bandaging system. European Journal of Vascular & Endovascular Surgery. 33(4):483-7, 2007 Apr.	3
Kalus U. Koscielny J. Grigorov A. Schaefer E. Peil H. Kiesewetter H. Improvement of cutaneous microcirculation and oxygen supply in patients with chronic venous insufficiency by orally administered extract of red vine leaves AS 195: a randomised, double-blind, placebo-controlled, crossover study. Drugs in R & D. 5(2):63-71, 2004.	2
Kane FM Brodie EE Coull A Coyne L Howd A Milne A Niven CC Robbins R. The analgesic effect of odour and music upon dressing change. British journal of nursing. 2004. 13(19): S4-12	2
Karlsmark T. Agerslev RH. Bendz SH. Larsen JR. Roed-Petersen J. Andersen KE. Clinical performance of a new silver dressing, Contreet Foam, for chronic exuding venous leg ulcers. Journal of Wound Care. 12(9):351-4, 2003 Oct.	1
Kaur C. Sarkar R. Kanwar AJ. Attri AK. Dabra AK. Kochhar S. An open trial of calcium dobesilate in patients with venous ulcers and stasis dermatitis. International Journal of Dermatology. 2003. 42(2): 147-52	3
Kavros SJ. Miller JL. Hanna SW. Treatment of ischemic wounds with noncontact, low-frequency ultrasound: the Mayo clinic experience, 2004-2006. Advances in Skin & Wound Care. 20(4):221-6, 2007 Apr.	2

Excluded RCTs	Reason
Kelechi TJ. Bonham PA. Measuring venous insufficiency objectively in the clinical setting. Journal of Vascular Nursing. 26(3):67-73, 2008 Sep.	3
Kelechi TJ. Haight BK. Herman J. Michel Y. Brothers T. EdlundB. Skin temperature and chronic venous insufficiency. Journal of Wound, Ostomy, & Continence Nursing. 30(1):17-24, 2003 Jan.	3
Kenkre JE. Hobbs FD. Carter YH. Holder RL. Holmes EP. A randomized controlled trial of electromagnetic therapy in the primary care management of venous leg ulceration. Family Practice. 13(3):236-41, 1996 Jun.	1
Kiesewetter H. Koscielny J. Kalus U. Vix JM. Peil H. Petrini O. van Toor BS. de Mey C. Efficacy of orally administered extract of red vine leaf AS 195 (folia vitis viniferae) in chronic venous insufficiency (stages I-II). A randomized, double-blind, placebo-controlled trial. Arzneimittel-Forschung. 50(2):109-17, 2000 Feb.	2
Kikta MJ. Schuler JJ. Meyer JP. Durham JR. Eldrup-Jorgensen J. Schwarcz TH. Flanigan DP. A prospective, randomized trial of Unna's boots versus hydroactive dressing in the treatment of venous stasis ulcers. Journal of Vascular Surgery. 7(3):478-83, 1988 Mar.	1
Kjaer ML. Mainz J. Soernsen LT. Karlsmark T. Gottrup F. Clinical quality indicators of venous leg ulcers: development, feasibility, and reliability. Ostomy Wound Management. 51(5):64-6, 68-72, 74, 2005 May.	4
Koch R. Comparative study of Venostasin and Pycnogenol in chronic venous insufficiency. Phytotherapy Research. 16 Suppl 1:S1-5, 2002	2
Koksal C. Bozkurt AK. Combination of hydrocolloid dressing and medical compression stockings versus Unna's boot for the treatment of venous leg ulcers. Swiss Medical Weekly. 133(25-26):364-8, 2003 Jun 28.	1
Kopera D. Kokol R. Berger C. Haas J. Low level laser: does it influence wound healing in venous leg ulcers? A randomized, placebo-controlled, double-blind study. British Journal of Dermatology. 152(6):1368-70, 2005 Jun.	6
Kralj B,Kosicek M. Randomised comparative trial of single-layer and multi-layer bandages in the treatment of venous leg ulcer. Proceedings of the 6th European Conference on Advances in Wound Management; 1995, 21-24 November; Harrogate, UK. 1997: 158-62	1
Krishnamoorthy, Harding KG, Griffiths, Moore, Leaper D, Poskitt K, et al.The clinical and histological effects of Dermagraft. *Phlebology* 2003;**18**(1):12–22.	1
Kucharzewski M Slezak A Franek A. Topical treatment of non-healing venous leg ulcers by cellulose membrane. Phlebologie. 2003. 32(6): 147-51	5
Kumar S. Samraj K. Nirujogi V. Budnik J. Walker MA. Intermittent pneumatic compression as an adjuvant therapy in venous ulcer disease. Journal of Tissue Viability. 12(2):42-4, 46, 48 passim, 2002 Apr.	1
Lagan KM. McKenna T. Witherow A. Johns J. McDonough SM. Baxter GD. Low-intensity laser therapy/combined phototherapy in the management of chronic venous ulceration: a placebo-controlled study. Journal of Clinical Laser Medicine & Surgery. 20(3):109-16, 2002 Jun.	2
Lascasas-Porto CL. Milhomens AL. Virgini-Magalhaes CE. Fernandes FF. Sicuro FL. Bouskela E. Use of microcirculatory parameters to evaluate clinical treatments of chronic venous disorder (CVD). Microvascular Research. 76(1):66-72, 2008 May.	2
Laudanska H. Gustavson B. In-patient treatment of chronic varicose venous ulcers. A randomized trial of cadexomer iodine versus standard dressings. Journal of International Medical Research. 16(6):428-35, 1988 Nov-Dec.	1
Laudanska H. Gustavson B. In-patient treatment of chronic varicose venous ulcers. A randomized trial of cadexomer iodine versus standard dressings. Journal of International Medical Research. 16(6):428-35, 1988 Nov-Dec.	1
Layer GT Powell S Pattison M Burnand KG. Early results of a trial of adjuvant fibrinolytic enhancement therapy in the healing of venous leg ulcers. Phlebology. 1986: 587-90	7
Lazareth I. Ourabah Z. Senet P. Cartier H. Sauvadet A. Bohbot S. Evaluation of a new silver foam dressing in patients with critically colonised venous leg ulcers. Journal of Wound Care. 16(3):129-32, 2007 Mar.	3

Excluded RCTs	Reason
Le Devehat C. Khodabandehlou T. Vimeux M. Kempf C. Evaluation of haemorheological and microcirculatory disturbances in chronic venous insufficiency: activity of Daflon 500 mg. International Journal of Microcirculation: Clinical & Experimental. 17 Suppl 1:27-33, 1997.	**2**
Leaper DJ Cameron S Hewitt H Winter A Lucarotti ME. A community- and hospital-based comparative evaluation of Comfeel ulcer dressing for chronic leg ulcers. J. DERMATOL. TREAT.. 1991. 2(3): 103-106	**3**
Lim KS. Tang MB. Goon AT. Leow YH. Contact sensitization in patients with chronic venous leg ulcers in Singapore. Contact Dermatitis. 56(2):94-8, 2007 Feb.	**3**
Lim KS. Tang MB. Goon AT. Leow YH. The role of topical traditional chinese medicaments as contact sensitisers in chronic venous leg ulcer patients. Annals of the Academy of Medicine, Singapore. 36(11):942-6, 2007 Nov.	**3**
Limova M. Evaluation of two calcium alginate dressings in the management of venous ulcers. Ostomy Wound Management. 49(9):26-33, 2003 Sep.	**1**
Limova M. Troyer-Caudle J. Controlled, randomized clinical trial of 2 hydrocolloid dressings in the management of venous insufficiency ulcers. Journal of Vascular Nursing. 20(1):22-32; quiz 33-4, 2002 Mar.	**1**
Lindgren C. Marcusson JA. Toftgard R. Treatment of venous leg ulcers with cryopreserved cultured allogeneic keratinocytes: a prospective open controlled study. British Journal of Dermatology. 139(2):271-5, 1998 Aug.	**1**
Lindsay G Latta D Lyons KGB Livingstone ED Thomson W. A study in general practice of the efficacy of cadexomer iodine in venous leg ulcers treated on alternate days. Acta Therapeutica. 1986. 12: 141-7	**1**
Liu JY, Hafner J, Dragieva G, Seifert B, Burg G. Autologous cultured keratinocytes on porcine gelatin microbeads effectively heal chronic venous leg ulcers. *Wound Repair and Regeneration* 2004;**12**(2):148–56.	**1**
Liu JY. Hafner J. Dragieva G. Seifert B. Burg G. Autologous cultured keratinocytes on porcine gelatin microbeads effectively heal chronic venous leg ulcers. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2004. 12(2): 148-56	**4**
Lok C. Paul C. Amblard P. Bessis D. Debure C. Faivre B. Guillot B. Ortonne JP. Huledal G. Kalis B. EMLA cream as a topical anesthetic for the repeated mechanical debridement of venous leg ulcers: a double-blind, placebo-controlled study. Journal of the American Academy of Dermatology. 40(2 Pt 1):208-13, 1999 Feb	**1**
Lopez AP Bello Y Phillips TJ. A pilot study to test the effects of a radiant heat bandage on chronic venous ulcers. Wound Repair and Regeneration. 1998. 6(3): A245	**3**
Lundeberg T. Malm M. Low-power HeNe laser treatment of venous leg ulcers. Annals of Plastic Surgery. 27(6):537-9, 1991 Dec.	**1**
Lundeberg T. Nordstrom F. Brodda-Jansen G. Eriksson SV. Kjartansson J. Samuelson UE. Pulsed ultrasound does not improve healing of venous ulcers. Scandinavian Journal of Rehabilitation Medicine. 22(4):195-7, 1990.	**1**
Lyon RT. Veith FJ. Bolton L. Machado F. Clinical benchmark for healing of chronic venous ulcers. Venous Ulcer Study Collaborators. American Journal of Surgery. 176(2):172-5, 1998 Aug.	**3**
MacLennan WJ. Wilson J. Rattenhuber V. Dikland WJ. Vanderdonckt J. Moriau M. Hydroxyethylrutosides in elderly patients with chronic venous insufficiency: its efficacy and tolerability. Gerontology. 40(1):45-52, 1994.	**2**
Mahajan R Mosley JG Use of a semipermeable polyamide dressing over skin grafts to venous leg ulcers. The British journal of surgery. 1995. 82(10): 1359-60	**4**
Maksimovic ZV. Maksimovic M. Jadranin D. Kuzmanovic I. Andonovic O. Medicamentous treatment of chronic venous insufficiency using semisynthetic diosmin--a prospective study. Acta Chirurgica Iugoslavica. 55(4):53-9, 2008.	**2**
Malm M. Lundeberg T. Effect of low power gallium arsenide laser on healing of venous ulcers. Scandinavian Journal of Plastic & Reconstructive Surgery & Hand Surgery. 25(3):249-51, 1991	**1**

Excluded RCTs	Reason
Marcusson JA, Lindgren C, Berghard A, Toftgard R. Allogeneic cultured keratinocytes in the treatment of leg ulcers: A pilot study.*Acta Dermatologica Venereologica* 1992;**72**(1):61–4.	**3**
Margolis DJ. Pentoxifylline in the treatment of venous leg ulcers. Archives of Dermatology. 136(9):1142-3, 2000 Sep.	**3**
Margolis, D.J.; Gross, E.A.; Wood, C.R.; Lazarus, G.S. Planimetric rate of healing I nvenous ulcers of the leg treated with pressure bandage and hydrocolloid dressing. J Am Acad Dermatol 1993:28: 418-421	**1**
Mariani F Mattaliano V Mosti G Gasbarro V Bucalossi M Blattler W et al. The treatment of venous leg ulcers with a specifically designed compression stocking kit: Comparison with bandaging. Phlebologie. 2008. 37(4): 191-7	**1**
Marinello J. Videla S. Group for the Assessment of the Transcutaneous Oxygen Pressure in Chronic Venous Insufficiency. Chronic venous insufficiency of the lower limbs: suitability of transcutaneous blood gas monitoring as an endpoint to evaluate the outcome of pharmacological treatment with calcium dobesilate. Methods & Findings in Experimental & Clinical Pharmacology. 26(10):775-80, 2004 Dec.	**7**
Marshall JL. Mead P. Jones K. Kaba E. Roberts AP. The implementation of venous leg ulcer guidelines: process analysis of the intervention used in a multi-centre, pragmatic, randomized, controlled trial. Journal of Clinical Nursing. 10(6):758-66, 2001 Nov.	**4**
Martinez-Zapata MJ. Moreno RM. Gich I. Urrutia G. Bonfill X. Chronic Venous Insufficiency Study Group. A randomized, double-blind multicentre clinical trial comparing the efficacy of calcium dobesilate with placebo in the treatment of chronic venous disease. European Journal of Vascular & Endovascular Surgery. 35(3):358-65, 2008 Mar.	**2**
McCulloch JM. Marler KC. Neal MB. Phifer TJ. Intermittent pneumatic compression improves venous ulcer healing. Advances in Wound Care. 7(4):22-4, 26, 1994 Jul.	**1**
McGuiness W; Dunn SV; Neild T; Jones MJ Developing an accurate system of measuring colour in a venous leg ulcer in order to assess healing. Journal of Wound, 2005 Jun; 14(6): 249-54	**4**
Meaume S. Ourabah Z. Romanelli M. Manopulo R. De Vathaire F. Salomon D. Saurat JH. Efficacy and tolerance of a hydrocolloid dressing containing hyaluronic acid for the treatment of leg ulcers of venous or mixed origin. Current Medical Research & Opinion. 24(10):2729-39, 2008 Oct.	**2**
Meaume S. Vallet D. Morere MN. Teot L. Evaluation of a silver-releasing hydroalginate dressing in chronic wounds with signs of local infection. Journal of Wound Care. 14(9):411-9, 2005 Oct.[erratum appears in J Wound Care. 2005 Nov;14(10):479].	**1**
Mehtar S. Fox D. A double-blind comparative study with mupirocin vs placebo base in the treatment of chronic leg ulcers. British Journal of Clinical Practice. 42(8):324-8, 1988 Aug.	**2**
Meyer FJ. Burnand KG. Lagattolla NR. Eastham D. Randomized clinical trial comparing the efficacy of two bandaging regimens in the treatment of venous leg ulcers. British Journal of Surgery. 89(1):40-4, 2002 Jan. [see comment]. Comment in: Br J Surg. 2002 Jun;89(6):810; author reply 810; PMID: 12028005	**1**
Meyer FJ. McGuinness CL. Lagattolla NR. Eastham D. Burnand KG. Randomized clinical trial of three-layer paste and four-layer bandages for venous leg ulcers. British Journal of Surgery. 90(8):934-40, 2003 Aug [see comment]. Comment in: Evid Based Nurs. 2004 Jan;7(1):21; PMID: 14994694	**1**
Milic DJ. Zivic SS. Bogdanovic DC. Perisic ZD. Milosevic ZD. Jankovic RJ. Visnjic AM. Jovanovic BM. A randomized trial of the Tubulcus multilayer bandaging system in the treatment of extensive venous ulcers. Journal of Vascular Surgery. 46(4):750-5, 2007 Oct.	**1**
Milward P. Comparing treatments for leg ulcers.. Nursing times.1991.87(13): 70, 72	**1**
Moffatt CJ Dorman MC Recurrence of leg ulcers within a community ulcer service. Journal of wound care. 1995. 4(2): 57-61	**4**
Moffatt CJ Franks PJ Oldroyd MI Greenhalgh RM. Randomized trial of an occlusive dressing in the treatment of chronic non-healing leg ulcers. PHLEBOLOGY. 1992. 7(3): 105-107	**1**
Moffatt CJ Oldroyd MI Franks PJ. Assessing a calcium alginate dressing for venous ulcers of the leg. Journal of Wound Care. 1992. 1(4): 22-4	**1**

Excluded RCTs	Reason
Moffatt CJ Simon DA Franks PJ Connolly M Fielden S Groarke L McCollum CN. Randomised trial comparing two four-layer bandage systems in the management of chronic leg ulceration. Phlebology. 1999 14(4) : 139-142	1
Moffatt CJ. McCullagh L. O'Connor T. Doherty DC. Hourican C. Stevens J. Mole T. Franks PJ. Randomized trial of four-layer and two-layer bandage systems in the management of chronic venous ulceration. Wound Repair & Regeneration. 11(3):166-71, 2003 May-Jun.	1
Mol M, Nanninga B, Eendenburg J, Westerhof W, Mekkes J, Ginkel C. Grafting of venous leg ulcers. *Journal of the American Academy of Dermatology* 1991;**24**(1):77–82.	1
Moody M. Comparison of Rosidal K and SurePress in the treatment of venous leg ulcers. British Journal of Nursing. 8(6):345-55, 1999 Mar 25-Apr 7.	1
Moss C Taylor AEM Shuster S. Comparison of cadexomer iodine and dextranomer for chronic venous ulcers. CLIN. EXP. DERMATOL. 1987. 12(6): 413-418	1
Mosti G. Iabichella ML. Picerni P. Magliaro A. Mattaliano V. The debridement of hard to heal leg ulcers by means of a new device based on Fluidjet technology. International Wound Journal. 2(4):307-14, 2005 Dec.	3
Mostow EN. Haraway GD. Dalsing M. Hodde JP. King D. OASIS Venus Ulcer Study Group. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. Journal of Vascular Surgery. 41(5):837-43, 2005 May.	1
Moustafa M. Bullock AJ. Creagh FM. Heller S. Jeffcoate W. Game F. Amery C. Tesfaye S. Ince Z. Haddow DB. MacNeil S. Randomized, controlled, single-blind study on use of autologous keratinocytes on a transfer dressing to treat nonhealing diabetic ulcers. Regenerative Medicine. 2(6):887-902, 2007 Nov.	4
Mulligan CM. Bragg AJ. O'Toole OB. A controlled comparative trial of Actisorb activated charcoal cloth dressings in the community. British Journal of Clinical Practice. 40(4):145-8, 1986 Apr.	1
Nagl M. Nguyen VA. Gottardi W. Ulmer H. Hopfl R. Tolerability and efficacy of N-chlorotaurine in comparison with chloramine T for the treatment of chronic leg ulcers with a purulent coating: a randomized phase II study. British Journal of Dermatology. 149(3):590-7, 2003 Sep	2
Navratilova Z, Slonkova V, Semradova V, Adler J. Cryopreserved and lyophilized cultured epidermal allografts in the treatment of leg ulcers: A pilot study. *Journal of the European Academy of Dermatology & Venereology* 2004;**18**(2):173–9.	1
Navratilova Z. Slonkova V. Semradova V. Adler J. Cryopreserved and lyophilized cultured epidermal allografts in the treatment of leg ulcers: a pilot study. Journal of the European Academy of Dermatology & Venereology. 18(2):173-9, 2004 Mar.	4
Neglen P. Raju S.A rational approach to detection of significant reflux with duplex Doppler scanning and air plethysmography. Journal of Vascular Surgery. 17(3):590-5, 1993 Mar.	3
Nehler MR. Moneta GL. Woodard DM. Defrang RD. Harker CT. Taylor LM Jr. Porter JM. Perimalleolar subcutaneous tissue pressure effects of elastic compression stockings. Journal of Vascular Surgery. 18(5):783-8, 1993 Nov.	3
Nelson EA. Prescott RJ. Harper DR. Gibson B. Brown D. Ruckley CV. A factorial, randomized trial of pentoxifylline or placebo, four-layer or single-layer compression, and knitted viscose or hydrocolloid dressings for venous ulcers. Journal of Vascular Surgery. 45(1):134-41, 2007 Jan.	1
Nelson EA. Harper DR. Prescott RJ. Gibson B. Brown D. Ruckley CV. Prevention of recurrence of venous ulceration: randomized controlled trial of class 2 and class 3 elastic compression.[see comment]. Journal of Vascular Surgery. 44(4):803-8, 2006 Oct. Comment in: Evid Based Nurs. 2007 Apr;10(2):55; PMID: 17384107	1
Nelson EA. Iglesias CP. Cullum N. Torgerson DJ. VenUS I collaborators. Randomized clinical trial of four-layer and short-stretch compression bandages for venous leg ulcers (VenUS I). British Journal of Surgery. 91(10):1292-9, 2004 Oct.	1
Nemeth KA; Harrison MB; Graham ID; Burke S Pain in pure and mixed aetiology venous leg ulcers: a three-phase point prevalence study.Journal of Wound Care 2003 Oct; 12(9): 336-40	2

Excluded RCTs	Reason
Neumann HA. van den Broek MJ. A comparative clinical trial of graduated compression stockings and O-(beta-hydroxyethyl)-rutosides (HR) in the treatment of patients with chronic venous insufficiency. Journal of Lymphology. 19(1):8-11, 1995 Aug.	2
Nicolaides AN. Cardiovascular Disease Educational and Research Trust. European Society of Vascular Surgery. ,The International Angiology Scientific Activity Congress Organization. International Union of Angiology. Union Internationale de Phlebologie at the Abbaye des Vaux de Cernay. Investigation of chronic venous insufficiency: A consensus statement Circulation. 102(20):E126-63, 2000 Nov 14.	3
Nicolaides AN. Miles C. Photoplethysmography in the assessment of venous insufficiency. Journal of Vascular Surgery. 5(3):405-12, 1987 Mar	3
Nikolova K. Treatment of hypertensive venous leg ulcers with nifedipine. Methods & Findings in Experimental & Clinical Pharmacology. 17(8):545-9, 1995 Oct.	2
Nikolova, K., Treatment of post-phlebitic syndrome and venous leg ulcers with flunarizine. Methods & Findings in Experimental & Clinical Pharmacology, 1994. **16**(8): p. 609-13.	4
Nikolovska S Pavlova LJ Petrova N Gocev G. The efficacy of intermittent pneumatic compression in the treatment of venous leg ulcers. Macedonian Medical Review. 2002. 5. p. 56-9	1
Nikolovska S. Arsovski A. Damevska K. Gocev G. Pavlova L. Evaluation of two different intermittent pneumatic compression cycle settings in the healing of venous ulcers: a randomized trial. Medical Science Monitor. 11(7):CR337-43, 2005 Jul.	1
Nikolovska S. Pavlova L. Petrova N. Gocev G. Ivanovski M. Pentoxifylline--efficient in the treatment of venous ulcers in the absence of compression?. Acta Dermatovenerologica Croatica. 10(1):9-13, 2002 Mar.	1
Northeast ADR Layer GT Stacey M Wilson NM Browse NL Burnand KG. The effect of fibrinolytic enhancement on venous ulcer healing. Phlebologie. 1989: 1167-9	5
O'Connell SM. Impeduglia T. Hessler K. Wang XJ. Carroll RJ. Dardik H. Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic lower-extremity ulcers. Wound Repair & Regeneration. 16(6):749-56, 2008 Nov-Dec.	3
Oluwatosin OM. Olabanji JK. Oluwatosin OA. Tijani LA. Onyechi HU. A comparison of topical honey and phenytoin in the treatment of chronic leg ulcers. African Journal of Medicine & Medical Sciences. 29(1):31-4, 2000 Mar	2
Omar AA. Mavor AI. Jones AM. Homer-Vanniasinkam S. Treatment of venous leg ulcers with Dermagraft. European Journal of Vascular & Endovascular Surgery. 27(6):666-72, 2004 Jun.	1
Ormiston MC Seymour MT Venn GE Cohen RI Fox JA Controlled trial of Iodosorb in chronic venous ulcers. British medical journal (Clinical research ed.) 1985; 291 (6491): 308-10	1
Ottillinger B Greeske K. Rational therapy of chronic venous insufficiency--chances and limits of the therapeutic use of horse-chestnut seeds extract. BMC cardiovascular disorders. 2001. 1 p. 5	2
Padberg FT Johnston MV Sisto SA. Structured exercise improves calf muscle pump function in chronic venous insufficiency: a randomized trial. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2004. 39(1): 79-87	2
Pappas PJ. DeFouw DO. Venezio LM. Gorti R. Padberg FT Jr. Silva MB Jr. Goldberg MC. Duran WN. Hobson RW 2nd. Morphometric assessment of the dermal microcirculation in patients with chronic venous insufficiency. Journal of Vascular Surgery. 26(5):784-95, 1997 Nov.	3
Paquet P. Quatresooz P. Braham C. Pierard GE. Tapping into the influence of keratinocyte allografts and biocenosis on healing of chronic leg ulcers: split-ulcer controlled pilot study. Dermatologic Surgery. 31(4):431-5, 2005 Apr.	1
Pardes JB. Carson PA. Eaglstein WH. Falanga V. Mupirocin treatment of exudative venous ulcers. Journal of the American Academy of Dermatology. 29(3):497-8, 1993 Sep.	1

Excluded RCTs	Reason
Partsch H Horakova MA. Compression stockings for the treatment of venous leg ulcers. WIEN MED WOCHENSCHR. 1994. 144(10-11): 242-249	1
Partsch H. Damstra RJ. Tazelaar DJ. Schuller-Petrovic S. Velders AJ. de Rooij MJ. Sang RR. Quinlan D. Multicentre, randomised controlled trial of four-layer bandaging versus short-stretch bandaging in the treatment of venous leg ulcers. Vasa. 30(2):108-13, 2001 May.	1
Pascarella L. Bergan JJ. Mekenas LV. Severe chronic venous insufficiency treated by foamed sclerosant. Annals of Vascular Surgery. 20(1):83-91, 2006 Jan.	3
Pasche-Koo F. Piletta PA. Hunziker N. Hauser C. High sensitization rate to emulsifiers in patients with chronic leg ulcers. Contact Dermatitis. 31(4):226-8, 1994 Oct.	2
Payne SP. Thrush AJ. London NJ. Bell PR. Barrie WW. Venous assessment using air plethysmography: a comparison with clinical examination, ambulatory venous pressure measurement and duplex scanning. British Journal of Surgery. 80(8):967-70, 1993 Aug.	3
Peschen M. Weichenthal M. Schopf E. Vanscheidt W. Low-frequency ultrasound treatment of chronic venous leg ulcers in an outpatient therapy. Acta Dermato-Venereologica. 77(4):311-4, 1997 Jul.	1
Pessenhofer H,Stangl M. The effect of a two-layered polyurethane foam wound dressing on the healing of venous leg ulcers. Journal of Tissue Viability. 1992. 2(57): 57-61	1
Petherick ES. O'Meara S. Spilsbury K. Iglesias CP. Nelson EA. Torgerson DJ. Patient acceptability of larval therapy for leg ulcer treatment: a randomised survey to inform the sample size calculation of a randomised trial. BMC Medical Research Methodology. 6:43, 2006.	3
Petrassi C. Mastromarino A. Spartera C. PYCNOGENOL in chronic venous insufficiency. Phytomedicine. 7(5):383-8, 2000 Oct.	1
Petruzzellis V Troccoli T Candiani C Guarisco R Lospalluti M Belcaro G Dugall M Oxerutins (Venoruton): efficacy in chronic venous insufficiency--a double-blind, randomized, controlled study. Angiology. 2002. 53(3): 257-63	2
Planinsek TR Effectiveness of non-alcohol film forming skin protector on the skins isles inside the ulcers and the healing rate of venous leg ulcers. EWMA Journal. 2007. 7(1):23-5	5
Pojda, Z. Struzyna, J. Treatment of non-healing ulcers with rhGM-CSF and skin grafts. Lancet. 343(8905):1100, 1994 Apr 30.	3
Polignano R. Bonadeo P. Gasbarro S. Allegra C. A randomised controlled study of four-layer compression versus Unna's Boot for venous ulcers. Journal of Wound Care. 13(1):21-4, 2004 Jan.	1
Polignano R. Guarnera G. Bonadeo P. Evaluation of SurePress Comfort: a new compression system for the management of venous leg ulcers. Journal of Wound Care. 13(9):387-91, 2004 Oct.	1
Poskitt K, James A, Lloyd-Davies E, Walton J, McCollum C. Pinch skin grafting or porcine dermis in venous ulcers: A randomised clinical trial. *British Medical Journal* 1987;**294**:674–6.	1
Quatresooz P. Kharfi M. Paquet P. Vroome V. Cauwenbergh G. Pierard GE. Healing effect of ketanserin on chronic leg ulcers in patients with diabetes. Journal of the European Academy of Dermatology & Venereology. 20(3):277-81, 2006 Mar.	2
Rasmussen LH Karlsmark T Avnstorp C Peters K Jorgensen M Jensen LT. Topical human growth hormone treatment of chronic leg ulcers.PHLEBOLOGY. 1991. 6(1): 23-30	7
Rehn D. Golden G. Nocker W. Diebschlag W. Lehmacher W. Comparison between the efficacy and tolerability of oxerutins and troxerutin in the treatment of patients with chronic venous insufficiency. Arzneimittel-Forschung. 43(10):1060-3, 1993 Oct.	2
Rehn D. Unkauf M. Klein P. Jost V. Lucker PW. Comparative clinical efficacy and tolerability of oxerutins and horse chestnut extract in patients with chronic venous insufficiency. Arzneimittel-Forschung. 46(5):483-7, 1996 May	1
Robinson C. Santilli SM. Warm-Up Active Wound Therapy: a novel approach to the management of chronic venous stasis ulcers. Journal of Vascular Nursing. 16(2):38-42, 1998 Jun.	3

Excluded RCTs	Reason
Romanelli M Dini V Bertone M Barbanera S Brilli C. OASIS wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. International wound journal. 2007 4(1): 3-7	2
Romanelli M. Dini V. Vowden P. Agren MS. Amelogenin, an extracellular matrix protein, in the treatment of venous leg ulcers and other hard-to-heal wounds: experimental and clinical evidence. [Review] [43 refs] Clinical Interventions In Aging. 3(2):263-72, 2008.	3
Romanelli M. Dini V. Vowden P. Agren MS. Amelogenin, an extracellular matrix protein, in the treatment of venous leg ulcers and other hard-to-heal wounds: experimental and clinical evidence.Clinical Interventions In Aging. 3(2):263-72, 2008.	3
Rosenthal D. Murphy F. Gottschalk R. Baxter M. Lycka B. Nevin K.Using a topical anaesthetic cream to reduce pain during sharp debridement of chronic leg ulcers. Journal of Wound Care. 10(1):503-5, 2001 Jan.	1
Roztocil K. Stvrtinova V. Strejcek J. Efficacy of a 6-month treatment with Daflon 500 mg in patients with venous leg ulcers associated with chronic venous insufficiency. International Angiology. 22(1):24-31, 2003 Mar. . Exclude – in an included SR	1
Rubin JR. Alexander J. Plecha EJ. Marman C. Unna's boot vs polyurethane foam dressings for the treatment of venous ulceration. A randomized prospective study. Archives of Surgery. 125(4):489-90, 1990 Apr. .	1
Ruckley CV Fowkes FGR Prescott RJ Morley SM Douglas WS Gibson B et al. Randomised controlled trial to evaluate the impact of implementation of national (SIGN) guidelines, with and without systematic nurse training on outcomes of care for chronic leg ulcer in Scotland. Health Bulletin. 1997. 55(4): 276	3
Ruffini I. Belcaro G. Cesarone MR. Dugall M. Efficacy of topical treatment with aescin + essential phospholipids gel in venous insufficiency and hypertension. Angiology. 55 Suppl 1:S19-21, 2004 May-Jun.	3
Rutherford RB. Padberg FT Jr. Comerota AJ. Kistner RL. Meissner MH. Moneta GL. Venous severity scoring: An adjunct to venous outcome assessment. Journal of Vascular Surgery. 31(6):1307-12, 2000 Jun.	4
Sabolinski ML. Alvarez O. Auletta M. Mulder G. Parenteau NL. Cultured skin as a 'smart material' for healing wounds: experience in venous ulcers. Biomaterials. 17(3):311-20, 1996 Feb.	1
Salim AS. Role of sulphydryl-containing agents in the management of venous (varicose) ulceration. A new approach. Clinical & Experimental Dermatology. 17(6):427-32, 1992 Nov.	1
Salim AS. The role of oxygen-derived free radicals in the management of venous (varicose) ulceration: a new approach. World Journal of Surgery. 15(2):264-9, 1991 Mar-Apr.	7
Sanchez-Vazquez R. Briseno-Rodriguez G. Cardona-Munoz EG. Galvez-Gastelum FJ. Totsuka-Sutto SE. Garcia-Benavides L. Isosorbide dinitrate spray as therapeutic strategy for treatment of chronic venous ulcers. Angiology. 59(1):64-71, 2008 Feb-Mar.	4
Santamaria N Carville K Ellis I Prentice J. The effectiveness of digital imaging and remote expert wound consultation on healing rates in chronic lower leg ulcers in the Kimberley region of Western Australia. Primary Intention. 2004. 12(2): 62-64	3
Saveljev VS Pokrovsky AV Kirienko AI Bogachev VU Bogdanetz LI Sapelkin SV et al Systemic treatment of venous trophic ulcers: results of the use of micronized diosmin (Detralex) Angiology and Vascular Surgery. 2002. 8(4): 47-52	5
Schuler JJ Maibenco T Megerman J Ware M Montalvo J. Treatment of chronic venous ulcers using sequential gradient intermittent pneumatic compression. Phlebology. 1996. 11(3): 111-116	1
Schultz-Ehrenburg U Muller B. Two multicentre clinical trials of two different dosages of O-(beta-hydroxyethyl)-rutosides in the treatment of leg ulcer. Phlebology. 1993 8(Suppl 1): 29-30	1
Scriven JM. Taylor LE. Wood AJ. Bell PR. Naylor AR. London NJ. A prospective randomised trial of four-layer versus short stretch compression bandages for the treatment of venous leg ulcers. Annals of the Royal College of Surgeons of England. 80(3):215-20, 1998 May.	1
Scurr JH Wilson LA Coleridge-Smith PD A comparison of calcium alginate and hydrocolloid dressings in the management of chronic venous ulcers. Wounds: A Compendium of Clinical Research and Practice. 1994. 6(1): 1-8	1

Excluded RCTs	Reason
Seeley MA. Harding KG. The effects of education and training on clinical practice in wound healing. International Wound Journal. 5(5):660-4, 2008 Dec.	3
Selim P Bashford C Grossman C Evidence-based practice: tap water cleansing of leg ulcers in the community. Journal of Clinical Nursing. 2001. 10(372-9)	3
Selkon JB. Cherry GW. Wilson JM. Hughes MA. Evaluation of hypochlorous acid washes in the treatment of chronic venous leg ulcers. Journal of Wound Care. 15(1):33-7, 2006 Jan.	3
Senet P. Bon FX. Benbunan M. Bussel A. Traineau R. Calvo F. Dubertret L. Dosquet C. Randomized trial and local biological effect of autologous platelets used as adjuvant therapy for chronic venous leg ulcers. Journal of Vascular Surgery. 38(6):1342-8, 2003 Dec.	7
Sibbald RG. Contreras-Ruiz J. Coutts P. Fierheller M. Rothman A. Woo K. Bacteriology, inflammation, and healing: a study of nanocrystalline silver dressings in chronic venous leg ulcers. Advances in Skin & Wound Care. 20(10):549-58, 2007 Oct.	3
Sibbald RG. Coutts P. Fierheller M. Woo K. A pilot (real-life) randomised clinical evaluation of a pain-relieving foam dressing: (ibuprofen-foam versus local best practice). International Wound Journal. 4 Suppl 1:16-23, 2007 Apr.	2
Simon DA Freak L Kinsella A Walsh J Lane C Groarke L McCollum C. Community leg ulcer clinics: a comparative study in two health authorities.BMJ. 1996. 312(7047): 1648-1651	3
Slezak A. Kucharzewski M. Franek A. Twardokes W. Evaluation of the efficiency of venous leg ulcer treatment with a membrane dressing. Medical Engineering & Physics. 26(1):53-60, 2004 Jan.	3
Smart V. Alavi A. Coutts P. Fierheller M. Coelho S. Linn Holness D. Sibbald RG. Contact allergens in persons with leg ulcers: a Canadian study in contact sensitization. International Journal of Lower Extremity Wounds. 7(3):120-5, 2008 Sep.	2
Smith BA. The dressing makes the difference. Trial of two modern dressings on venous ulcers. Professional Nurse. 9(5):348, 350-2, 1994 Feb.	1
Smith JM Dore CJ Charlett A Lewis JD. A randomized trial of biofilm dressing for venous leg ulcers. PHLEBOLOGY. 1992. 7(3): 108-113	1
Spilsbury K Cullum N Dumville J O'Meara S Petherick E Thompson C. Exploring patient perceptions of larval therapy as a potential treatment for venous leg ulceration.. Health expectations : an international journal of public participation in health care and health policy. 2008. 11 (2) : 148-59	3
Stacey MC. Burnand KG. Layer GT. Pattison M. Browse NL. Measurement of the healing of venous ulcers. Australian & New Zealand Journal of Surgery. 61(11):844-8, 1991 Nov.	4
Stacey MC. Burnand KG. Layer GT. Pattison M. Transcutaneous oxygen tensions in assessing the treatment of healed venous ulcers. British Journal of Surgery. 77(9):1050-4, 1990 Sep	7
Stacey MC. Jopp-Mckay AG. Rashid P. Hoskin SE. Thompson PJ. The influence of dressings on venous ulcer healing--a randomised trial. European Journal of Vascular & Endovascular Surgery. 13(2):174-9, 1997 Feb.	1
Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. Journal of Vascular Surgery. 21(1):71-8; discussion 79-81, 1995 Jan.	2
Steele K Irwin G Dowds N. Cadexomer iodine in the management of venous leg ulcers in general practice. The Practitioner. 1986. 230(1411): 63-8	1
Steenvoorde P. van Doorn LP. Jacobi CE. Oskam J. An unexpected effect of Dermacyn on infected leg ulcers. Journal of Wound Care. 16(2):60-1, 2007	3
Stegmann WAE Deichmann B Hübner K Müller B Therapeutic benefit of hydroxyethylrutosides (HR) in venous ulcer treatment A controlled multicentre study. Phlebology. 1986 p. 617-20	5
Stewart AJ Leaper DJ Treatment of chronic leg ulcers in the community: a comparative trial of Scherisorb and Iodosorb. Phlebology. 1987. 2: 115-121	2

Excluded RCTs	Reason
Stiller MJ. Pak GH. Shupack JL. Thaler S. Kenny C. Jondreau L. A portable pulsed electromagnetic field (PEMF) device to enhance healing of recalcitrant venous ulcers: a double-blind, placebo-controlled clinical trial. British Journal of Dermatology. 127(2):147-54, 1992 Aug.	1
Stubb S,Lillieborg S A placebo-controlled study to compare the analgesic effect of 5 and 20 minutes' application time of EMLA 5% cream prior to the debridement of leg ulcers. Astra Pain Control. 1989	7
Svedman P Irrigation treatment of leg ulcers. Lancet 1983. 2(8349): 532-4	2
Taddeucci P. Pianigiani E. Colletta V. Torasso F. Andreassi L. Andreassi A. An evaluation of Hyalofill-F plus compression bandaging in the treatment of chronic venous ulcers. Journal of Wound Care. 13(5):202-4, 2004 May.	1
Tan, J.; Abisi, S.; Smith, A. and Burnand, K. A painless method of ultrasonically assisted debridement of chronic leg ulcers: a pilot study. Eur J Vasc Endovasc Surg 2007. 33:234-238	3
Taradaj J. Franek A. Brzezinska-Wcislo L. Cierpka L. Dolibog P. Chmielewska D. Blaszczak E. Kusz D. The use of therapeutic ultrasound in venous leg ulcers: a randomized, controlled clinical trial. Phlebology. 23(4):178-83, 2008.	2
Tarvainen K. Cadexomer iodine (Iodosorb) compared with dextranomer (Debrisan) in the treatment of chronic leg ulcers. Acta Chirurgica Scandinavica - Supplementum. 544:57-9, 1988.	1
Tarvainen K. Cadexomer iodine (Iodosorb) compared with dextranomer (Debrisan) in the treatment of chronic leg ulcers. Acta Chirurgica Scandinavica - Supplementum. 544:57-9, 1988.	1
Tausche A, Skaria M, Bohlen L, Liebold K, Hafner J, Friedlein H,et al.An autologous epidermal equivalent tissue-engineered from follicular outer root sheath keratinocytes is as effective as splitthickness skin autograft in recalcitrant vascular leg ulcers. *Wound Repair and Regeneration* 2003;**11**(4):248–52.	1
Tavadia S. Bianchi J. Dawe RS. McEvoy M. Wiggins E. Hamill E. Urcelay M. Strong AM. Douglas WS. Allergic contact dermatitis in venous leg ulcer patients. Contact Dermatitis. 48(5):261-5, 2003 May.	3
Tawes RL Barron ML Coello AA Joyce DH Kolvenbach R. Optimal therapy for advanced chronic venous insufficiency.. Journal of vascular surgery : official publication, the Society for Vascular Surgery [and] International Society for Cardiovascular Surgery, North American Chapter. 2003. 37(3): 545-51	4
Taylor A Taylor R Marcuson R Comparative healing rates and cost of convenional and four-layer treatment of venous ulcers. Phlebology. 1995 10(85)	1
Taylor AD Taylor RJ Marcuson RW. Prospective comparison of healing rates and therapy costs for conventional and four-layer high-compression bandaging treatments of venous leg ulcers. Phlebology 1998 13(1): 20-24	1
Teepe RG. Roseeuw DI. Hermans J. Koebrugge EJ. Altena T. de Coninck A. Ponec M. Vermeer BJ. Randomized trial comparing cryopreserved cultured epidermal allografts with hydrocolloid dressings in healing chronic venous ulcers. Journal of the American Academy of Dermatology. 29(6):982-8, 1993 Dec.	1
Thomas S. Banks V. Bale S. Fear-Price M. Hagelstein S. Harding KG. Orpin J. Thomas N. A comparison of two dressings in the management of chronic wounds. Journal of Wound Care. 6(8):383-6, 1997 Sep.	1
Thomas S. Sorbsan in the management of leg ulcers. Pharmaceutical Journal. 1989. 243: 706-9	3
Ting AC. Cheng SW. Wu LL. Cheung GC. Air plethysmography in chronic venous insufficiency: clinical diagnosis and quantitative assessment. Angiology. 50(10):831-6, 1999 Oct.	3
Todd DJ. Heylings DJ. Allen GE. McMillin WP. Treatment of chronic varicose ulcers with pulsed electromagnetic fields: a controlled pilot study. Irish Medical Journal. 84(2):54-5, 1991 Jun.	3
Tomljanovic-Veselski M. Lipozencic J. Lugovic L. Contact allergy to special and standard allergens in patients with venous ulcers. Collegium Antropologicum. 31(3):751-6, 2007 Sep.	3

Excluded RCTs	Reason
Tondi P. Gerardino L. Santoliquido A. Pola R. Gabrielli M. Papaleo P. Gasbarrini A. Pola P. Flore R. Treatment of ischemic ulcers of the lower limbs with alprostadil (prostaglandin E1). Dermatologic Surgery. 30(8):1113-7, 2004 Aug.	2
Travers JP Dalziel KL Makin GS. Assessment of a new one-Layer adhesive bandaging method in maintaining prolonged limb compression and effects on venous ulcer healing. PHLEBOLOGY. 1992 7(2): 59-63	1
Tritapepe R Pozzi C Maggioni Moratti E. Topical 5'-methylthioadenosine in the treatment of chronic venous ulcers: results of a double-blind, placebo-controlled clinical trial. European Journal of Plastic Surgery. 1990. 20 vol 2 (Pt 2): A17	7
Tse MM. Ng JK. Chung JW. Visual stimulation as pain relief for Hong Kong Chinese patients with leg ulcers. Cyberpsychology & Behavior. 6(3):315-20, 2003 Jun.	2
Tsouderos Y. Are the phlebotonic properties shown in clinical pharmacology predictive of a therapeutic benefit in chronic venous insufficiency? Our experience with Daflon 500 mg. International angiology : a journal of the International Union of Angiology. 1989. 8 vol. 4 Suppl: 53-9	1
Tumino G. Masuelli L. Bei R. Simonelli L. Santoro A. Francipane S. Topical treatment of chronic venous ulcers with sucralfate: a placebo controlled randomized study. International Journal of Molecular Medicine. 22(1):17-23, 2008 Jul.	4
Ukat A. Konig M. Vanscheidt W. Munter KC. Short-stretch versus multilayer compression for venous leg ulcers: a comparison of healing rates. Journal of Wound Care. 12(4):139-43, 2003 Apr.	1
Unkauf M. Rehn D. Klinger J. de la Motte S. Grossmann K. Investigation of the efficacy of oxerutins compared to placebo in patients with chronic venous insufficiency treated with compression stockings. Arzneimittel-Forschung. 46(5):478-82, 1996 May.	1
Valtonen V. Karppinen L. Kariniemi AL. A comparative study of ciprofloxacin and conventional therapy in the treatment of patients with chronic lower leg ulcers infected with Pseudomonas aeruginosa or other gram-negative rods. Scandinavian Journal of Infectious Diseases Supplement. 60:79-83, 1989.	1
van Bemmelen PS. Mattos MA. Hodgson KJ. Barkmeier LD. Ramsey DE. Faught WE. Sumner DS. Does air plethysmography correlate with duplex scanning in patients with chronic venous insufficiency?. Journal of Vascular Surgery. 18(5):796-807, 1993 Nov.	3
Van den Hoogenband HM. Treatment of leg ulcers with splitthickness skin grafts. *Journal of Dermatology, Surgery and Oncology* 1984;**10**(8):605–8.	1
Vanscheidt W Jost V Wolna P Lücker PW Müller A Theurer C Patz B Grützner KI. Efficacy and safety of a Butcher's broom preparation (Ruscus aculeatus L. extract) compared to placebo in patients suffering from chronic venous insufficiency.. Arzneimittel-Forschung. 2002. 52(4) : 243-50	1
Vanscheidt W. Rabe E. Naser-Hijazi B. Ramelet AA. Partsch H. Diehm C. Schultz-Ehrenburg U. Spengel F. Wirsching M. Gotz V. Schnitker J. Henneicke-von Zepelin HH. The efficacy and safety of a coumarin-/troxerutin-combination (SB-LOT) in patients with chronic venous insufficiency: a double blind placebo-controlled randomised study. Vasa. 31(3):185-90, 2002 Aug.	1
Vanscheidt W. Ukat A. Horak V. Bruning H. Hunyadi J. Pavlicek R. Emter M. Hartmann A. Bende J. Zwingers T. Ermuth T. Eberhardt R. Treatment of recalcitrant venous leg ulcers with autologous keratinocytes in fibrin sealant: a multinational randomized controlled clinical trial. Wound Repair & Regeneration. 15(3):308-15, 2007 May-Jun.	4
Varelias A Cowin AJ Adams D Harries RH Cooter RD Belford DA Fitridge RA Rayner TE. Mitogenic bovine whey extract modulates matrix metalloproteinase-2, -9, and tissue inhibitor of matrix metalloproteinase-2 levels in chronic leg ulcers. Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society. 2006. 14(1): 28-37	3
Vin F. Teot L. Meaume S. The healing properties of Promogran in venous leg ulcers. Journal of Wound Care. 11(9):335-41, 2002 Oct.	1
Vowden KR. Mason A. Wilkinson D. Vowden P. Comparison of the healing rates and complications of three four-layer bandage regimens. Journal of Wound Care. 9(6):269-72, 2000 Jun.	1

Excluded RCTs	Reason
Vowden KR. Wilkinson D. Vowden P. The K-Four bandage system: evaluating its effectiveness on recalcitrant venous leg ulcers. Journal of Wound Care. 2001. 10(5) : 182-4	3
Ward DJ Bennett JP Burgos H Fabre J. The healing of chronic venous leg ulcers with prepared human amnion. British journal of plastic surgery. 1989. 42(4): 463-7	4
Watson J. Nelson EA. An exploration of the use of ultrasound in the treatment of chronic venous leg ulcers. Journal of Wound Care. 15(1):39-41, 2006 Jan.	3
Weichenthal M Mohr P Stegmann W Breitbart EW. Low-frequency ultrasound treatment of chronic venous ulcers. Wound Repair and Regeneration. 1997. 5(1): 18-22	1
Weingarten MS. Branas CC. Czeredarczuk M. Schmidt JD. Wolferth CC Jr. Distribution and quantification of venous reflux in lower extremity chronic venous stasis disease with duplex scanning. Journal of Vascular Surgery. 18(5):753-9, 1993 Nov.	3
Weiss RA Weiss MA Ford RW. Randomized comparative study of cutinova foam and allevyn with Jobst UlcerCare stockings for the treatment of venous stasis ulcers. Phlebology. 1996. 11 (SUPPL. 1) : 14-16	1
Weitgasser H The use of pentoxifylline ('Trental' 400) in the treatment of leg ulcers : results of a double-blind trial. Pharmatherapeutica 1983. 3 (Suppl 1): 143-51	1
Welch HJ. Faliakou EC. McLaughlin RL. Umphrey SE. Belkin M. O'Donnell TF Jr. Comparison of descending phlebography with quantitative photoplethysmography, air plethysmography, and duplex quantitative valve closure time in assessing deep venous reflux. Journal of Vascular Surgery. 16(6):913-9; discussion 919-20, 1992 Dec.	3
Werber J Gottlieb A Sherbanny A. Activated bovine platelet releasate healing of chronic leg ulcers in a double blind study. Journal of Investigative Dermatology. 1989. 92(3). 540	3
Werner-Schlenzka H. Kuhlmann RK. Treatment of venous leg ulcers with topical iloprost: a placebo controlled study. Vasa. 23(2):145-50, 1994.	1
Werner-Schlenzka H. Lehnert W. Topical treatment of venous leg ulcers with a prostacyclin hydrogel: a double blind trial. Prostaglandins Leukotrienes & Essential Fatty Acids. 51(3):203-6, 1994 Sep.	1
Widmer L. Biland L. Barras JP. Doxium 500 in chronic venous insufficiency: a double-blind placebo controlled multicentre study. International Angiology. 9(2):105-10, 1990 Apr-Jun.	1
Wieman T J. Efficacy and safety of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic venous ulcers: a pilot study. Wounds: A Compendium of Clinical Research and Practice. 2003 15(8): 257-64	7
Wilkinson E. Buttfield S. Cooper S. Young E. Trial of two bandaging systems for chronic venous leg ulcers. Journal of Wound Care. 6(7):339-40, 1997 Jul [see comment][erratum appears in J Wound Care 1998 Jan;7(1):89]. Comment in: J Wound Care. 1997 Sep;6(8):368; PMID: 9341425, Comment in: J Wound Care. 1997 Sep;6(8):368, 370;	1
Williams D. Enoch S. Miller D. Harris K. Price P. Harding KG. Effect of sharp debridement using curette on recalcitrant nonhealing venous leg ulcers: a concurrently controlled, prospective cohort study. Wound Repair & Regeneration. 13(2):131-7, 2005 Mar-Apr.	3
Williams DT Harris K Price P Harding KG. Sharp debridement of intransigent venous leg ulcers stimulates healing. Wound Repair and Regeneration. 2003. 11(5): A20	3
Wipke-Tevis D.D., Stotts N.A., Williams D.A., Froelicher E.S. & Hunt T.K. (2001) Tissue oxygenation, perfusion, and position in patients with venous leg ulcers. Nursing Research 50, 24–32.	7
Wollina U. Schmidt WD. Kronert C. Nelskamp C. Scheibe A. Fassler D. Some effects of a topical collagen-based matrix on the microcirculation and wound healing in patients with chronic venous leg ulcers: preliminary observations. International Journal of Lower Extremity Wounds. 4(4):214-24, 2005 Dec.	3
Wong I. Assessing the value of a leg ulcer education programme in Hong Kong. Journal of Wound Care. 2003. 12(1): 17-9	3
Wright DD. Franks PJ. Blair SD. Backhouse CM. Moffatt C. McCollum CN. Oxerutins in the prevention of recurrence in chronic venous ulceration: randomized controlled trial. British	7

Excluded RCTs	Reason
Journal of Surgery. 78(10):1269-70, 1991 Oct	
Wysocki A Baxter CR Bergstresser PR Grinnell F Horowitz MS Horowitz B. Topical fibronectin therapy for treatment of a patient with chronic stasis ulcers. Archives of dermatology 1988 124(2): 175-7	**3**
Yamaki T. Nozaki M. Sasaki K. Color duplex ultrasound in the assessment of primary venous leg ulceration. Dermatologic Surgery. 24(10):1124-8, 1998 Oct.	**3**
Yamaki T. Nozaki M. Sakurai H. Takeuchi M. Soejima K. Kono T. Comparison of manual compression release with distal pneumatic cuff maneuver in the ultrasonic evaluation of superficial venous insufficiency. European Journal of Vascular & Endovascular Surgery. 32(4):462-7, 2006 Oct.	**4**
Yamaki T. Nozaki M. Sasaki K. Quantitative assessment of superficial venous insufficiency using duplex ultrasound and air plethysmography. Dermatologic Surgery. 26(7):644-8, 2000 Jul. Assessment	**3**
Yang D., Van Dongen Y.K. & Stacey M.C. (1999) Effect of exercise on calf muscle pump function in patients with chronic venous disease. British Journal of Surgery 86(3), 338–341	**3**
Zajkowski PJ. Proctor MC. Wakefield TW. Bloom J. Blessing B. Greenfield LJ. Compression stockings and venous function. Archives of Surgery. 137(9):1064-8, 2002 Sep.	**4**
Zuccarelli A Taccoen A Coget JM Furderer CR Hermann P Kalis B et al. Treatment of venous ulcers with Troxerutin: a randomised double-blind controlled study. International Angiology. 1996. 15(Suppl 1 to No 2)p. 53	**7**
Zuccarelli A Taccoen A Coget JM Furderer CR Hermann P Kalis B et al. Treatment of venous ulcers with Troxerutin: a randomised double-blind controlled study. International Angiology. 1996. 15(Suppl 1 to No 2)p. 53	**3**

APPENDIX FOUR

Venous Leg Ulcer Guideline Development Committee. Disclosure of Interest and Confidentiality

Committee Members Responsibilities re Disclosure of Interest and Confidentiality

Adapted with permission from NHMRC and utilises content from the NHMRC document Members' Responsibilities regarding Disclosure of Interest and Confidentiality.

Introduction

Members of the AWMA Venous Leg Ulcer Guideline Development Committee (VLUGDC) are drawn from the membership of the Australian Wound Management Association and have a diverse range of expertise and experience with people who have venous, mixed aetiology or arterial disease of lower limbs.

These guidelines are provided to members of the AWMA VLUGDC in order that either actual or potential conflict of interest can be addressed in a transparent and appropriate manner.

The guidelines are designed to guide the committee and coopted members enlisted in assisting with the development of the Venous Leg Ulcer Guideline project in the exercise of their responsibilities in order to ensure all conflicts of interest are addressed in a way that accords with the requirements of the National Health and Medical Research Council Act 1992 (the Act). The AWMA VLUGDC project 2008/2009 is a listed NHMRC 2008/2009 project and is therefore being progressed with NHMRC guidance.

Scope

These guidelines apply to:

*Members of the AWMA Venous Leg Ulcer Guideline Development Committee and

*All other persons appointed, engaged or coopted to assist the work of the AWMA VLUGD Committee.

Conflict Of Interest

A conflict of interest arises in any situation in which a ***member or related person*** has an interest which influences, or may appear to influence, the performance of the members responsibilities to the AWMA Venous Leg Ulcer Guideline Development project. The appearance of a conflict of interest is as important as any actual conflict of interest.

Definitions

A member is any person who is or has been appointed to the AWMA Venous Leg Ulcer Guideline Development Committee or who is coopted to assist with the project.

A related person is the spouse or partner of the member, a member of the member's family or a close friend of the member.

An interest while difficult to define is generally regarded as one of three types of interest which may overlap. These are: Direct pecuniary interest; Indirect pecuniary interest; Non pecuniary interest

Direct Pecuniary Interest

- A Direct pecuniary interest arises wherever there is a potential for a member or related person to directly gain financially from the AWMA VLUGDC project either in discussions or decision making processes to which the member contributes. This may included situations such as:
    - A directorship of or shareholdings in a company that may benefit from a decision of the AWMA VLUGDC to which the member contributes;
    - A financial investment in an organisation such as a Trust that may benefit from a decision of the AWMA VLUGDC to which the member contributes;
    - A consultancy or a grant involving financial gain to the member's employer (e.g. a hospital or higher education institution) in circumstances where the member will benefit financially from their involvement, or
    - A relationship based on a common interest such as professional or institutional allegiance that may benefit from a decision of the AWMA VLUGDC to which the member contributes.

Indirect Pecuniary Interest

- An indirect pecuniary interest arises from member's employment or professional interests or from their relationships. They include:
    - Situations of members holding a formal position of authority in a non commercial organisation such as an educational institution e.g. as a member of a working committee where he or she would have an indirect pecuniary interest in the project, grant, consultancy for which a member of that university had applied, and a head of department would have a similar interest whenever departmental members are involved.
    - An application for a consultancy or grant by a member's partner or relative, a close personal friend or a close professional colleague.

Non Pecuniary Interest

- Actual or potential non-pecuniary interests arise where a member simultaneously has an appointment to, or employment or consultancy or other involvement with, another organisation or body that is in some way involved with AWMA VLUGDC. The interest may arise if the interests of AWMA VLUGDC and the other body or organisation are in conflict, or if access to information arising from AWMA VLUGDC could be used to unfair advantage if divulged to another organisation or body.
- Such an interest will also arise where a member has a relationship, whether professional – as with a colleague in an employment context or a professional association – or personal, with a person who may benefit from a decision of the AWMA VLUGDC to which the member contributes.

Managing a Conflict of Interest

A conflict of interest, or the appearance of a conflict, is likely to undermine the credibility of the project, process or decision. This may in turn undermine the status and damage the reputation of the AWMA VLUGDC. Managing conflicts of interest in a vigorous consistent and transparent process is essential. The two main ways of managing situations of conflict are **disclosure** and **exclusion.**

Disclosure of Interest upon joining the AWMA VLUGDC

Before joining the AWMA VLUGDC a written statement and should be provided stating any interests or activities that the member may have in the matters to be considered or activities undertaken within the guideline project. This should be attached to the signed A Disclosure of Interest Form and Statement of Confidentiality

Disclosure of Interest during tenure

The responsibility to identify and report an interest that is in potential conflict or actual conflict with their responsibilities, or has the appearance of such a conflict, is always that of a member.

Members during their tenure who identify an interest must as soon as possible disclose the nature of the interest.

- Members of the committee as soon as possible after and other facts come to their knowledge, disclose to the Chair of the Committee the nature of the interest, If the member is the Chair then the AWMA President is informed;
- If a disclosure is made, a member must not be present when the AWMA VLUGDC considers the matter or take part in the decision making;
- However if the Chair or AWMA President decides otherwise, the above does not apply.

Procedure at Meetings

Chair of the meetings must provide opportunity for members to declare an interest in any activity of, or matters being considered by, the AWMA VLUGDC and any supporting working committee. This should be a standing agenda item for all committee meetings and any supporting working committees. At the commencement of each meeting, the Chairperson should invite members to declare or discuss relevant matter.

In all cases, the member's disclosure must be recorded in the minutes of the meeting or if given outside the meeting, be recorded in the minutes of the next meeting after disclosure.

Exclusion

If the Chairperson of the AWMA VLUGDC has declared an interest, he or she must not be present when the AWMA VLUGDC considers the matter, or take part in any decision of the AWMA VLUGD Committee in relation to the matter unless the AWMA President otherwise determines.

If a member of the AWMA VLUGDC has declared an interest, he or she must not be present when the AWMA VLUGDC considers the matter, or take part in any decision of the AWMA VLUGDC in relation to the matter, unless the Chairperson of the AWMA VLUGDC otherwise determines.

If a member of the AWMA VLUGDC, has declared an interest, he or she must not be present when the AWMA VLUGDC considers the matter, or take part in any decision of the committee in relation to the matter, unless the Chairperson of the AWMA VLUGDC otherwise determines.

Policy

These guidelines cannot cover all cases of where a conflict of interest may occur. Members may find themselves in situations that are not clear-cut where there is a genuine doubt as to whether a conflict of interest exists. Where there is doubt that is sufficient reason for members to declare their interest.

Confidentiality

These guidelines are designed to draw AWMA VLUGDC members' attention to the importance of 'confidential commercial information' –not confidential information generally. AWMA VLUGDC members may be privy to matters that involve confidential information, which may or not necessarily be information of a commercial nature. Confidential information can be defined as information that:

a) is by its nature confidential, and includes information provided to AWMA VLUGDC to be used only in the exercise of its functions other than functions that will involve public disclosure of the information.
b) The member(s)/person(s) assisting the AWMA VLUGDC knows or ought to know is confidential
c) Is designated by the AWMA VLUGDC as confidential, but does not include information that:

(i) is or becomes public knowledge, other than by unlawful means or by breach of confidentiality by the member(s) or person(s) assisting the AWMA VLUGDC

(ii) is in the possession of the member(s)/person(s) assisting the AWMA VLUGDC without restriction in relation to disclosure before the date of receipt from the AWMA VLUGDC

(iii) has been independently developed or acquired by the member(s)/person(s) assisting the AWMA VLUGDC

Information may be designated confidential by government, by grant application, or by any person or body which has made submissions or has dealings with AWMA VLUGDC.

Situations where confidential information may be being considered can vary widely, and may include situations such as where:

- draft recommendations are being developed
- information that has not yet been publicly released is being considered.

It is the responsibility of all members or persons assisting the AWMA VLUGDC not to disclose to any person any confidential information (including confidential commercial information), to which they become privy as a result of the exercise of their responsibilities to the AWMA VLUGDC.

Responsibility of Secretariats and Chairpersons

Secretariats are to ensure that their chairperson and members are made aware of these guidelines, that the necessary certifications are completed; and that minutes of meetings properly record disclosure of interests.

All certifications are to be kept in safe custody by the AWMA VLUGDC Secretary then when project completed forwarded to AWMA Secretary

- Secretariats are to ensure that Chairpersons are aware of their responsibilities. The Chairperson of the AWMA VLUGDC is obliged to ensure that members are familiar with these guidelines and to ensure that members have completed *Disclosure of Interest* and a *Deed of Confidentiality.*
- At the beginning of any meeting, members are to be given the opportunity to declare any interests that may be seen to conflict with any matters on the agenda
- At the beginning of any meeting, members are reminded of their responsibilities and obligations in relation to disclosure of confidential information and confidential commercial information
- The minutes of the meeting are to record any interest declared, and conflict of interest and any decision made in relation to such a declaration.

Disclosure of Members' Personal Information

The Privacy Act allows disclosure of personal information in a number of circumstances, including where the individual has been made aware that information of that kind is usually disclosed, or the person has consented to the disclosure.

Therefore members are advised – and are asked to acknowledge – that their names, official positions outside AWMA VLUGDC, relevant expertise and biographical details may be included on AWMA VLUDGC documentation including the AWMA website.

AGREEMENT OF CONFIDENTIALITY

I have read and understand the accompanying document AWMA VLUGDC document titled Disclosure of Interest and Confidentiality and the attachment B addendum

☐ **I agree to respect the AWMA VLUGDC Agreement of Confidentiality**

Dated this day of 2009

_____

Name of signatory Signature

_____

Chairperson AWMA VLUGC Signature

It is agreed as follows:

1. Interpretation

1.1 **In this statement unless contrary intention appears:**

Confidential Information' means all information made available to the AWMA VLUGDC member for the purposes of the development of Venous Leg Ulcer Guideline project, whether orally or in writing, or by any other means and includes information that:

(a) is by its nature confidential; or
(b) is designated by AWMA or AWMA VLUGDC as confidential; or
(c) the Member knows or ought to know is confidential;

(a) But does not include information which:

(d) is or becomes public knowledge other than by breach of this Agreement of Confidentiality
(e) is in the possession of the Member without restriction in relation to disclosure before the date of receipt from the AWMA VLUGDC; or
(f) has been independently developed or acquired by the member.

1.2 No variation of this agreement is binding unless it is agreed in writing between the parties.

2. Protection of Confidential Information

2.1 The member must not disclose Confidential Information to any person other than current members of the AWMA VLUGDC without prior approval in writing from the Chairperson or Vice chair person. In giving approval the relevant person may impose such terms and conditions as he or she thinks fit.

2.2 The Member must not use any Confidential Information except for the purpose of fulfilling his or her duties as a Member.

2.3 The obligations on the member under this clause will not be breached if the Confidential Information is required by law to be disclosed and the disclosure is made pursuant to that disclosure. This may involve members who have statutory obligations to their full time employer.

2.4 Property in any document or thing containing confidential information (in the form of a document, article, or removable medium) vests or will vest in the AWMA VLUGDC. The member shall:

(a) secure all copies within his or her control against loss and unauthorised use or disclosure; and
(b) on the expiration or termination of his or her appointment to the AWMA VLUGDC deliver all copies to the AWMA or otherwise deal with all copies as directed by the Chairperson or Vice Chairperson of the AWMA .

2.5 Neither the AWMA or the AWMA VLUGDC gives any undertaking to treat the members information, or this agreement, as confidential. The member acknowledges that the AWMA or AWMA VLUGDC may disclose information relevant to this Agreement or this Agreement itself, to any person.

3. Indemnity

3.1 The member shall indemnify The AWMA VLUGDC its officers, employees and agents ('those indemnified') from and against all actions, claims demands, costs and expenses (including the costs of defending or settling any action, claim or demand) made, sustained, brought or prosecuted against those indemnified where those actions, claims, demands, costs or expenses arise as a result of wilful or deliberate disclosure by a member.

(a) in breach of this Agreement

3.2 The member agrees that the AWMA VLUGC will be taken to be the acting agent for and on behalf of those indemnified from time to time

3.3 The indemnity referred to in this clause 3 survives the expiration or termination of the member's appointment.