Australian and New Zealand Clinical Practice Guideline for Prevention and Management of Venous Leg Ulcers

AWMA
Australian Wound
Management Association Inc.
National

New Zealand
Wound Care
Society

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This guideline was developed by the Australian Wound Management Association and the New Zealand Wound Care Society. The guideline presents a comprehensive review of the assessment, diagnosis, management and prevention of venous leg ulcers within the Australian and New Zealand healthcare context, based on the best evidence available up to January 2011. 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.

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. The guideline should be implemented in a culturally safe and respectful manner in accordance with the principles of protection, participation and partnership.

Copies of this guideline can be downloaded from the Australian Wound Management Association website: www.awma.com.au or the New Zealand Wound Care Society website: www.nzwcs.org.nz

New Zealand GUIDELINES GROUP
Te Rōpū Rarangi Tohutohu
Promoting Effective Health and Disability Services

These guidelines have been reviewed and endorsed by the New Zealand Guidelines Group

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Publication Approval

Australian Government
National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 8 August 2011 under Section 14A of the National Health and Medical Research Council Act 1992. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of 5 years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

CONTENTS

1. INTRODUCTION

1.1 Venous leg ulcers in the community

Accurate prevalence of venous leg ulcers (VLUs) in Australia is difficult to estimate due to a range of methodologies used in prevalence studies, accuracy of reporting and the range of methods and inconsistent definitions of ulcers of venous aetiology.[1]

In 2003 the global prevalence of leg ulceration was estimated at 0.1 to 1.1%.[2] Historically the literature indicates that the primary aetiology of leg ulceration is venous.[3,4] Baker and Stacey's 1994 report suggested a prevalence of VLUs of 1% in the overall Australian population.[5] More recent data has not been reported; however, estimates indicate that leg ulcers affect up to 3.0 per 1,000 of the Australian adult population, suggesting a sizeable impact on the community.[6]

Rate of recurrence of VLUs is high. In the United Kingdom (UK) in 1995 a comparison of studies in different care settings indicated a recurrence rate of between 22 and 69%.[2] A report more than 10 years later in 2008 indicated recurrence to be between 26% and 69%.[3] Other studies have reported recurrence rates within three months of approximately 50%,[4] 56%[5] and 70%.[6] Although specific recurrence rates are difficult to accurately determine, it is evident that they are high, thereby increasing the health burden of VLUs.

It is well established that VLUs occur more often in older adults. Australian data indicates that approximately 99% of individuals with a VLU are aged 60 years or over.[7] Prevalence has been reported at 4% in adults aged over 65 years.[8] In a recent United States (US) cohort study, the incidence of VLUs over two years was 1.7% in patients over 65 years of age.[9] Viewed in the context of the ageing Australian population, with the proportion of the population aged over 65 years estimated to increase from 13% in 2007 to between 23% and 25% in 2056,[10] the financial, health and personal burden of VLUs is significant.

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.[11] A capture-recapture analysis that incorporates an estimation of missed cases suggested a point prevalence of ulcers of 2.48 per 1000 adults.[12] 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%.[13]

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.[14] The ageing Australian population, as reported above, will be a significant burden on government-funded health care provision.

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.[14] 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. Access to appropriate services for diagnosis and management of VLUs for all Australians will significantly improve health outcomes and quality of life (QOL).

The Australian Wound Management Association (AWMA) and the New Zealand Wound Care Society (NZWCS) aim 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 Use of the recommendations

This guideline was developed by the AWMA in conjunction with the NZWCS. The guideline presents a comprehensive review of the assessment, diagnosis, management and prevention of VLUs within the Australian and New Zealand health care context, based on the best evidence available up to January 2011.

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 judgement of each individual case and in consideration of the patient's personal preferences. The guideline should be implemented in a culturally safe and respectful manner in accordance with the principles of protection, participation and partnership.

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:

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1.4 Commonly used abbreviations

4LB	Four-layer bandages/ing
ABPI	Ankle brachial pressure index
AWMA	Australian Wound Management Association
BMI	Body mass index
CALD	Culturally and linguistically diverse
CBR	Consensus-based recommendation
CEAP	**C**linical severity, (a)**e**tiology, **a**natomy, **p**athophysiology
CI	Confidence interval
CWIS	Cardiff Wound Impact Schedule
CVI	Chronic venous insufficiency
CVIQ	Chronic Venous Insufficiency Questionnaire
DVT	Deep vein thrombosis
EMLA®	Eutectic mixture of local anaesthetic
GIT	Gastrointestinal tract
HBOT	Hyperbaric oxygen therapy
HCSE	Horse chestnut seed extract
ITT	Intention to treat
LLLT	Low-level laser therapy
MPFF	Micronised purified flavanoid fraction
N	Number (of participants)
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
OR	Odds ratio
QOL	Quality of life
P value (p)	Probability value
PEMT	Pulsed electromagnetic therapy
RCT	Randomised controlled trial
RR	Relative risk
RRR	Relative risk reduction
SR	Systematic review
SSI	Static stiffness index
VAC	Vacuum-assisted closure
VAS	Visual analogue scale
VLU	Venous leg ulcer
WBP	Wound bed preparation
WMD	Weighted mean difference

1.5 Glossary

Ankle flare	Distended veins in foot arch or ankle region.
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 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 as ivory/white depressed atrophic plaques with prominent red blotching within the scar.
Bioengineered skin grafts	Manufactured skin replacement products derived from human or animal skin cells.
Chronic venous insufficiency (CVI)	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.
Haemosiderin pigmentation	A reddish brown pigmentation due to deposits of haemosiderin in the lower legs as a result of venous insufficiency.
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. Seen as fibrosis of the underlying subcutaneous tissue.
Microcirculation	The flow of blood or lymph throughout the system of smaller vessels (diameter of 100 µm or less) of the body.
Macrocirculation	The large blood vessels that transport blood to the organs.
Pain	In the context of this guideline, pain refers to an unpleasant sensory and emotional experience associated with a leg ulcer. Patients may use varying words to describe pain including discomfort, distress and agony.
Patient	Any person receiving health assessment, care or treatment.
Post-thrombotic syndrome	Describes 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.
pH	A measure on a scale from 0 to 14 of the acidity or alkalinity of a solution, with 7 being neutral, greater than 7 is more alkaline and less than 7 is more acidic.
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 cleansing 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 (e.g. 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 (e.g. 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 (VLU)	Full-thickness defect of the skin that persists due to venous disease of the lower leg.
Working pressure	The sub-bandage pressure experienced as the patient walks.

2. QUICK REFERENCE FLOW CHARTS

The following two pages present:

- Flow chart for assessment of venous leg ulcers
- Flow chart for management of venous leg ulcers

FLOW CHART FOR ASSESSMENT OF VENOUS LEG ULCERS

Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers

AWMA Australian Wound Management Association Inc. National — Healing Wounds Together

New Zealand Wound Care Society

Patient presents with an ulceration on the lower leg

1 ASSESSMENT

HISTORY

Patient's clinical history (page 20)

- venous disease
- family history of leg ulceration
- decreased calf muscle pump function
- surgery or trauma of affected leg
- chest pain or pulmonary embolism
- prolonged standing or sitting
- varicose veins
- phlebitis
- obesity
- number of pregnancies
- previous or current DVT

Comprehensive assessment of the patient (page 20)

- medications
- psychosocial
- comorbidities
- quality of life
- nutrition
- pain

Patient's leg ulcer history (page 20)

- 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

EXAMINATION

Venous characteristics (page 22)

Associated changes in the leg

- Firm ("brawny") oedema
- Haemosiderin deposit (reddish brown pigmentation)
- Lipodermatosclerosis (skin hard and woody)
- Evidence of healed ulcers
- Dilated and torturous superficial veins
- Hair is evident
- Atrophie blanche (white areas of intact skin)
- Venous eczema (dry or wet itchy scaly skin)
- Altered shape – inverted "champagne bottle"
- Ankle flare (distended veins in foot arch or ankle region)
- Leaking oedema may result in maceration, pruritis and scale
- Limb may be warm – heat and/or itch

Ulcer location and characteristics

- Anterior to medial malleolus
- Pretibial area (lower third of leg)
- Shallow with ragged, irregular edges
- Ruddy granulation tissue
- Wound exudate moderate to high
- May be odorous

Pain

- Varying from nil, to mild or extreme
- May be relieved by elevation of leg

Arterial characteristics

Associated changes in the leg

- Oedema may be observed if infection present
- Thin, shiny skin often with minimal hair growth
- Leg shape is often straight with minimal shape
- Limb cool to touch
- Elevated toes/leg become pale, dependent rub (+ve Beurger's test)
- Weak or absent pedal or leg pulses

Ulcer location/characteristics

- Ulcer margins well demarcated with "punched out" appearance
- Poorly perfused wound bed
- Necrotic tissue that may be tenacious (difficult to remove)
- Minimal wound exudate unless infected
- Prone to infection

Pain

- Claudication or rest pain, may be worse at night or if leg is elevated

Atypical ulcer characteristics

- None or minimal venous and arterial ulcers characteristics
- Pain is extreme
- Oedema
- Ulcer has an unusual appearance or atypical distribution
- Suspicion of malignancy
- Deterioration in ulcer or necrotic tissue present
- Ulcer that has not healed in three months

INVESTIGATIONS

Non-invasive diagnostic tests may be ordered: (page 24)

- Pedal and leg pulses
- ABPI
- TBPI
- X-ray
- Wound swab
- Arterial and/or venous duplex scanning
- Photoplethysmography
- $TCPO_2$
- Pulse oximetry

Invasive diagnostic tests may be ordered: (page 24)

- Blood profiles
- Wound tissue biopsy
- MRI

2 DIAGNOSIS

ABPI < 0.8 or > 1.2 or
Atypical or arterial characteristics

ABPI 0.8–1.2 or
Characteristics of venous aetiology
Use CEAP classification

3 REFERRAL

Referral to specialist health professional (page 26)

4 MANAGEMENT

Refer to other side for management of the **Venous** ulcer

FLOW CHART FOR MANAGEMENT OF VENOUS LEG ULCERS

Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers

Patient assessed as having a venous ulcer on the lower leg

1 THE PATIENT

Provide appropriate **PAIN MANAGEMENT** (page 28)

Provide patient **EDUCATION** (**Grade C**, page 30)
- Leg elevation
- Nutrition
- Compression therapy including use and care of hosiery
- Exercise

Provide access to appropriate **PSYCHOSOCIAL** support (page 31)

Recommend **ELEVATION** of the lower limb to reduce oedema (**Grade C**, page 32)

PROGRESSIVE RESISTANCE EXERCISE to improve calf muscle function (**Grade C**, page 33)

Encourage optimal **NUTRITION AND HYDRATION** to assist healing (page 34)

2 PREPARE THE LEG AND WOUND

Prepare the surrounding skin:
- **CLEANSE** the leg at dressing changes (page 35)
- **MAINTAIN SKIN INTEGRITY** of surrounding leg skin (page 36)
- **CONTROL VENOUS ECZEMA** (**Grade C**, page 36)

Wound bed preparation:
- **CLEANSE** the ulcer at dressing changes (page 35)
- Consider **DEBRIDEMENT** of non-viable tissue (**Grade C**, page 37)
- Consider treating **CLINICAL INFECTION** (page 38–47)
- Select appropriate **PRIMARY DRESSING** (**Grade B**, page 47)

3 COMPRESSION

Graduated compression therapy (**Grade B**, page 53)
In the absence of arterial disease or diabetes mellitus
aim for > 30 mmHg (elastic) or high stiffness system (inelastic)
***Caution:* Compression should be applied by a trained health professional and according to manufacturer's guidelines**

Patients receiving compression therapy should be **MONITORED CLOSELY** to ensure they are able to tolerate compression and to monitor signs of healing

4 REVIEW

Review and consider referral (page 26)
Ulcers not reduced in size by 25% in four weeks or failing to heal in 12 weeks should be considered for specialist referral

5 PREVENT RECURRENCE

Prevention of recurrence
Measure and fit compression hosiery providing 18–40 mmHg (**Grade B**, page 62)

Ongoing encouragement should be given related to exercise, leg elevation and nutrition

Hosiery should be renewed at least annually

3. SUMMARY OF RECOMMENDATIONS

Table 3.1: Recommendation grades[15]	
Evidence-based gradings developed from critical appraisal of the 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
Consensus-based recommendation (CBR)	
CBR	Consensus evidence — a graded recommendation could not be made due to a lack of evidence from SRs or RCTs in populations with VLUs. The CBRs are supported by all members of the Expert Working Committee.

PREVENTING INITIAL OCCURRENCE OF VLUs	Grade
Prevent and manage venous hypertension by: • providing deep vein thrombosis (DVT) prophylaxis • detecting and managing DVT early • promoting access to venous surgery and phlebology interventions.	**CBR**
When there are no contraindications, apply compression therapy to prevent the initial development of a VLU in those at risk.	**CBR**
ASSESSMENT, DIAGNOSIS AND REFERRAL	**Grade**
A health professional trained in the assessment and management of VLUs should conduct a comprehensive assessment of all patients presenting with a leg ulcer. A comprehensive assessment should include: • clinical, pain and leg ulcer history • examination of the leg and ulcer • investigations to support diagnosis.	**CBR**
A comprehensive assessment of the leg ulcer should be made on initial presentation and at regular intervals thereafter to guide ongoing management.	**CBR**
Use CEAP classification to evaluate and classify venous disease.	**CBR**
Refer patients with a non-healing or atypical leg ulcer for consideration of biopsy.	**CBR**
Local guidelines should provide clear indication of appropriate criteria for referral to specialist health professionals.	**CBR**
MANAGING PAIN ASSOCIATED WITH VLUs	**Grade**
Provide adequate pain management to promote QOL and VLU healing.	**CBR**
When there are no contraindications, apply EMLA® cream to reduce pain associated with the debridement of VLUs.	**A**
Electrotherapy could be considered for reducing pain from VLUs.	**C**
MANAGEMENT OF VLUs	**Grade**
Managing the patient	
Provide patients with appropriate education on their condition and its management.	**C**
Provide psychosocial assessment and support as an essential component in the patient's management plan.	**CBR**
Elevate the patient's leg to promote changes in microcirculation and decrease lower limb oedema.	**C**
Progressive resistance exercise may improve calf muscle function.	**C**
Optimise the patient's nutrition and hydration to promote healing in patients with VLUs.	**CBR**

Prepare the leg and ulcer	
Cleanse the leg and ulcer when dressings and bandages are changed.	**CBR**
Treat venous eczema and impaired peri-ulcer skin promptly.	**CBR**
Consider using topical barrier preparations to reduce peri-ulcer erythematous maceration in patients with VLU.	**C**
Enzymatic debriding agents have no effect in promoting healing in VLUs.	**C**
Consider other debridement methods to prepare the ulcer bed for healing.	**CBR**
Treat clinical infection	
Cadexomer iodine could be used to promote healing in VLUs when there is known increased microbial burden.	**B**
Silver products offer no benefit over standard care in reducing the healing time of VLUs.	**C**
Honey offers no benefits over standard care in promoting healing in VLUs.	**A**
Topical antimicrobial agents should not be used in the standard care of VLUs with no clinical signs of infection.	**B**
There may be a role for judicious use of topical antimicrobials when there is known or suspected increased microbial burden.	**CBR**
Use topical antibiotics judiciously in managing VLUs as there is a concern that their use is associated with antibiotic resistance and sensitivities.	**CBR**
Systemic antibiotics should not be used in the standard care of VLUs that show no clinical signs of infection.	**B**
Select a dressing and topical treatment	
No specific dressing product is superior for reducing healing time in VLUs. Select dressings based on clinical assessment of the ulcer, cost, access and patient/health professional preferences.	**B**
Consider using dressings or bandages impregnated with zinc oxide to provide comfort and promote epithelialisation of a healthy granulated, superficial VLU.	**CBR**
Topical, pale, sulphonated shale oil could be used to promote healing in VLUs.	**C**
Apply compression	
When there are no contraindications, apply compression therapy to promote healing in VLUs.	**B**
Other interventions	
Consider bi-layered, bioengineered skin grafts to promote healing in persistent VLUs.	**B**
Health professionals benefit from education on VLUs and their management. Patient outcomes may be superior when ulcer care is conducted by a trained health professional.	**C**
When there are no contraindications, pentoxifylline could be used to promote healing in VLUs.	**B**
When there are no contraindications, micronised, purified flavanoid fraction may be used to decrease the healing time for VLUs.	**C**
Rural and remote populations	
Where access to specialist services is limited, health professionals could contact a VLU specialist via telecommunications for advice and support in assessing and managing a patient with a VLU.	**CBR**
PREVENTING RECURRENCE OF VLUs	**Grade**
Maintaining practices that promote the health of the legs may reduce the risk of VLU recurrence.	**CBR**
Consider the continued use of compression therapy to reduce the risk of VLUs recurrence.	**B**

4. BACKGROUND

4.1 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.[16] Venous hypertension accounts for nearly 80% of all leg ulcers.[17] Venous ulceration is strongly related to risk factors such as family history of, or previous surgery for varicose veins; venous disease; phlebitis; DVT; congestive cardiac failure; obesity; immobility[18] and previous leg injury.[17]

Currently VLU management is a significant burden on patients, their families and the health care system. In recent years management of VLUs has moved from the acute care sector to the community.[19] VLUs are the most common clinical wound problem seen in general practice and community nurses spend some 50% of their time treating leg ulcers.[6,20,21] This was supported in a recent pilot study in which 86% of participants indicated the involvement of their general practitioner in managing a VLU and 43% indicated that wound specialists and/or district nurses were involved in their care.[19]

Viewed in the context of an ageing Australian population, the management of 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.

4.2 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.[8,22]
- Many rural patients, 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 guideline related to VLUs exists for the Australian and New Zealand health care context. Clinical guidelines have been developed in other regions including 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 VLUs.
- VLU research is not a funding priority.

4.3 Aim of the guideline

The aim of the guideline is to increase awareness of VLUs and promote optimal care of VLUs. The guideline specifically seeks to assist health professionals to:

- identify patients at risk of VLUs
- accurately diagnose and assess VLUs
- optimise management and promote self-management
- prevent or delay complications associated with VLUs
- optimise QOL
- reduce the risk of recurrence.

The guideline may also be used as an educational source and for use by policy developers in developing local practice policies and procedures.

4.4 Scope and target population

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

The guideline is intended for use in health care settings in metropolitan, regional, rural and remote areas of Australia and New Zealand and refers to people of all ages.

The guideline also seeks 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 or Pacific Island background
- people from ethnically, culturally and linguistically diverse (CALD) backgrounds.

4.5 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.

Specific questions the literature search focused on were:

Prevention

1 What are the most effective interventions to prevent the initial occurrence of VLUs?

Assessment, diagnosis and referral

1 What are the most reliable and valid methods of assessing patients with VLUs?
2 What are the most reliable and valid diagnostic criteria?
3 When should a patient with a VLU be referred to a specialist?

Management

1 What are the most effective interventions to manage pain associated with VLUs?
2 What are the most effective pharmacological and non-pharmacological interventions to manage VLUs?

Preventing recurrence

1 What are the most effective interventions to prevent recurrence of VLUs?

4.6 Process

The Expert Working Committee (Appendix A) 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) Guideline Assessment Register (GAR) consultant. The process used to develop the guideline is outlined in full detail in the process report (Appendix B). The recommendations for which evidence was identified have been graded using a system based on *NHMRC Levels of evidence and grades for recommendations for developers of guidelines (2009)*[15] outlined in Table 4.1.

Table 4.1: Recommendation grades[15]	
Evidence-based recommendations	
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
Consensus-based recommendations (CBR)	
CBR	Consensus evidence — a graded recommendation could not be made due to a lack of evidence from SRs or RCTs in populations with VLUs. The CBRs are supported by all members of the Expert Working Committee.

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

Process for evidence-based recommendations (grades A to D)

The full process for the development of recommendations is outlined in the process report (Appendix B). A systematic search for literature (Appendix E) published from January 1985 to September 2009 was conducted in eight major databases and studies providing Level I evidence or Level II evidence on the NHMRC levels of evidence scale[15] (Appendix B) were considered for inclusion. An additional abridged search for research published from September 2009 to January 2011 was conducted in two major databases. Individual research papers that met the inclusion criteria were critically appraised using checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN)[28] and given an overall descriptive quality of high, moderate or low.

A summary of the supporting evidence used to grade the recommendation is provided with each evidence-based recommendation. The Expert Working Committee considered one low-quality study on an intervention to be insufficient evidence on which a graded recommendation could be made. It was also considered inappropriate to make recommendations for interventions not currently available in Australia and New Zealand; however, research summaries are provided for the clinician's education.

Each evidence-based recommendation is supported by a grading from A to D 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 *Levels of evidence and grades for recommendations for developers of guidelines (NHMRC, 2009)*.[15]

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. The body of evidence assessment matrix, listing all the components that were considered when assessing the evidence, together with the grades used, is in Appendix B.[15]

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* available from the AWMA website, http://www.awma.com.au/ and the NZWCS website, http://www.nzwcs.org.nz/

Evidence-based graded recommendations are shaded in red throughout the guideline.

Process for CBRs (grade CBR)

CBRs have been made for areas in which no research conducted in populations with VLUs was identified in the literature search. These recommendations address topics considered important by the Expert Working Committee. After conducting the full literature searches and failing to locate SRs or RCTs, the expert opinion recommendations were developed through group discussion and email. Discussion continued until consensus was reached regarding topics appropriate to include and the content of each recommendation.

The NHMRC grading system does not recognise non-analytical studies, discussion, case studies or opinion of experts, therefore fields for which this is the best available evidence fall outside the grading system. A full search for these lower levels of evidence was not conducted; however, other opinion-based guidelines or reviews conducted in similar populations (for example, patients with chronic wounds) have been used to support the expert opinion recommendations. The most recent international evidence-based VLU and Australian wound management guidelines were identified by committee members as appropriate supporting literature for expert opinion recommendations.

CBRs are shaded in blue throughout the guideline.

Practice points

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.

Most recommendations are accompanied by practice points to assist clinicians to implement the recommendation. The practice points were developed by the Expert Working Committee and reflect their considerable experience in assessing and managing VLUs in a range of clinical settings. A full search of the literature was not conducted for each practice point. Practice points are supported by:

- studies and research included in the review
- manufacturer product information
- evidence beyond the scope of the literature review (for example, guidelines referring to general management of chronic wounds).

In some instances, practice points are included for products for which there was no evidence. These tips seek to guide clinicians or their patients who judiciously choose to use the product.

4.7 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 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 patient's 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
- 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. Adverse events reported in the research included in the review have been reported in the evidence summaries and caution statements. All products should be used according to manufacturer's directions.

Surgical interventions

At commencement of the guideline development project, surgical intervention was not a routine consideration in the prevention or management of simple VLUs. As such, the search was not designed to retrieve research related to surgical intervention. The Expert Working Committee acknowledges the role that venous surgery now plays in treating venous hypertension and preventing the development of VLUs.

Search date

The guideline is based on the best evidence published from January 1985 to January 2011. Evidence published before and after these dates has not been reviewed or considered for the guideline.

Outcome measures

The outcome measure most frequently reported in the evidence was "healing of VLUs". The Expert Working Committee acknowledges that some products may have other beneficial outcomes (for example, preparing the wound bed for other treatments) that have not been investigated or reported in the research. The Expert Working Committee has attempted to address this in the practice points.

Lack of evidence

For some interventions there was limited evidence from which to draw conclusions on potential effectiveness. These interventions have received a lower grade due to an insufficient body of evidence at this stage. The Expert Working Committee considered a single, low-quality study alone to be insufficient evidence on which to make a recommendation. The research on topics for which there was insufficient evidence to make a recommendation is presented in section 13.

Some interventions may provide benefit for outcomes that have not been addressed in the research (for example, patient wellbeing). The Expert Working Committee acknowledges that **lack of evidence is not evidence of lack of effect**.

Some interventions were not supported, or received a lower grade, because research indicated there was a lack 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 outcomes do not exceed beneficial effects that can be expected from a placebo therapy or standard care.

5. PREVENTING INITIAL OCCURRENCE OF VENOUS LEG ULCERS

What are the most effective interventions to prevent initial occurrence of VLUs?

5.1 Management of venous hypertension

Prevention of VLUs requires the management of underlying venous disease. Early detection, management and prevention of 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. Detection and management of venous hypertension is highlighted by the Expert Working Committee as a priority in the prevention of VLUs.

Recommendation

Prevent and manage venous hypertension by:

- **providing DVT prophylaxis**
- **detecting and managing DVT early**
- **promoting access to venous surgery and phlebology interventions (CBR).**

5.2 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. This lack of evidence was 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.

Recommendation

When there are no contraindications, apply compression therapy to prevent the initial development of a VLU in those at risk. (CBR)

Caution

Refer to the caution statement and the contraindications in the recommendation for use of compression therapy in the treatment of VLUs. (section 8.5)

Practice points

- 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 usually be within the range of 18–30 mmHg.
- Further practice points can be found in the section on compression therapy for the treatment of VLUs (section 8.5).

Supporting literature

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 the studies were conducted in populations without diagnosed chronic venous insufficiency (CVI). The Expert Working Committee considered that compression therapy is effective in preventing the development of VLUs, for patients at high risk of VLU. *(Expert opinion)*

One good-quality, randomised crossover trial[29] (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 were 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.[29] *(Level II evidence)*

6. ASSESSMENT, DIAGNOSIS AND REFERRAL

6.1 Assessment

What are the most reliable and valid methods of assessing patients with VLUs?

What are the most reliable and valid diagnostic criteria?

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.[30]

Using a formal leg ulcer assessment process such as the New Zealand Leg Ulcer Pathway[31] can simplify ongoing monitoring and assessment of ulcer. The VLU pathway provides a model for national/international analysis on VLU management, complications, outcomes and resources. VLU pathways enable clinicians to compare outcomes, based on this VLU guideline, from different practice settings, treatment options and demographic groups.

The Expert Working Committee concurs with other expert groups[25,32-34] that patient assessment is crucial to the appropriate management of VLUs.

Recommendation

A health professional trained in the assessment and management of VLUs should conduct a comprehensive assessment of all patients presenting with a leg ulcer.

A comprehensive assessment should include:

- **clinical, pain and leg ulcer history**
- **examination of the leg and ulcer**
- **investigations to support diagnosis. (CBR)**

6.1.1 Clinical, pain and leg ulcer history

Essential in comprehensive assessment is the identification of the aetiology of the leg ulcer. **Specifically, an assessment to identify the aetiology of the ulcer is essential before commencing compression therapy as damage to the lower limb can result if compression is applied to underlying arterial aetiology**.[33,34] Assessment should seek to identify comorbidities that may influence treatment of the VLU and/or require concurrent management. Comorbidities that require further investigation and management include peripheral arterial disease, rheumatoid arthritis, vasculitis, a past history of multiple skin cancers (lesions) and diabetes mellitus.[33,34]

Assessment should be conducted and documented by a health professional with education and experience in the management of VLUs.[25,32-34] Assessment should include a medical and surgical history, examination of the leg, vascular assessment, biochemical analysis, microbiological analysis, nutritional assessment, psychological and social assessments and past treatments for venous ulcers.

Medical and surgical history

A clinical history indicative of a leg ulcer of venous origin includes:[34]

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

- obesity
- multiple pregnancies.

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:[34]

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

Nutritional assessment

A nutritional assessment should be conducted.[25,32] This may include:

- weight and/or body mass index (BMI)[25,32,34,35]
- food and fluid intake[30]
- hair and skin changes[30]
- validated nutritional assessment.[30]

Pain assessment

A pain assessment that investigates pain with a validated pain scale should be conducted.[25,30,32,34] This may include:

- location of the ulcer-related pain
- quantity/severity of the pain
- quality/characteristics of the pain
- when pain occurs (for example, at dressing changes, background pain)
- triggers and relievers
- impact of the pain on QOL.

Psychosocial, QOL and social assessments

Conduct psychosocial assessments using appropriate, validated assessment tools.[25,32] These may include:

- mini mental examination[30]
- QOL scales for specific health populations,[30,36] for example the Cardiff Wound Impact Schedule (CWIS) and Chronic Venous Insufficiency Questionnaire (CVIQ) have both been validated in patients with venous disease.[36]

Supporting literature

The literature search did not identify evidence on assessment of a patient with VLUs.

One international clinical guideline based on an SR of the literature also found no evidence of a level above case reports and non-analytical studies related to assessment of patients with leg ulcers. The clinical guideline suggested that comorbidities including obesity, poor nutritional status and mobility may influence treatment decisions and should be assessed initially. The guideline also made opinion-based recommendations to screen patients for peripheral arterial disease, systemic vasculitis, rheumatoid arthritis and diabetes mellitus in an initial assessment.[33] *(Expert opinion)*

A low-quality SR[36] 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 CWIS and CVIQ. The CWIS is specific to, and has been validated in, VLU populations. It includes sections on physical symptoms and daily living, social life, wellbeing and overall health-related QOL. The CVIQ has been validated in populations with venous insufficiency and for people with a VLU, and 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.[36] This review did not report on the effectiveness or impact of using the tools in assessment. *(Level 1 evidence)*

6.1.2 Examination of the leg and ulcer

Recommendation

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

A bilateral limb assessment[25,32,34] and gait assessment should be conducted. Signs and symptoms that are indicators of VLUs are outlined in Table 6.1.

Table 6.1: Clinical indicators of venous leg ulcers[37]

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	Confirmed venous disease History of DVT, varicose veins, phlebitis, chest pain, haemoptysis or pulmonary embolism Obesity Familial history of venous ulcers Trauma or surgery to the leg/s Decrease of calf muscle pump function Occupations of prolonged standing or sitting Multiple pregnancies
Associated changes in the leg	Firm ("brawny") oedema Haemosiderin deposit (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 (gaiter region)
Ulcer characteristics	Irregular shaped edges Ruddy granulation tissue Predominantly viable tissue
Ulcer-related pain	Pain varying from nil, to mild or extreme Pain may be relieved by elevation of leg
Surrounding area **Peri-ulcer**	Leaking oedema may result in maceration, pruritus and scale Heat and/or itch
Pulses	Normal foot/leg pulses

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 research 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 research-based recommendations could be made. The Expert Working Committee concurs with other expert groups[25,32-34] that patient assessment is crucial to the appropriate management of VLUs.

Ulcer assessment includes:

- measurement of the ulcer size[25,32-34]
- amount and type of exudate[25,32]
- appearance of the ulcer bed[25,32,33]
- condition of the ulcer edges[25,32,33]
- signs of clinical infection (for example, inflammation, increased pain, increased exudate, pyrexia)[25,32,33]

- peri-ulcer skin[30]
- ulcer odour.[30]

Practice points

- The acronym HEIDI can be used to guide assessment and diagnosis:[38]
  - **H**istory
  - **E**xamination
  - **I**nvestigations
  - **D**iagnosis
  - **I**ndicators
- Measurement of the ulcer should include length, width[25,32,33] and depth.[34]
- Tracing the ulcer margins provides a reliable indication of the progress of wound healing.[25,32,33] Other techniques for measuring ulcer size include using a disposable ruler or photography, including a calibrated measure.[39]
- Computerised calculation (planimetry) of the ulcer area from wound tracings or digital photography could be considered if resources are available.[39]
- The patient's position should be replicated as closely as possible when re-measuring the ulcer to increase the accuracy of results.[39]
- Characteristics of the ulcer and peri-ulcer skin should be documented regularly. The documentation system used should allow comparison of ulcer characteristics over time to evaluate progress.[39]
- When ongoing assessment indicates that the VLU is not healing at an optimal rate (25% improvement within four weeks[40]) dressing choice and overall management should be reviewed.

Supporting literature

The literature search did not identify evidence on assessment of VLUs. One international clinical guideline based on an SR of the literature also found no evidence of a level above case reports and non-analytical studies related to assessment of the patient's legs. The clinical guideline recommends assessing legs for signs of venous disease, oedema and joint mobility. The guideline reports one small trial that suggests serial measurements of ulcer margins should be used to assess healing. Other suggestions regarding ulcer assessment based on opinion include description of the ulcer edges, base and location.[33] *(Expert opinion)*

6.1.3 Investigations to support diagnosis

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[25,32-34] that patient investigations could be used to support diagnosis.

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 6.2 describes investigations that can assist in the diagnosis of ulcer aetiology.

Table 6.2: Investigations	
Blood pressure (BP)[25,32,34,35]	Measures the pressure of the blood on the vessel walls using a sphygmomanometer. It provides an indication of the possible presence of a range of cardiovascular diseases. The systolic BP is used in the calculation of ABPI.
Ankle brachial pressure index (ABPI)[25,30,32-35]	A non-invasive vascular test using Doppler ultrasound that identifies large vessel peripheral arterial disease in the leg. It is used to determine 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 measurements, ABPI is calculated as the highest systolic blood pressure from the foot arteries (either dorsalis pedis or posterior tibial artery) divided by the highest brachial systolic pressure, which is the best estimate of central systolic blood pressure.[41] An ABPI of 0.8 to 1.2 is usually considered indicative of good arterial flow in the absence of other clinical indicators for arterial disease. An ABPI of less than 0.8 and a clinical picture of arterial disease should be considered as arterial insufficiency. An ABPI above 1.2 is suggestive of possible arterial calcification. ABPI = $\frac{\text{highest systolic foot pressure}}{\text{Highest systolic brachial blood pressure}}$
Duplex ultrasound[30]	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.[42]
Photoplethysmography (PPG)[30]	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 requires the patient to perform calf muscle pump exercises for brief periods followed by rest.[43] 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[33,35]	A non-invasive test that measures the red and infrared light absorption of oxygenated and deoxygenated haemoglobin in a digit. Oxygenated haemoglobin absorbs more infrared light and allows more red light to pass through a digit. Deoxygenated haemoglobin 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.[33,35]
Toe brachial pressure index (TBPI)	A non-invasive test that 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 highest brachial systolic pressure, 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 which may occur in patients with diabetes and renal disease.[44]
Transcutaneous oxygen ($TCPO_2$)[30]	Measures the amount of oxygen reaching the skin through blood circulation. There is insufficient evidence to recommend this investigation as the primary diagnostic test.[33,35]

Doppler ultrasound measurement of ABPI is the investigation most frequently used to identify arterial aetiology.[25,32-35] However, results can be unreliable when ABPI is conducted by untrained health professionals and in patients with calcification or diabetes.[34] It may also be difficult to perform accurately in patients with severe oedema, lymphoedema, very painful ulcers or extensive ulceration.[35]

TBPI may prove more accurate for identifying arterial perfusion in the feet and toes of patients with diabetes and renal disease with an ABPI of greater than 1.3 mmHg.[44]

Pulse oximetry could be considered to support the diagnosis of a venous ulcer; however, there is insufficient evidence (one low-quality study) to recommend this investigation as a primary diagnostic tool.[33,35]

Biochemical analysis

Appropriate biochemical analysis may include:

- blood glucose[25,30,32,34]
- haemoglobin[30]
- urea and electrolytes[30]
- serum albumin[30]
- lipids[30]
- rheumatoid factor[30]
- auto antibodies[30]
- white blood cell count[30]
- erythroctye sedimentation rate[30]
- C-reactive protein[30]
- liver function tests.[30]

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 bacteriological analysis[30]
- wound biopsy if malignancy or other aetiology is suspected.[30,33,34]

Recommendation

Patients with a non-healing or atypical leg ulcer should be referred for consideration of biopsy. (CBR)

Practice points

- Bacterial swabs should only be taken when the ulcer shows clinical signs of infection.[33,34]
- A structured, systematic leg ulcer assessment tool can assist in a clearly documented, accurate and comprehensive assessment. An example of an appropriate tool is the NZWCS Venous Ulcer Clinical Pathway[31] and its companion tool the Venous Leg Ulcer Assessment Form.[45]

Supporting literature

The literature search identified one low-quality study on pulse oximetry. No research was identified on other assessments for VLUs.

A low-quality observational cohort trial[35] investigated the reliability of pulse oximetry in assessing patients before 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.[35] *(Level III evidence)*

One international clinical guideline based on an SR of the literature also found no evidence of a level above case reports and non-analytical studies related to investigations besides pulse oximetry (one case control study) to support the diagnosis of a VLU. The guideline recommended the use of ABPI to assess for presence of arterial disease and provided evidence from a cohort trial conducted in patients with vascular disease (but not VLUs) to support the recommendation. The guideline also made a recommendation based on non-analytical trials that non-healing or atypical ulcers should be referred for consideration of biopsy.[33] *(Expert opinion)*

6.2 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 include:[46]

- peripheral artery disease
- malignancy
- blood disorders
- infection
- metabolic disorders
- iatrogenic effects
- self-harm
- hypertension
- autoimmunity.

The CEAP classification is an international consensus method of assessing venous disease. It incorporates clinical, 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 or more active VLUs 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.

Table 6.3: CEAP clinical classification[47]	
C0	No signs of venous disease
C1	Telangiectasias or reticular veins
C2	Varicose veins
C3	Presence of oedema
C4a	Eczema or pigmentation
C4b	Lipodermatosclerosis or atrophie blanche
C5	Evidence of a healed VLU
C6	Active VLU

Recommendation

Use CEAP classification to evaluate and classify venous disease. (CBR)

Practice points

- Other pathophysiology should be considered when VLUs fail to heal, or if they recur or remain persistently infected. Appropriate investigations include plain X-rays, bone scan or magnetic resonance imaging (MRI). 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 four weeks[40]) the diagnosis should be reviewed.

6.3 When should a patient with a venous leg ulcer be referred to a specialist?

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 literature review addressed referral of patients with VLUs. The Expert Working Committee reached consensus that referral to specialists should be considered for some patients. This opinion was supported by an international clinical guideline[33] that also found no high-level evidence.

Recommendation

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

Possible indicators for specialist referral include:

- diagnostic uncertainty[34]
- atypical ulcer characteristics or location[33]
- suspicion of malignancy[33,34]
- treatment of underlying conditions including diabetes, rheumatoid arthritis and vasculitis[33,34]
- peripheral arterial disease indicated by an ABPI less than 0.8[33,34]
- ABPI above 1.2[34]
- contact dermatitis[33,34]
- ulcers that have not healed within three months[34]
- recurring ulceration[34]
- healed ulcers with a view to venous surgery[34]
- antibiotic-resistant infected ulcers
- ulcers causing uncontrolled pain.

Practice points

- Early referral to specialists and/or a leg ulcer clinic can help 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 leg ulcer clinic as soon as possible.
- In locations where specialist services are not readily available (for example, rural or remote areas) 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.[48] However, this is not to be considered a replacement for specialist review.
- Offer investigations of venous disease in patients with healed VLUs and no previous diagnosis.

Supporting literature

The literature search did not identify any research on diagnosis of VLUs. One international clinical guideline based on an SR of the literature also found no evidence of a level above case reports and non-analytical studies related referral of patients with a VLU to specialist services. The guideline suggested that early referral should be considered where there was suspicion of malignancy, in patients with arterial disease, diabetes, vasculitis, rheumatoid arthritis, atypical ulcer distribution or in the case of non-healing ulcers.[33] *(Expert opinion)*

7. MANAGEMENT OF PAIN ASSOCIATED WITH VENOUS LEG ULCERS

What are the most effective interventions to manage pain associated with VLUs?

7.1 Pain management

Patients with VLUs regularly report moderate to severe pain using various descriptors. Venous ulcers are often reported to be particularly painful at dressing changes. Increased pain can increase healing times by decreasing patient concordance with management strategies (for example, compression, dressing attendance and exercise). Adequate pain management is essential to promote QOL and VLU healing.[34]

It is vital to conduct an initial assessment of wound-related pain and frequently reassess. A management plan should be developed and regularly reviewed.[33,49] The patient should be prescribed adequate analgesia and pain management strategies and be referred to a pain specialist when pain is not managed effectively. No high-level research on the most appropriate general pain management strategies for VLUs was identified; however, the Expert Working Committee reached consensus that pain management is an important aspect of holistic care. This consensus recommendation was supported by a recent literature review[49] and an international evidence-based VLU guideline[33], both of which highlight the importance of adequate pain management.

Recommendation

Provide adequate pain management to promote QOL and VLU healing. (CBR)

7.2 EMLA® cream

EMLA® cream is a topical anaesthetic agent combining lignocaine and prilocaine. It is absorbed through the skin or ulcer to produce a numbing effect before painful procedures including wound debridement and dressing changes. It is also appropriate to use before skin grafting.[50] 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 consistently showing a moderate effect in relieving pain.[51]

Recommendation

When there are no contraindications, apply EMLA® cream to reduce pain associated with the debridement of VLUs. (Grade A)

Caution

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.

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.[50] 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.[52] The manufacturer reports that rarely a serious allergic reaction can occur, and when used in large doses there is a risk of methaemoglobinaemia.[50]

Practice points

- 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 prior to debridement.
- Apply EMLA® cream according to the manufacturer's instructions.
- EMLA® cream should be applied 30 minutes before debriding the VLU.[50]
- EMLA® cream should be covered with a dressing (such as film) following application. It is also available as a patch that does not require additional dressings.[50]

Evidence summary

A good-quality meta-analysis[51] 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 VLUs less than 50 cm² 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 visual analogue scale (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 before the procedure.[51] *(Level I evidence)*

A total of 159 participants were treated with EMLA® 5% cream 30 minutes before 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 the cream was removed (OR 1.72, 95% CI 0.74 to 4.01, p=0.21) or itching when the cream was removed (OR 1.68, 95% CI 0.64, 4.38, p=0.29).[51] *(Level I evidence)*

7.3 Electrotherapy

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.[53,54] 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.[53] Two low-quality RCTs reported the pain relieving effect of electrotherapy.

Recommendation

Electrotherapy could be considered for reducing pain from VLUs. (Grade C)

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.[55] Electrotherapy is contraindicated in patients with electrical implants (for example, pacemakers), epilepsy, malignancy or who are pregnant. Electrotherapy should be used with caution in patients with impaired circulation.[56]

Practice points

- If a patient is experiencing moderate to severe pain, the ulcer and its management, and the patient's pain management plan should be reviewed.

Evidence summary

A low-quality RCT[57] 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 the four-month follow-up (p=0.01) and was also significant compared with 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.[57] *(Level II evidence)*

A low-quality trial[55] 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 the eight-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.[55] *(Level II evidence)*

8. MANAGEMENT OF VENOUS LEG ULCERS

What are the effective pharmacological and non-pharmacological interventions for the management of VLUs?

8.1 Manage the patient

8.1.1 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 an SR reporting various interventions including support groups to improve knowledge and concordance with therapy. An additional, low-quality RCT investigated the effect of written education material in improving knowledge of patients with VLUs.

Recommendation

Provide patients with appropriate education on their condition and its management. (Grade C)

Practice points

- Both verbal and written education leads to improvements in patient knowledge about management of their VLU.[58]
- 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 comorbidities (for example, diabetes).
- Leg ulcer support groups provide patients with education and psychosocial support to manage their ongoing disease, although they are not available in all locations.
- Patients in rural or remote areas may consider accessing online supports.

Evidence summary

A low-quality RCT[58] investigated the effectiveness of written information in improving the knowledge patients with VLU have about 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 four to six 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.[58] *(Level II evidence)*

A moderate-quality SR[59] 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 patient support groups focused on social interaction, patient participation, role modelling and interactive education (early detection and prevention). Although methods of assessment were not reported, failure of patients to initiate or continue with recommended therapies reduced from 17% at commencement of the clubs to 5% after 11 months. Of those patients who failed to concord with recommended therapy by the end of the trial, the majority of patients had concurrent diagnosis of dementia. An audit of similar clinics reported only three out of 10 patients who had attended a support group failed to implement recommendations for 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 (for example, patient selection) seem likely to have influenced the results.[59] *(Level I evidence)*

8.1.2 Psychosocial support

Chronic disease is reported to have a negative psychosocial impact. The literature reported patients with VLUs may be at an increased risk of negative psychosocial outcomes including depression, low self-esteem, social isolation, fear and anger. Pain, functional limitations, impact of compression bandaging (for example, 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.[36,60]

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

Recommendation

Provide psychosocial assessment and support as an essential component in the patient's management. (CBR)

Practice points

- Include patients in the development of their management plan. This may increase the feasibility of the plan and the patient's concordance with therapy.[60]
- Provide patients with clear information about their own progress (for example, graphs of wound size). This may contribute to patient concordance with management.[60]
- QOL scales specific to populations with VLU and/or venous disease (for example, the CWIS and CVIQ) include assessment of psychosocial factors.[36]

- Support groups provide patients with education and support to manage their ongoing disease, although they are not available in all locations.
- Patients in rural or remote areas may consider accessing online supports.

Supporting literature

The literature search did not identify evidence on strategies to provide psychosocial support; however, the research acknowledged that VLUs impacts QOL.

A low-quality SR[36] 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.[36] The review did not investigate the use of such tools. *(Level I evidence)*

A moderate-quality qualitative SR[60] 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 (for example, 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 (for example, 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 (for example, 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 a holistic assessment before recommending therapy was reported as a factor that may increase the relevance of interventions to the patient's lifestyle. Ensuring the patient had a pain management plan, particularly before commencing compression therapy, was considered important. Providing the patient with knowledge (for example, 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 (for example, healing rates, reduction in oedema) with the patient to improve motivation.[60] *(Level IV evidence)*

8.1.3 Elevation

Oedema associated with venous hypertension contributes to poor healing of VLUs. Elevation of lower limbs to reduce oedema may, therefore, increase healing;[61] however, there is no research conducted in patients with VLUs.

Two low-quality RCTs investigating the effect of elevation were identified in the literature search. Trials reported consistent changes to microcirculation associated with elevation; however, this did not translate to a significant improvement in ulcer healing in one trial. The Expert Working Committee recommends that elevation is appropriate to incorporate into a VLU management plan.

Recommendation

Elevate the patient's leg to promote changes in microcirculation and decrease lower limb oedema. (Grade C)

Practice points

- For optimal effect, 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.[62]

Evidence summary

In a small observational trial[62] the relationship between VLU healing and time spent elevating the leg was investigated. Participants (n=29) had VLUs of at least six weeks' duration and an ABPI above 0.9. At baseline the median ulcer size for participants was 2.8 cm^2. Exclusion criteria were vasculitis; renal, hepatic or haematological disease; and those taking corticosteroids. Participants wore a validated data-logging device for six weeks, which recorded time spent elevating limbs and the angle of elevation. Ulcers were measured weekly using wound tracings. The median ulcer percentage reduction over six 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 limited advantages from elevation above the concurrent four-layer compression bandaging participants wore; or that the intermittent elevation regimen was insufficient to achieve benefit.[62] *(Level II evidence)*

Another small prospective trial[61] investigated the effect on microcirculation of the skin of elevated limbs by participants with VLUs. Participants (n=13) with VLUs of more than two 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, four hours after 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.[61] *(Level II evidence)*

8.1.4 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.[63-65]

The exercises reported in the literature review were implemented in conjunction with compression therapy and consisted of two different regimens:

- active planter flexion using resistance (4 kg) implemented under supervision for a minimum of seven days, with the exercises performed for a minimum of three sets daily of six minutes length[66]
- heel raises conducted in three sets at 80% maximum repetitions on alternate days for 12 weeks.[65]

The evidence underpinning this recommendation comes from two small RCTs conducted in participants with VLU. The studies indicated that exercise designed to improve calf muscle strength and mobility has an effect in improving calf muscle function; however, the relationship to ulcer healing requires further research. The Expert Working Committee recommends progressive resistance exercise be incorporated into the patient's management plan.

Recommendation

Progressive resistance exercise may improve calf muscle function. (Grade C)

Practice points

- Exercises should be designed to improve calf muscle strength, for example weight-bearing foot and ankle exercises and heel-toe walking. Ensure that the patient can perform exercises in a safe manner and with consideration to personal tolerance levels.
- 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 summary

A good-quality, small RCT[65] investigated the effectiveness of progressive resistance exercises in improving calf muscle pump function and healing VLUs. Participants were adults with VLUs recruited from a leg ulcer clinic that were able to perform heel-raise exercises and did not have a history of rheumatoid arthritis. Participants were randomised to receive a home-based exercise regimen (n=21) consisting of an individualised program of heel-raise exercises, progressively adjusted throughout the 12-week study to ensure participants performed three sets of repetitions at 80% of individual maximum. The usual care group received home visits on the same regimen as the exercise group. Both groups received compression therapy. Adherence to the exercise program was reported as high (above 80%). After 12 weeks, there were no significant differences between the groups in change in ejection volume, venous volume, venous filling index, residual volume or residual volume fraction. Compared with the usual care group, the exercise group had a significant improvement in ejection fraction (mean difference in change 18.5%, 95% CI 0.03 to 36.6%, p<0.05). These results suggested that the exercise program contributed to improvement in calf muscle strength but not in overall venous function. The usual care group had a greater reduction in ulcer area; however, there was no significant difference between the groups in change in ulcer area (between group difference of 5.9%, 95% CI –4.8 to 36.5%, p=0.13). There was no significant difference in time to complete ulcer healing (OR of ulcer healing 0.55, 95% CI 0.16 to 1.95). The exercise group experienced more adverse events including infection, pain, ulcer or skin deterioration and development of new ulcers was higher in the exercise group (OR of an adverse event 1.32, 95% CI 0.95 to 1.85). The results suggested that small improvements in calf muscle strength were not associated with a significant improvement in VLU healing.[65] *(Level II evidence)*

A low-quality RCT[66] 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 six minutes daily for seven 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 seven (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.[66] *(Level II evidence)*

8.1.5 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.[67]

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. This opinion was supported by a best practice guideline for the management of general chronic wounds.[67]

Recommendation

Optimise the patient's nutrition and hydration to promote healing in patients with VLUs. (CBR)

Practice points

- Nutritional requirements should be based on energy/caloric requirements with additional consideration to the stress response to illness.[67]
- 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.[67]
- There is no research on the effect of L-arginine supplements in improving VLU healing.
- Oral zinc supplements are not effective for improving wound healing unless zinc deficiency is diagnosed (see recommendation 12.8).
- Patients with heavily exudating VLUs may require an increase in fluid intake[67] if they have no fluid restrictions related to comorbidities, particularly in warmer weather.

- Patients with heavily exudating VLUs may require closer electrolyte and albumin management, especially in warmer climates.

Supporting literature

The research did not identify evidence on nutritional interventions for patients with a VLU. One clinical guideline on the management of pressure ulcers highlighted the importance of promoting optimal hydration and nutrition to promote healing. The guideline provided recommendations on basic nutritional needs in patients with exudating ulcers of all sorts.[67] *(Evidence-based guideline in similar population)*

8.2 Prepare the leg and ulcer

8.2.1 Skin and ulcer hygiene

Leg and ulcer hygiene is important in maintaining overall skin integrity. Regular washing of the ulcer removes exudate and topical product residue that may aggravate peri-ulcer 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 bandage changes to reduce odour and promote skin integrity.

The literature search did not identify research specific to the maintenance of VLU hygiene; however, there is extensive literature related to the care of chronic wounds in general. The full body of evidence in this field was beyond the scope of this guideline, hence the recommendation is based on expert opinion and supported by an evidence-based guideline for the management of chronic wounds in general.[30] An international clinical guideline on VLU management[33] and a guideline for managing general chronic wounds[30] provided support for this recommendation.

Recommendation

Cleanse the leg and ulcer when dressings and bandages are changed. (CBR)

Practice points

Leg hygiene

- Cleanse the leg with a pH-appropriate skin cleanser. To obtain optimal ulcer and skin pH, avoid the use of alkaline soaps and cleansers.[30]
- 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:[30]
  - showering in potable water
  - washing the leg in a dedicated bowl of potable water
  - wiping the leg with a moist cloth.
- Applying a moisturiser contributes to the maintenance of the healthy skin.

Ulcer care

- Avoid cleansing the ulcer aggressively unless the goal of care is debridement or removal of foreign bodies.[30]
- Clean wound management technique (using potable water) should be used in most instances. Aseptic wound management techniques should be considered when:[30]
  - the patient is immunosuppressed
  - the wound-healing environment is compromised.

Supporting literature

The literature search did not identify any research on wound cleansing conducted in populations with a VLU. One international clinical guideline based on an SR of the literature also found no evidence related to maintenance of skin and ulcer hygiene. The guideline suggested that ulcers should be washed regularly in tap water and carefully dried.[33] *(Expert opinion)*

One guideline on the management of chronic wounds provided evidence-based guidance on skin and wound hygiene. The guideline recommended washing in normal water unless the patient was immunocompromised and highlighted the importance of regular skin care of surrounding areas.[30] *(Evidence-based guideline in similar population)*

8.2.2 Management of surrounding skin

Prevalence of venous eczema in patients with venous hypertension is between 3% and 12%.[68] Red, inflamed skin with flakiness or scaling indicates venous eczema. The skin may have blistering or cuts. Venous eczema can result from venous hypertension. Hypersensitivity to topical products also occurs frequently in patients with VLUs, particularly those of long duration requiring ongoing dressings.[69]

The Expert Working Committee recommends venous eczema be investigated and managed promptly to prevent skin breakdown, relieve discomfort and promote overall healing of VLUs.

The evidence underpinning the recommendation that topical barrier preparations are effective for reducing peri-ulcer erythema was two low-quality trials that had conflicting findings regarding the effectiveness in reducing erythema.

Recommendations

Treat venous eczema and impaired peri-ulcer skin promptly. (CBR)

Consider using topical barrier preparations to reduce peri-ulcer erythematous maceration in patients with VLU. (Grade C)

Practice points

- Red skin near the ulcer may be related to infection, venous eczema and/or hypersensitivity that will require further investigation and treatment.
- Review current topical agents with consideration to hypersensitivity.
- Consider applying a topical barrier preparation to the peri-ulcer skin to protect it from exudate.[33]
- Venous eczema may be treated with a wide range of products including:[33]
  - topical corticosteroids
  - topical zinc-impregnated bandages (see recommendation 8.4.2)
  - other dermatological preparations.

Evidence summary

A low-quality trial[70] compared the effectiveness of Cavilon™ No Sting Barrier Film (NSBF) with 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 four weeks' 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 NSBF (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.[70] *(Level II evidence)*

A second, low-quality RCT[71] 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 two 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 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.[71] *(Level II evidence)*

8.2.3 Wound debridement

Debridement is commonly performed on VLUs to remove non-viable or infected tissue and debris in order to prepare the wound bed to receive therapeutic healing products (wound bed preparation) with an aim of maximising the healing process. Non-viable tissue can prolong the healing process by increasing inflammation, levels of bacteria and toxins, and inhibiting re-epithelialisation.[72] The most commonly used methods of debridement are surgical (sharp), conservative sharp, autolytic, larval, enzymatic and mechanical.[73] Surgical debridement, which is beyond the scope of this guideline, is rapid, although it requires either general or topical anaesthetic and can be painful.[72,73] Conservative sharp debridement is the removal of loose avascular 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.[72,73] 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.[72-74] Larval debridement is the application of sterile, green bottle fly (*Lucilia sericata*) 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 moderate- and low-quality trials consistently indicated that these products are not more effective than placebo or autolytic products in healing VLUs.[75] There was insufficient evidence to make a recommendation on other methods of debriding.

Recommendations

Enzymatic debriding agents have no effect in promoting healing in VLUs. (Grade C)

Consider other debridement methods to prepare the ulcer bed for healing. (CBR)

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.[76]

Practice points

- Mechanical debridement methods, such as ultrasound, high-pressure irrigation or wet to dry dressings, 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 wound debridement should only be performed by health professionals with appropriate training.

Evidence summary

One moderate-quality RCT[74] 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 one 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.[74] *(Level II evidence)*

A low-quality RCT[72] investigated the comparative effectiveness of an enzymatic debriding agent (n=27) with an autolytic debriding product (n=15). Participants were adults with CVI and a VLU of at least six weeks' 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 seven 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.[72] *(Level II evidence)*

In another low-quality RCT,[77] the effectiveness of an enzymatic debriding agent, streptokinase-streptodornase, in cleansing ulcers of pus and debris was compared with 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. A blinded observer evaluated the ulcers using a four-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 were significantly more ulcers in the treatment group that had small or no amounts of pus and debris compared with 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 the groups 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.[77] *(Level II evidence)*

Supporting literature

The literature search did not identify any research on the effectiveness of other methods of debriding VLUs. One international clinical guideline based on an SR of the literature also found no evidence related to debridement. The guideline suggests that removal of unhealthy tissue reduces risk of infection and promotes healing; however, no guidance on the most appropriate method is provided.[33] *(Expert opinion)*

One Australian guideline provided evidence-based guidance on wound management. The guideline recommended performing adequate wound debridement to minimise wound contamination by exogenous micro-organisms.[30] *(Evidence-based guideline in similar population)*

8.3 Treat clinical infection

Wound infection interrupts the normal healing process. It is imperative that an assessment of the patient and their ulcer is performed to determine infection, its severity and appropriate subsequent management is implemented. Antimicrobial therapy, which includes topical agents such as cadexomer iodine, silver,

honey and other topical antiseptics, as well as systemic antibiotics, can be prescribed when a wound exhibits signs of infection. **All products should be used in accordance with the manufacturer's directions.**

8.3.1 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 promote autolytic debridement of the wound bed.[78]

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.[78] Results were generally consistent and showed that there is a moderate effect on ulcer healing.

Recommendation

Cadexomer iodine could be used to promote healing in VLUs when there is known increased microbial burden. (Grade B)

Caution

Unless the patient has a hypersensitivity to iodine, cadexomer iodine is usually not associated with significant adverse events.[79,80] Cadexomer iodine ointments and impregnated dressings should not be used in patients with a history of Hashimoto's thyroiditis, Graves' disease, lithium medications, 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.[80] In some trials, patients treated with topical cadexomer iodine have experienced local burning sensations;[79] however, this was not reported in the trials included in this review.

Practice points

- Cadexomer iodine should not be used for longer than three months continuously.[80]
- Cadexomer iodine dressings should only be used when there is evidence of heavy bacterial load/local wound infection and these dressings should be stopped once local infection has been controlled.
- Cadexomer iodine should not be covered with povidone iodine-soaked gauze/tulle gras as this practice results in the dumping of iodine, increasing toxicity.

Evidence summary

One good-quality Cochrane review[78] reported the results of 10 moderate-quality RCTs investigating the use of the antimicrobial agent cadexomer iodine for the treatment of VLUs. *(Level I evidence)*

Ten RCTs investigated the use of cadexomer iodine. Four trials compared cadexomer iodine with standard care, with no trial reporting baseline infection status. In one trial (n=28) patients received alternate day dressings. After four weeks there was no significant difference in the 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 six 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 (weighted mean difference [WMD] 0.47 cm^2 per week, 95% CI 0.26 to 0.69, p=0.00002).[78] *(Level II evidence)*

Three trials compared cadexomer iodine and compression with compression alone. The first two trials (total n=132) reported complete healing at four and six 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 colonisation with *Staphylococcus aureus* in ulcers treated with cadexomer iodine (RR 31.31, 95% CI 1.95 to 503.29, p=0.015).[78] *(Level II evidence)*

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 were only 27 participants and 30% were excluded from the final analysis. One trial (n=153) compared cadexomer iodine with 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 compared with 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).[78] *(Level II evidence)*

A moderate-quality, non-blinded RCT[81] compared the effectiveness in healing VLUs of a silver dressing with a cadexomer iodine dressing. Participants were recruited from community nursing agencies. The inclusion criteria included having a lower leg ulcer not more than 15 cm^2, not being treated with topical antiseptics within one week or antibiotics within two days of inclusion and not using corticosteroids. Participants were also required to have at least one clinical sign of infection or critical colonisation (for example, cellulitis, suppuration, sepsis, bacteraemia, malodour, new slough, delayed healing) Patients with malignancy or diabetes were excluded. Participants received either a nanocrystalline silver dressing (n=140) or a cadexomer iodine dressing (n=141). These dressing were applied until signs of infection or colonisation were absent for one week. After this time a non-antimicrobial dressing was applied. If signs of infection or colonisation reappeared within the study period, the silver or cadexomer iodine dressing (maintaining the same treatment to which the patient was randomised) was reapplied. All participants received concurrent compression therapy. After randomisation, the groups were non-equivalent at baseline for average total wound surface area and granulation tissue area, with the silver group having significantly smaller average ulcer area and granulation area (p<0.05); however, this was considered in the analysis methods. The groups were equivalent for other baseline variables including signs of infection, wound duration and wound depth. At 12 weeks, there was no significant difference between the two groups in the total number of healed ulcers (silver 64% healed, iodine 63% healed, p>0.05). Analysis of healing rate showed that, although there was no difference in overall healing in the study period, the ulcers treated with silver had faster healing within the first two weeks of treatment. Additional analysis showed that the effect of silver observed in the first two weeks of treatment was evident for ulcers that did not heal in the study period (p<0.01), ulcers of shorter duration (p<0.01), ulcers of longer duration (p<0.01), smaller ulcers (p<0.01) and larger ulcers (p<0.01). The effect was not evident in ulcers that did heal within the 12-week study time frame. The researchers concluded that the silver antimicrobial would be a superior choice for hard-to-heal ulcers (larger ulcers, those with heavy exudate and those of longer duration).[81] *(Level II evidence)*

8.3.2 Topical 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, amount of silver and the mode of delivery differ with a variety of products.[82,83]

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.[84]

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. However, an additional, moderate-quality RCT found some effect for short-term use of silver, indicating inconsistencies in the research. There was insufficient evidence on bacterial load as an outcome measure.

Recommendation

Silver products offer no benefit over standard care in reducing the healing time of VLUs. (Grade C)

Caution

Potential renal toxicity should be considered when using topical silver agents for extended periods (for example, greater than four weeks) on large wound beds. The risk appears to be low but caution is warranted. As with other antimicrobial therapies there is a risk of bacterial resistance with extended use of silver products.[85]

Practice points

- For trained health professionals or patients who choose to use silver, despite the current lack of high-level evidence for an effect in healing VLUs:
  - use silver products as directed by the manufacturer
  - there is insufficient evidence to indicate any one specific silver product is superior to others.
- Colloidal silver, either internally or topically, is not recommended.

Evidence summary

A good-quality SR[82] 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 moderate to low quality.[82] *(Level I evidence)*

One RCT in participants with ulcers of at least three months' duration compared silver sulphadiazine cream (n=28) with both tripeptide copper-complex cream (n=29) and placebo cream (n=29) applied to VLU for a treatment period of four weeks. None of the ulcers treated with tripeptide copper-complex cream and one ulcer treated with placebo cream healed, compared with 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 with 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 with 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 with 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 with hydrocolloid dressing alone.[82] *(Level II evidence)*

Six trials in this review compared silver-containing dressings with conventional dressings, a calcium alginate dressing or different types of silver dressings. One low-quality study compared a silver foam dressing (n=65) with a hydrocellular foam (n=64) in patients with leg ulcers of mixed aetiology. Although the median relative reduction in ulcer area was significantly larger in the group treated with the silver product (45% vs 25% p=0.034) after four 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 with 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).[82] *(Level II evidence)*

One large trial (n=415) that compared the treatment of mixed aetiology ulcers with silver-foam dressings compared with 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 for median ulcer sizes.[82] *(Level II evidence)*

Another low-quality trial compared silver dressing (n=38) with a calcium alginate dressing (n=33) for treating VLUs for four 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).[82] *(Level II evidence)*

A moderate-quality SR[86] reported findings from three RCTs that 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 with 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. *(Level II evidence)*

In addition, a low-quality RCT[87] investigated the effectiveness of a silver dressing compared with a regular foam. Participants had VLUs with clinical signs of infection and a mean size of 2 cm^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 regular foam (n=21) covered in short-stretch bandaging for nine weeks. Randomisation and allocation concealment techniques were not reported and baseline equivalence for ulcer duration and concurrent medical conditions was unclear. After nine weeks, 81% of the treatment group compared with 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.[87] *(Level II evidence)*

A moderate-quality, non-blinded RCT[81] compared the effectiveness in healing VLUs of a silver dressing with a cadexomer iodine dressing. The trial is reported in full in section 7.4.1 under cadexomer iodine. The trial found that, although the healing rate over 12 weeks was not significantly different for ulcers treated with silver compared with cadexomer iodine, ulcers achieved faster healing within the first two weeks of treatment with a silver dressing.[81] *(Level II evidence)*

8.3.3 Topical honey

Honey is a supersaturated sugar solution containing glucose, fructose, sucrose and water. Honey has been used for treating wounds for centuries.[88] Honey is thought to aid in wound healing through an osmotic effect that draws fluid from the wound to the wound tissue surface, through the promotion of a moist healing environment and the lowering of wound pH, all of which aid in autolysis.[89] More recently it has been proposed for use due to potential antibacterial properties, particularly Manuka honey, a variety found in Australia and New Zealand.[88]

The recommendation that honey offers no benefits over standard therapy for healing VLUs is underpinned by a good-quality SR reporting two good-quality RCTs that had consistent results. The studies were not designed to assess the effect of honey as a debriding agent, and although the studies were not designed to assess the antibacterial effect of honey, VLUs treated with honey were reported to have no reduction in rate of infection.

Recommendation

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.[90] An SR found that adverse events (for example, ulcer pain, deterioration of the VLU and increased exudate) were more likely to occur in VLUs treated with honey compared with those treated with hydrogel or standard dressings and there was no difference in infection rates.[88]

Practice points

- For trained health professionals or patients who choose to use honey despite the current lack of evidence for an effect in healing VLUs:
  - use honey products according to the manufacturer's instructions
  - 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 sterilising processes will destroy the UMF in the honey.
- Honey may increase exudate levels thus warranting more frequent dressing changes.

Evidence summary

A good-quality Cochrane review[88] 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 intention to treat (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 (111 vs 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 four and 12 weeks is more effective than standard care for treating VLUs. *(Level I evidence)*

8.3.4 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 (for example, until the next time the dressing is changed). Most products come in a range of forms or concentrations designed to promote healing through the reduction in or eradication of bacteria in the wound.[78]

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 10 moderate-quality studies with small numbers of participants that were reported in narrative summary in a good-quality Cochrane SR.[78] Trials generally reported the primary outcome measure as healing and in some trials the bacterial status of VLUs at baseline was unclear. The Expert Working Committee recommends that there may be a role for some topical antimicrobials where there is known increased microbial burden.

Recommendations

Topical antimicrobial agents should not be used in the standard care of VLUs healing with no clinical signs of infection. (Grade B)

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

Caution

The Expert Working Committee does not recommend the use of hydrogen peroxide in wound management. Deaths have been reported as a result of irrigation of closed cavity wounds with hydrogen peroxide.[91-93]

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.[93-95]

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.[96] It has been demonstrated that there is no dilution of acetic acid that is toxic to bacteria without being toxic to fibroblasts.[95]

Practice points

- When using povidone iodine 10% solution it should be used at full concentration and rinsed off after two to five minutes.[97]
- Topical antiseptic solutions should generally only be used for treatment of topical contamination or minor skin infections and should be avoided on clean, healing ulcers.[98]
- The length of treatment with topical antimicrobials should be determined by the response of the VLU and the patient.[98]
- 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 summary

One good-quality Cochrane review[78] 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. *(Level I evidence)*

Povidone iodine

Five trials reported the effectiveness of povidone iodine. Three trials compared povidone iodine plus compression with hydrocolloid dressing plus compression. In the first trial (n=200) participants were stratified according to ulcer size. For ulcers over 4 cm 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 per cent 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 with either hydrocolloid or paraffin gauze and found no differences in rate of healing.[78] *(Level II evidence)*

One trial (n=100) compared povidone iodine with dextranomer in participants with ulcers colonised with bacteria at baseline. Mean time to healing was significantly shorter in those treated with dextranomer (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 with recombinant tissue growth factor applied as a spray solution. After four weeks there was no significant difference in number of ulcers healed (RR 0.57, 96% CI 0.22 to 1.52, p=0.26).[78] *(Level II evidence)*

Peroxides

Three trials reported on the use of peroxides. One trial (n=31) had three different arms comparing different concentrations of benzoyl peroxide with saline dressing in VLUs with unknown infection status at baseline. After 42 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 with standard care plus compression. In both trials patients received systemic antibiotics before 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 area in those treated with peroxide (p<0.05) and the second trial also favoured peroxide (p<0.005).[78] Deaths associated with hydrogen peroxide used in wound care have been reported in the literature.[91-93] *(Level II evidence)*

Other treatments

One trial (n=253) investigated daily treatment with ethacridine lactate 0.1% lotion plus compression compared with placebo lotion plus compression and found ethacridine lactate was associated with significantly greater reduction in ulcer area 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 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 six weeks there was no significant difference in time to healing.[78] *(Level II evidence)*

Overall, the SR provided evidence from moderate-quality trials that most topical antimicrobial agents have no significant effect in the healing of VLUs.[78] 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.[78]

An additional, moderate-quality SR[86] 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. The findings were presented in a narrative summary.[86] *(Level I evidence)*

The review[86] reported seven small (fewer 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 colonisation 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 with 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 10 cm^2. Withdrawals due to local irritation were similar between the groups (allopurinol=1, placebo=1, dimethyl sulphoxide=2).[86]

8.3.5 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.

Recommendation

Use topical antibiotics judiciously in managing VLUs as there is a concern that their use is associated with antibiotic resistance and sensitivities. (CBR)

Caution

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

Practice points

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

8.3.6 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.[78]

Antibiotic resistance is a significant concern due to the overuse or inappropriate use of antibiotic therapy.[78,99] 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 with placebo.[78] 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 and showed that there is no effect on ulcer healing, and the one RCT that found an effect was small and of low quality.

Recommendation

Systemic antibiotics should not be used in the standard care of VLUs that show no clinical signs of infection. (Grade B)

Caution

Adverse effects for systemic antibiotics were not reported in the trials. Side effects include gastrointestinal tract (GIT) signs and symptoms and signs of allergic reaction (for example, skin rash, itching and, rarely, difficulty breathing). Interactions with other medications are common.[99] 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 points

- All ulcers should be assessed regularly for indicators of infection.[98]
- 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 binding.[98]
- The length of treatment with systemic antibiotics should be determined by the response of the ulcer and the patient.[98]
- For complex, unresponsive, recalcitrant or recurrent VLU infection, consider consulting a microbiologist or infectious disease specialist.[98]

Evidence summary

One good-quality Cochrane review[78] reported the results of five 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. *(Level I evidence)*

In one RCT participants (n=48) received co-trimoxazole, gentamicin or amikacin (according to sensitivities) for 10 days. At the 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).[78] *(Level II evidence)*

Two trials compared ciprofloxacin with standard care or placebo. In the first trial, participants (n=26) were eligible if they had VLUs colonised 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 the 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 the number of ulcers healed (RR 1.39, 95% CI 0.44 to 4.43, p=not reported). 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 with placebo (RR 8.65, 95% CI 1.76 to 42.60, p=0.008).[78] *(Level II evidence)*

One trial compared trimethoprim (n=12) to placebo (n=10) over 16 weeks. There was 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).[78] *(Level II evidence)*

One trial compared systemic amoxicillin with 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).[78] *(Level II evidence)*

One trial (n=59) compared levamisole two days per week for 20 weeks with 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 with 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.[78] *(Level II evidence)*

The SR[78] 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. *(Level II evidence)*

8.4 Select a dressing and topical treatment

8.4.1 Dressings

The dressing complements the main aim of therapy, which is compression.

Dressings or devices are applied to an ulcer in order to promote an optimal healing environment. Ulcer healing is based on the principles of moist wound healing and wound bed preparation.[100]

There is no evidence to suggest a superior dressing for promoting ulcer healing. 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.[101-103] Other potential benefits (for example, odour reduction) were not investigated in the research.

The recommendation that there is no specific superior dressing for managing VLUs is underpinned by five SRs[104-108] 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.

Recommendation

No specific dressing product is superior for reducing healing time in VLUs. Select dressings based on clinical assessment of the ulcer, cost, access and patient/health professional preferences. (Grade B)

Caution

Trials investigating the effectiveness of primary dressings were generally conducted in populations without clinically infected ulcers, 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.[100,103,106,109,110]

Practice points

- 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:[101-103,110,111]
  - ease of application and removal
  - ability to absorb exudate and odour
  - 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:
  - wound bed preparation:
    - ulcer size and location and tissue characteristics
    - level of bacterial burden
    - amount and type of wound exudate
  - patient tolerance and preference
  - skill and knowledge of the health professional
  - cost and availability
  - presence of pain and/or odour.
- Select a dressing that does not adhere to the wound bed.[30]
- 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 QOL.[102]
- If the wound is exudating heavily, select a dressing that is reported to have a high absorptive capacity.[101-103]
- Prolonged or continued heavy wound exudate should be investigated and managed appropriately.

Evidence summary

One good-quality SR[108] 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 the lack of evidence of superiority of any product, choice of dressing should be based on convenience, access and cost-effectiveness.[108] Results are summarised below. *(Level I evidence)*

Eight RCTs (n=792) comparing hydrocolloid dressings to low-adherent dressings on total ulcer healing over four to 12 weeks were included in meta-analysis. The difference in complete healing was not significant (eight trials, significant heterogeneity, RR 1.02, 95% CI 0.83 to 1.25, p=0.88; seven trials, no heterogeneity, RR 0.98, 95% CI 0.85 to 1.12). *(Level II evidence)*

Pooled results from four RCTs (n=311) comparing 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 with 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 eight 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.[108] *(Level II evidence)*

The results from two RCTs (n=203) comparing foam dressings with low-adherent dressings for 12 and 17 weeks were pooled in meta-analysis and showed no significant difference in healing (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).[108] *(Level II evidence)*

Five trials investigated hydrogel compared with 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 were two RCTs comparing different types of hydrogel; however, meta-analysis was not possible due to incomplete data. Results reported in the SR 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).[108] *(Level II evidence)*

One trial (n=60) comparing alginate with low-adherent dressings and another trial comparing two types of alginate dressings both showed no difference in healing rates.[108] One low-quality RCT (n=95) compared cadexomer iodine powder with standard treatment. There was a 34% reduction in mean percentage of ulcer area cadexomer iodine group compared with a 5% increase in the standard therapy group after six weeks of treatment. One RCT (n=24 ulcers) compared a hyaluronan-derivative fleece dressing with a paraffin gauze dressing used for eight 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 activated-charcoal dressing with a dressing applied according to the stage of healing and showed no significant difference between the two dressing types over six weeks.[108] *(Level II evidence)*

Another good-quality SR[112] supported the conclusions of the Palfreyman[108] 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[108] review, were generally of low- to moderate-quality. Nine RCTs compared hydrocolloid dressings with 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 with 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.[112] *(Level I evidence)*

A moderate-quality SR[107] 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 nine studies showed a statistically significant effect. Five RCTs investigating human skin equivalent (HSE) dressings were reported; however, the trials were heterogeneous and the 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 dressings, of which only two showed significant results. A pooled analysis from the eight RCTs using a random effects model favoured growth factor dressings over control dressings (for example, gauze pad, Adaptic™, hydrocolloid). Growth factor 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.[107] *(Level I evidence)*

A second, moderate-quality SR[106] 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.[107] 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 10 cm^2 and other trials limiting inclusion to ulcers less than 100 cm^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 eight RCTs (n=397) comparing hydrocolloid dressings with conventional dressings (for example, gauze with paraffin or povidone iodine, non-adherent knitted viscose, paraffin-soaked gauze) for 10 weeks to six 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 with either polyurethane, another hydrocolloid or alginate dressings for six 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 three RCTs (n=238) investigating polyurethane dressings compared with 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).[106] *(Level I evidence)*

One low-quality SR[105] 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 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 hydrofibre 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.[105] *(Level I evidence)*

One low- quality, unblinded RCT[104] investigated the efficacy of a biocellulose wound dressing (BWD XCELL®) compared with standard care of an Adaptic™ dressing in 24 patients diagnosed with CVI. These participants had VLUs of at least two months' duration and the VLUs were considered to require debridement. After 12 weeks of 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.[104] *(Level II evidence)*

A low-quality RCT[100] that failed to report methods of randomisation, allocation concealment or blinding or baseline comparability compared a lipidcolloid dressing (Urgotul®) with Duoderm® used in conjunction with compression for up to eight weeks. Participants (n=91) had an ABPI of at least 0.8, ulcer duration of two to 18 months and ulcer size between 4 and 40 cm^2. Ulcer area was measured weekly using wound tracings, photography and planimetry. At eight weeks there was no significant difference in reduction of ulcer surface area (Urogtul 61.3 ± 39.7% vs Duoderm 52.1 ± 66.2%) or mean time to healing (Urgotul 33.3 ± 11.0 days vs Duoderm 29.8 ± 7.1 days).[100] *(Level II evidence)*

A low-quality, unblinded RCT[111] compared the effectiveness of a lipidcolloid dressing impregnated with nano-oligosaccharide factor (NOSF) compared with an oxidised regenerated cellulose *(ORC)* dressing. Participants had an ABPI of at least 0.8, had been compliant with compression therapy for at least two months, had a mean ulcer duration of 11 months, a mean ulcer size at baseline of 10 cm^2 and 61% of ulcers were recurrent. Wounds were redressed every three days following mechanical debridement as required for 12 weeks or until the wound was completely re-epithelialised. 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 with 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.[111] *(Level II evidence)*

A low-quality, unblinded RCT[113] investigated healing rate of VLUs treated with an oxidised, regenerated cellulose collagen matrix dressing compared with 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 three months' duration and no systemic inflammatory disease or malignancy. The trial lasted for 12 weeks and wounds were assessed on days five, 14 and 28 for wound size (method not reported) and MMP-2, gelatinase, elastase and plasmin activity from exudate 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 with the control group; however, this did not translate to a significant difference in wound healing time. Adverse events were not reported.[113] *(Level II evidence)*

In a low-quality RCT[110], researchers investigated the effectiveness of a hydrocellular foam dressing compared with 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 seven days for 12 weeks or until complete ulcer healing was achieved. Wound tracings were performed every 14 days. There was no significant difference in primary outcome measures related to wound healing, including rate of healing (0.41 cm^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 (for example, 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 or ease of removal. *(Level II evidence)*

A low-quality RCT[109] 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 two 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 the 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). The findings may have been influenced by a high withdrawal rate (29.5%), primarily due to mild adverse events and the definition of complete healing, which referred to the entire limb rather than the reference ulcer. It is unlikely the study was sufficiently powered to measure an effect given the concurrent randomisation of compression therapy. Participants in both groups reported improved pain levels after dressing changes and progressively throughout the trial, with no between group differences. *(Level II evidence)*

Trials investigating ability of dressings to handle exudate

A low-quality RCT[103] investigated the ability of a hydropolymer dressing compared with an alginate dressing to manage heavy wound exudate from VLUs. 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 1 cm in depth and less than 11 cm 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 more than 20% of participants who withdrew from the trial due to adverse events. The results showed a significantly longer wear time for the hydropolymer dressing compared with the pooled alginate dressing groups (p=0.001) and no significant difference in healing rates. The findings should be considered cautiously because the dressing change protocol allowed for dressing changes for reasons unrelated to the dressing ability to control exudates (for example, the protocol included suspected infection, dressing displacement due to activity or dressing in place more than seven 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.[103] *(Level II evidence)*

A low-quality RCT[102] compared an extra absorbent dressing, (n=10) with an alginate dressing (n=9) for the management of heavily exudating VLUs for a maximum of six weeks. Participants had an ABPI of 0.8 or higher, ulcers no larger than 28 cm^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 with 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 QOL and decrease isolation for patients; however, this was not formally assessed in the trial.[102] *(Level II evidence)*

A low-quality RCT[101] compared the effectiveness of a hydrocapillary dressing with 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 four weeks' duration, which had a maximum size of 8 cm^2. Participants 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 the dressing leaked or estimates of absorption by weighing the dressing). Subjective ratings by patients of comfort favoured the hydrocapillary dressing (p<0.001). *(Level II evidence)*

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 with a traditional dressing to compare withdrawal rates and adverse events.[106] 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).[106] *(Level II evidence)*

A low-quality RCT[100] reported significantly more (p=0.039) adverse events including eczema and infection were recorded in the group treated with Duoderm compared with those treated with Urgotul. (23 adverse events vs 10 adverse events). *(Level II evidence)*

One low-quality RCT[103] reported significantly more adverse events for an alginate dressing compared with a hydropolymer dressing over a maximum treatment period of four 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 this change the adverse event rate was similar between the alginate group (19%) and hydropolymer dressing group (20%).[103] *(Level II evidence)*

A small, low-quality RCT[110] investigated the effectiveness and tolerability of a hydrocellular foam dressing (Versiva®) compared with composite foam dressing (Allevyn*) and reported on adverse events. Adverse events including maceration, erythema and eczema were experienced by 24% of participants in the group treated with the hydrocellular foam dressing and 29% of participants in the group treated with the foam dressing. There was no statistical difference between the groups.[110] *(Level II evidence)*

A low-quality RCT[109] 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. *(Level II evidence)*

8.4.2 Zinc-impregnated bandages

Zinc-impregnated bandages are thought to have an effect in the treatment of chronic wounds by stimulating epithelialisation.[114]

The literature search identified no SRs or RCTs specifically reporting on the effectiveness of zinc-impregnated bandages for treatment of VLUs. However, the Expert Working Committee recommends that these bandages could be used for managing non-infected VLUs in conjunction with compression. An evidence-based guideline[33] supports this opinion.

Recommendation

Consider using dressings or bandages impregnated with zinc oxide to provide comfort and promote epithelialisation of a healthy granulated superficial VLU. (CBR)

Practice points

- Zinc-impregnated bandages can be used to soothe venous eczema and associated inflammation[115] (see section 8.2.2).
- 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 of bandages and prevent skin damage.
- Apply zinc-impregnated bandages according to the manufacturer's directions.

Supporting literature

The literature search did not identify any research on zinc-impregnated bandages conducted in populations with a VLU. One international clinical guideline based on an SR of the literature also found no evidence related to zinc-impregnated bandages. The guideline suggested that zinc products have not been reported as sensitisers and could be considered for soothing and protecting skin.[33] *(Expert opinion)*

8.4.3 Topical pale shale oil

The literature search identified one trial that investigated the application of pale sulphonated shale oil (PSSO) for promoting healing in VLUs. PSSO derives from marine sediments in carbonised rock. It has a high hydrogen/carbon ratio and low nitrogen content. PSSO 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.[116] The evidence underpinning the recommendation that PSSO is effective for treating VLUs was one good-quality trial showing an effect in reducing VLU size, but no effect on management of fibrinous discharge, necrosis or pain.

Recommendation

Topical pale sulphonated shale oil could be used to promote healing in VLUs. (Grade C)

Caution

PSSO may cause minor skin irritation and has been reported as a flammable agent.[116] In the trial reported in the evidence base, participants experienced adverse skin reactions at the same rate as those treated with a placebo gel.[117]

Evidence summary

A good-quality trial[117] 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 3 cm^2. The exclusion criteria were severe cardiac, respiratory, gastrointestinal, liver or renal disease, malignancy, signs of wound infection and pregnancy or lactation. 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 two weeks. At the final assessment, after 20 weeks of treatment, the group treated with PSSO achieved a significant reduction in overall ulcer area compared with the placebo group (mean 6.2 cm^2 vs 10.8 cm^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 significant 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.[117] *(Level II evidence)*

8.5 Apply compression

Compression therapy aims to promote venous return, reduce venous pressure and prevent venous stasis. To achieve this, compression bandages or stockings are applied to the legs. When elastic bandages are applied with an even tension, a graduated compression is achieved in a leg of normal proportions, 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.

Recommendation

When there are no contraindications, apply compression therapy to promote 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 and may be contraindicated in some patients.[24] Other contraindications in the high-risk patient may include:

- **heart failure**
- **peripheral arterial disease**
- **an ABPI below 0.8 mmHg or above 1.2 mmHg**
- **peripheral neuropathy**
- **some vasculitic ulcers.**

Although compression may relieve lower limb oedema, the aetiology should be determined and the patient's condition monitored closely 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 (for example, 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 (for example, tissue necrosis, skin trauma, discolouration, pain, pallor, paraesthesia, impaired capillary return)
- reduction in the level of compression
- increased padding/comfort layer under the compression

- reviewing the initial diagnosis
- referral to a pain management specialist if the patient continues to experience uncontrolled pain

8.5.1 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 (for example, number of times it has been washed), the application technique and the skill of the clinician applying the compression system, shape and circumference of the leg.[118]

Sub-bandage pressures are proportional to the strength of the applied compression system. Sub-bandage pressure can be measured in the gaiter area (approximately 8 cm above the ankle bone) in both the standing and lying positions to gauge the stiffness of the compression. The difference between lying and standing pressures is referred to as the static stiffness index (SSI). Higher SSIs (usually considered to be above 10 mmHg) indicate a more inelastic compression system that produces a higher level of compression when standing and a lower pressure when resting.[119]

Table 8.1: Examples of available compression systems

Compression system	Also referred to as	Description and function
Multi-component system	Two-, three- and four-layer bandaging (4LB)	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. Can also refer to a system that consists of several layers using a combination of elastic and inelastic bandages (i.e. 4LB system). This system is also available as a kit.
Inelastic compression bandages	Short-stretch bandages	Bandages with minimal or no elastomers. Low extensibility and high stiffness (high SSI). Low resting pressure and high working pressure.
Single-component bandage system		Compression bandaging system that has only one layer or aspect to the system. Most bandage systems currently used in practice include a padding layer and so are not described as single-component systems.
Medical-grade compression hosiery	Tubular stockings, compression stockings, multi-layer hosiery systems	Available in a range of compression levels. International consensus on compression scales is lacking and different scales are used around the world. Two scales and/or classifications of compression hosiery commonly used by Australian and New Zealand manufacturers include: Scale one:[120] • extra light (5 mmHg) • light (15 mmHg) • mild (18–24 mmHg) • 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 points

- A general rule is that higher pressure is better than lower pressure and some pressure is better than no pressure.
- Incorrectly applied compression systems may not be effective or may cause tissue damage. Clinicians and patients require education and experience to ensure that bandaging is applied correctly and achieves an appropriate level of compression.[121] (recommendation 8.6.2)
- There is minimal evidence to suggest that there is a superior compression system. Moderate- and low-quality RCTs suggest that:
  - a single-component bandage compression system is less effective than 4LB[122,123]
  - different variations of 4LB systems are as effective as each other[122,123]
  - two-layer, medical-grade compression hosiery is more effective than inelastic (short-stretch) bandaging[122]
  - medical-grade compression hosiery is comparable to multi-layer bandaging systems in its effectiveness[124]
  - when using two- or three-layer component compression systems, an elastic component is more effective than an inelastic component[122]
  - two- and 4LB systems have similar effectiveness[118,125]
  - pneumatic compression is as effective as bandaging systems.[126]
- In the absence of any good-quality evidence supporting specific compression systems, the Expert Working Committee recommends that choice of a compression system should be made in consideration of:
  - shape and size of the leg
  - patient tolerance and preference
  - clinician experience in application
  - the environment (for example, temperature)
  - ease of application and removal
  - access to systems
  - presence of other disease
  - level of activity/weight bearing
  - 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.
- There is no evidence to show anti-embolic stockings will heal 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 (for example, the foot arch and posterior medial malleoulus region)
  - adaptations such as the Southland Snail[127] or stasis pads can provide localised supplemental pressure over the ulcer area to flatten wound edges and 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.[121]
- There is some evidence that medical-grade compression hosiery is associated with less pain than compression bandaging.[122]
- 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 manufacturer's 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 summary

One good-quality SR[118] reported the results from seven moderate- and low-quality RCTs investigating the effect of compression bandaging compared with 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 completely healed ulcers after 12 months (RR 2.30, 95% CI 1.29 to 4.10, p=0.0047). In one trial comparing 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% vs 25%). The other trials were small, had uneven groups and were at a high risk of bias.[118]

A second, good-quality SR and meta-analysis[123] supported these findings. This earlier review[123] identified eight trials, five of which are reported by O'Meara *et al.*[118] 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).[123] *(Level I evidence)*

One good-quality, crossover RCT (n=81)[125] reported the effectiveness of two-layer bandaging compression system compared with 4LB 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.[125] *(Level II evidence)*

One moderate-quality RCT[126] (n=16) investigated the effectiveness of intermittent pump compression compared with 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 six months. The trial was inadequately powered and did not report on adverse events.[126] *(Level II evidence)*

One low-quality SR[121] 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 could be improved through education programs; however, the effects may not be sustained beyond 10 weeks. None of the trials were randomised or adequately powered.[121] *(Level I evidence)*

8.6 Other interventions

8.6.1 Skin grafting

When VLUs remain unhealed for extended periods, skin grafting can be used to promote wound closure provided arterial insufficiency has been eliminated or corrected. Skin grafts can be derived from the patient's own skin (autograft), preserved animal skin (xenograft) or bioengineered skin substitutes (allograft).[128] 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.[129]

Recommendation

Consider bi-layered, bioengineered skin grafts to promote 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 (for example, allergic reaction to medications).[130] 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.[128]

Practice points

- Compression is required after skin grafting to ensure the graft takes and to prevent further leg oedema.

Evidence summary

A Cochrane review[128] investigated the effectiveness of different types of skin grafting in healing VLUs. Seventeen trials compared skin grafts with 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 six months) and were of moderate to low methodological quality.[128] *(Level I evidence)*

Autografts compared with hydrocolloid dressings

Two trials investigated the effectiveness of split-thickness autografts to hydrocolloid dressings. One trial (n=102) found no significant differences between the two treatments and the other trial reported a significant effect for skin grafting. The difference in healing in the control groups was large between the two trials, although both used populations with hard-to-heal ulcers and conducted a six-month follow-up. The findings were insufficient to make a recommendation on the effectiveness of autografts compared with hydrocolloid dressings.[128] *(Level II evidence)*

Allografts compared with standard care

Three trials (n=80) compared frozen allografts with standard care (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 with standard care (non-adherent dressings) and pooled results showed no significant differences in healing. However, pooling of the results from trials comparing either frozen or fresh allografts with 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).[128] *(Level II evidence)*

HSE compared with standard care

Two trials (n=345) compared bi-layered (dermal-thickness) grafting with simple dressings with compression in participants with hard-to-heal ulcers. Both trials reported superior healing in VLUs treated with the bi-layered 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 with 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.[128] *(Level II evidence)*

Comparison of different graft types

Five trials compared different graft types with each other and none of the trials provided strong evidence for a superior effect of a specific type of graft product.[128] *(Level II evidence)*

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.[128]

One good-quality SR[129] reported the results from nine trials investigating bi-layered split-skin grafts (BSSs) used to treat VLUs. Most of the trials were also reported in the Cochrane review.[128] 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 with Unna's boot. At six months, significantly more patients treated with Apligraf® had complete ulcer closure (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 with 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 with 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 Promogra™ (n=73) compared with 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 with compression with split-thickness skin graft. There was no significant difference in healing at 12 weeks or six months. Two trials compared cytopreserved, cultured allografts to a hydrocolloid. One (n=27) was of low quality, and the second trial (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 with placebo and compression reported no significant difference in healing after six 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 SR 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 were unknown and a description of the comparative treatments was lacking.[129] *(Level I evidence)*

8.6.2 Health professional education

Given the complex nature of the assessment and management of leg ulcers, education and training is considered 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 (for example, performing ABPI using Doppler ultrasound and performing compression bandaging) and QOL issues for VLUs.[48,131-133] 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.[134] 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 that nurses' knowledge improved when they received 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.

Recommendation

Health professionals benefit from education on VLUs and their management. Patient outcomes may be superior when ulcer care is conducted by a trained health professional. (Grade C)

Evidence summary

One low-quality RCT[48] 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 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 about 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 the most 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 might improve nursing knowledge, there were 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.[48] *(Level II evidence)*

One low-quality trial[133] conducted in Hong Kong investigated the ability of an ulcer-specific education program in improving the knowledge and skills of 42 enrolled and registered nurses in caring for patients with VLUs. The nurses worked in community settings and had varying baseline knowledge levels. The education program administered to the nurses included didactic teaching, open discussion, multimedia 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.[133] *(Level II evidence)*

Another non-randomised trial[131], 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 multimedia 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.[131] *(Level II evidence)*

However, a second non-randomised study[132] conducted in the UK to compare the effects of a four-hour educational program designed to incorporate different learning styles and needs with the effects 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. The program 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.[132] *(Level II evidence)*

One low-quality study[134] 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 three-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 with the patients in the control group, although there were no significant differences between the two groups for time spent wearing compression. The results may have been influenced by the experimental group performing leg elevation for longer durations. The trial suggested that nurse education may be a factor in improving patient adherence to therapy and reduction of VLU recurrence.[134] *(Level II evidence)*

Practice points

- Education in the assessment and management of VLUs 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.

8.6.3 Pentoxifylline

Pentoxifylline is a haemorheologic agent that increases blood circulation and oxygenation of tissues.[135-137] The medication increases the efficiency of blood flow through an effect in decreasing blood viscosity, platelet aggregation and fibrinogen levels.[135-138] 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 with placebo.

Recommendation

When there are no contraindications, pentoxifylline could be used to promote healing in VLUs. (Grade B)

Caution

Pentoxifylline is not recommended for patients with a history of severe haemorrhage (for example, 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 patients with mild renal or liver disease.[137] Pentoxifylline has not been tested in children or pregnant or breastfeeding women.[136,137]

Pentoxifylline is related to a higher incidence of GIT side effects than placebo.[135,136] Other common side effects include dizziness and headaches.[136] 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.[138]

Practice points

- Although some of the evidence suggested that pentoxifylline is more effective than compression therapy in healing VLUs,[135] best practice supports the use of compression therapy wherever possible and, if used, pentoxifylline should be concurrent with compression therapy.
- Regularly monitor the blood pressure of hypertensive patients taking pentoxifylline.[137]
- Pentoxifylline should be taken with meals to reduce GIT side effects.[136]
- Pentoxifylline may take up to eight weeks to show full effects.[136,137]
- Patients should inform their surgeon or dentist if they are taking pentoxifylline before undergoing major procedures.[136,138]

Evidence summary

A good-quality Cochrane SR[135] included 12 RCTs published up to 2009 that investigated the effectiveness of pentoxifylline 400 mg (twice or three times daily) for the treatment of VLUs. Of the trials included in the review, quality ranged from moderate to low. *(Level I evidence)*

Results from 11 trials (n=841) comparing pentoxifylline with 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 (for example, published versus unpublished trials, based on duration, based on primary outcome measure). The only sensitivity analysis without significant heterogeneity was in studies that excluded hard-to-heal patients. 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 result translated to an absolute increase in healing of 21% (95% CI 8% to 34%) and an NNT ranging from 3 (95%CI 2 to 12) to 11 (95%CI 6 to 43) for pentoxifylline compared with placebo.[135] *(Level I evidence)*

Pooled results from seven trials comparing pentoxifylline with 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 result translated to an absolute increase in healing of 23% (95% CI 4% to 43%) and an NNT ranging from three (95% CI 2 to 8) to four (95% CI 2 to 9) for pentoxifylline without concurrent compression therapy.[135] *(Level I evidence)*

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). GIT side effects were the most experienced adverse event.[135] *(Level I evidence)*

8.6.4 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.[139]

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

Recommendation

When there are no contraindications, micronised purified flavanoid fraction may be used to decrease the healing time for VLUs. (Grade C)

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 interactions.[139]

Evidence summary

One moderate-quality SR[140,141] investigated the effect of 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 was 19.6 months (range 1 to 237 months); and average ulcer disease duration of 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 mmHg 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 5 cm^2 and of shorter duration created homogeneity and showed an RRR of 45% (95% CI 23% to 71%). A subgroup analysis of participants with ulcers more than 5 cm^2 in area (four trials) showed an RRR of 53% (95% CI 15 to 103%) for complete healing in six months with MPFF. Results from five trials showed an RRR 44% (95% CI 7 to 94%; p=0.015) of complete healing in two months for MPFF, but the results for healing at four months were not significant. *(Level I evidence)*

The results of this SR 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.[140,141] One of these did not report complete healing at six months and 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-blind 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 for this review, suggest that the outcome should be considered cautiously until further good evidence from placebo-controlled, blinded RCTs investigating the role of MPFF in ulcer healing. *(Level I evidence)*

9. PREVENTING RECURRENCE OF VENOUS LEG ULCERS

What are the effective interventions to prevent recurrence of VLUs?

Ongoing management is considered essential in preventing recurrence of VLUs, as underlying venous disease remains a causative factor once an initial VLU heals. Referral to a vascular surgeon for assessment is appropriate, but beyond the scope of this clinical guideline (see discussion in section 9.3). Diligent maintenance of leg care and ongoing compression are recommended.

9.1 Maintenance of leg care

Recommendation

Maintaining practices that promote the health of legs may reduce the risk of VLU recurrence. (CBR)

Practice points

- Progressive resistance exercise may help to promote calf muscle function.[65]
- Regular moisturising of the lower limbs helps to maintain skin integrity.
- Elevation of the limbs when sitting and avoidance of standing for prolonged periods assists in controlling oedema.
- Support groups can promote uptake of and concordance with practices that help maintain skin integrity and provide long-term psychosocial support.

9.2 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 (recommendation 8.5).

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

Recommendation

Consider the continued use of compression therapy to reduce the risk of recurrence of VLUs. (Grade B)

Caution

Refer to the caution statement and the contraindications in the recommendation for use of compression therapy in the treatment of VLUs (recommendation 8.5).

Practice points

- There is minimal evidence to suggest that there is a superior compression system to prevent recurrence of VLUs.[118,142] 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%, $p<0.05$).[122]
- The Expert Working Committee recommends that after healing has been achieved it is ideal that compression bandaging be maintained to the same degree for two to four weeks before changing to medical-grade compression hosiery.
- Mild to moderate compression may be as effective as 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 compression hosiery to prevent ulcer recurrence withdrew due to "stocking-related events".[143] Another RCT reported that a more moderate grade compression was better tolerated than high-grade compression.[142] A patient survey indicated that patients were less likely to wear medical-grade compression hosiery if they were uncomfortable.[144]
- 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).[144]
- Further practice points can be found under compression therapy for the treatment of VLUs (recommendation 8.5).

Evidence summary

One good-quality Cochrane review[142] 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 with those who participated in the trial (RR 2.58, 95% CI 1.33 to 5.01).[142] *(Level I evidence)*

A second, good-quality Cochrane review[118] reported one moderate- to low-quality RCT (n=233) comparing compression with no compression for preventing recurrence of VLUs. There were no significant differences in likelihood of ulcer recurrence or time to reccurrence within 12 months (p=0.38) between a 4LB system and usual care. The trial was underpowered to detect a significant result. In another trial (n=30) there were no cases of recurrence within six months in VLUs treated for 12 weeks with single-layer elastic bandaging, 4LB or a four-component compression with paste bandaging. There was no non-compression comparison group.[118] *(Level I evidence)*

One good-quality RCT[143] 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 value not reported). However, 22% of participants in the compression stocking group withdrew from the trial due to undefined, stocking-related events.[143] *(Level II evidence)*

9.3 Venous surgery

The underlying physiological problem responsible for the development of venous ulceration is venous hypertension. This hypertension is commonly due to reflux or obstruction in the venous superficial or deep system, which is a frequent clinical problem. Venous surgery for isolated superficial reflux or for mixed superficial and deep reflux does not improve healing rates, but is an important intervention to reduce the 12-month recurrence rate after healing of the ulcer. Other venous surgical procedures, such as deep vein valvular repair or replacement, or venous bypass operations, may have a role in reducing venous hypertension and thus reduce the venous ulcer recurrence rate.

It is recommended that all patients with venous ulceration should be reviewed by a surgeon with an interest in venous surgery to ensure all surgical management options have been considered.

10. SPECIAL POPULATIONS

10.1 Aboriginal and Torres Strait Islander people and Maori and Pacific Islander people

There is no specific published data on the incidence of VLUs in Aboriginal and Torres Strait Islander people in Australia or Maori and Pacific Islander people in New Zealand. The health of Indigenous populations differs from that of the general population in both countries.[145-147] 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.[146,147] 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.[145,148] In addition, people from Indigenous backgrounds often reside in rural and remote locations, creating greater disparity due to more difficulty specialist accessing health services (see section 10.3).

No research specific to the management of VLUs in Australian and New Zealand Indigenous populations was identified in the literature search. As discussed in section 10.2, the effectiveness of therapies did not appear to be related to ethnicity when therapy was delivered as part of a research study.

10.2 People from culturally and linguistically diverse (CALD) backgrounds

No research specific to the management of VLUs in CALD populations was identified in the research; however, much of the research (particularly that conducted on compression therapy and dressings) was conducted in study sites located worldwide. Research conducted at multiple research sites generally showed no variation in findings associated with study sites, suggesting that there is no variation in effectiveness of therapies associated with ethnicity.

10.3 People from rural and remote locations

People living in rural and remote regions may have limited access to specialist leg ulcer services. The greatest impact of rural and remote living is likely to arise from reduced access to:

- health professionals with specific training and experience in assessing and diagnosing the aetiology of VLUs
- diagnostic investigations (for example, ABPI)
- specialist health professionals (for example, vascular surgeons) for assessment of complicated VLUs.

As outlined in the guideline, the mainstay intervention for managing VLUs is compression therapy. Compression therapy systems are available through pharmacy suppliers and should be accessible in all locations.

The recommendations in this guideline seek to provide health professionals with education on assessment and diagnosis of ulcer aetiology, and highlight a range of diagnostic options. Investigations support a clinical assessment of ulcer aetiology and are not essential for diagnosis, where the health professional has experience in conducting a comprehensive assessment.

There was insufficient evidence on which to make a graded recommendation for assessment and management of VLUs in people in rural and remote areas. One low-quality study investigated a teleconferencing intervention to assist nurses in community locations to assess and manage VLUs. The study indicated that receiving teleconferencing advice from a VLU expert might improve the skill of nurses caring for a patient with a VLU. The Expert Working Committee recommends that support be attained from health professionals with specialist skills in assessing and managing VLUs, particularly when the aetiology of the ulcer is uncertain.

Recommendation

Where access to specialist services is limited, health professionals could contact a VLU specialist via telecommunications for advice and support in assessing and managing a patient with a VLU. (CBR)

Supporting literature

One low-quality RCT[48] 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 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 about 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 the most 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 might improve nursing knowledge, there were 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.[48] *(Level II evidence)*

11. COST IMPLICATIONS

In Australia health care expenditure on management of venous ulcers has been steadily rising. Annual costs have risen from A$400 million reported in 1994[22] to A$3 billion annually in 2005.[149] In 1996 the private hospital cost for a mean stay of 23.9 days for management of chronic leg ulceration was estimated to be A$8734.[7] However, since there has been a move towards community management of VLUs, care costs have been passed on to the patient as dressing products are not fully subsidised by the Australian Government.[19]

Estimates of the financial cost to the patient of managing a VLU in the community are varied. In the Silver Chain study conducted in 1996–97, the mean cost of treating a VLU in the community was A$2300.[150] In 2000–01 a similar survey conducted in Department of Veterans' Affairs patients predominately aged over 80 years found the mean cost to heal any leg ulcer was A$1436 when comprehensive assessment was implemented. This study 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.[151] A more recent pilot study showed a mean monthly financial cost to the patient of A$114 (range over two months A$57 to A$751, annual expenditure A$1368).[19] The vast majority (about 61%) of cost was associated with primary dressings. Secondary dressings and fees for health services each accounted for about 13% of patient expenses. The balance of costs to the patient was for transport, medication and other expenses. Heavily exudating ulcers were more costly to manage than those with light exudate.[19] There was no correlation between ulcer duration and financial costs.[19]

It is anticipated that the burden of VLUs will rise over time due to an ageing Australian population,[152] as well as an increase in other significant risk factors for VLU such as obesity and chronic venous circulatory conditions.[153] With limited government funding of key evidence-based management strategies, the tangible cost to government may not reflect the true financial burden of managing VLUs, which is primarily borne by patients. However, cost implication to government may be reflected in increased health care costs where patients receive in-patient management, increased cost of pharmaceuticals to manage complications (pain, infection) and intangible costs such as reduced productivity.

11.1 Cost implications of the recommendations in Australia

Since the move towards community management of VLUs, the cost of key treatments is primarily funded by the patient. This guideline highlights the importance of compression therapy in initial prevention, management and prevention of recurrence of VLUs. No research has been conducted in the Australian setting on the cost comparison of compression therapy to less effective management strategies. In the majority of situations, the cost of compression therapy is borne by the patient and there are no cost implications to government funding. The same is true for other recommendations in this guideline, including dressings, topical treatments and specialised therapies such as electrotherapy. This guideline includes recommendations that have minimal cost implications to patients, including progressive resistance exercise and elevation, both of which can be performed in the home environment at no cost.

Implementing the recommendations in this guideline may increase immediate patient costs. However, implementing the most appropriate prevention and treatment strategies is likely to reduce the development of VLUs and promote more rapid healing of existing VLUs, as shown in the research presented throughout this guideline. Faster healing decreases the long-term expense of ulcer management.

Where appropriate management with compression therapy is not implemented (for example, when the patient cannot afford or access therapy) there may be cost implications to government health funding. Poorly managed VLUs have an increased risk of infection that may require management with pharmaceuticals. Persistent VLUs may require in-patient management (for example, management of systemic infection, skin grafting). This guideline recommends skin grafting strategies that do not require the use of autografting, which may reduce resources and surgery time compared with split-skin grafting; however, the research did not investigate such cost implications.

The cost implications of patient and health professional education are also uncertain. In many settings, the cost of patient education is shared by the patient (for example, in time paid to a district nurse) and the health care service (for example, in time spent on education and in preparing written material). Health professional education is also a shared expense, often directly funded by clinicians themselves. The production of this guideline by AWMA and NZWCS provides an educational resource at no expense.

11.2 Cost implications of the recommendations in New Zealand

There is no available national research data on the cost implications of managing a VLU in the New Zealand setting; however, the trends are likely to be similar to Australia. Cost implications are likely to be significant given the ageing population and an increased demand on health care resources. The tangible costs of not implementing evidence-based management of VLUs is likely to increase from associated complications such as infection, increased hospital admissions, higher expenditure on pharmaceuticals (analgesia, antibiotics) and surgical procedures (debridement, grafting). There are also intangible costs to government, such as reduced productivity and lower tax revenue if patients are unable to work.

In New Zealand, there are two different funding streams: secondary care and primary care. In the secondary care sector, patients who are eligible for service provision under the DOM1 contract for specialist community nursing[154] have nursing management, compression bandaging and dressings funded. Funding of compression stockings is variable. The funding of compression therapy is variable. Some District Health Boards provide funding for an initial pair of compression stockings for patients who have completed a course of compression bandaging; however, in other regions compression stockings are patient-funded. As compression therapy is already recognised as an essential component of VLU management, the recommendation in this guideline should not have significant cost implications. Where health services have not implemented compression bandaging as a management strategy, there may be an increase in immediate health service costs should this recommendation be adopted; however, the extent of this implication is unknown.

The New Zealand primary health care is a bulk funding model based on consumer need, age groups, and socio-economic variables. In primary care settings, compression therapy is generally funded by the patient (with some funding available via Accident Compensation if a claim for an initial trauma is accepted).

The participation of the NZWCS in the development of this guideline will enable New Zealanders to access this up-to-date resource without cost. The national challenge is sustainable health care and an increased awareness of best practice in decision-making helps to reduce costs associated with delayed healing of VLUs.

12. OTHER 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.

12.1 Phlebotics

Phlebotics are venoactive drugs that are reported to have effects on both the macrocirculation (for example, improving venous tone) and microcirculation (for example, decreasing capillary hyperpermeability). The group of drugs known as phlebotics consists of both natural flavonoids that are manufactured from plant extracts and synthetic products.[155]

One good-quality SR[155] reported findings from moderate- to low-quality RCTs. One meta-analysis showed no significant effect for phlebotics compared with placebo; another had results bordering on significance. Individual trials had inconsistent findings.

Recommendation

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

Evidence summary

A Cochrane review[155] 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 (one to three 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 with 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 phlebotics are effective in treating CVI; and the findings regarding effect in preventing VLUs were inconsistent.[155]

12.2 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 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.[156,157] These are variously theorised to provide benefits through enzymatic fibrinolysis; stimulation of protein synthesis; and an increase in cell proliferation that stimulates an increase in inflammation and promoting angiogenesis. However, there is insufficient research in this area to determine the validity of these theories.[156] 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 five to 10 minutes. Treatment length varied from between three and 12 weeks, with treatment generally applied at a weekly or twice-weekly frequency.[156,158]

The evidence supporting the recommendation on ultrasound therapy comes from a good-quality meta-analysis of results from studies at high risk of bias. Results indicated that there is no effect on total ulcers healing of either high- or low-frequency ultrasound compared with no ultrasound treatment. These results were supported by a second meta-analysis that was of a lower quality.

Recommendation

Therapeutic ultrasound therapy should not be used to promote healing in VLUs. (Grade B)

Caution

In trials conducted in patients with VLUs there were no significant adverse events associated with ultrasound therapy. Ultrasound is not recommended for patients with a pacemaker or other implanted electrical devices.[159]

Evidence summary

A Cochrane review[51] reported on the effectiveness of ultrasound therapy for the treatment of VLUs. The review was of good quality; however, the trials included were at high risk of bias and included small numbers of participants.

High-frequency ultrasound therapy compared with no ultrasound

The results of six RCTs trials that compared high-frequency ultrasound to no ultrasound were pooled using a fixed effect model. The trials generally used a regimen of ultrasound 1 MHz at 0.5W/cm^2 for 10 minutes two to three times weekly and participants in both treatment and control groups continued to receive standard care (varied between trials but generally included support or compression bandaging or hose). Individual trials had conflicting findings, with some showing an effect for the ultrasound intervention. Pooled results from two studies (n=152) found an RR of total ulcer healing at 12 weeks of 1.47 (95% CI 0.99 to 2.2, p=0.059). Results from five studies (n=341) showed an RR of 1.4 (95% CI 1 to 1.96, p=0.051) of total healing at seven or eight weeks and pooled results from all six trials (n=406) showed an RR of complete healing by the conclusion of the study (varying time frames) of 1.34 (95% CI 0.99 to 1.80, p=0.059). The Cochrane reviewers concluded that there was insufficient evidence to suggest high-frequency ultrasound is effective for healing VLUs.[51]

Low-frequency ultrasound therapy compared with no ultrasound

Two small trials compared low-frequency ultrasound therapy to no ultrasound. Participants in both trials continued standard therapy that consisted of hydrocolloid dressing and compression in one trial and antibiotics, antiseptics and an occlusive dressing in the second trial. At follow-up (25 weeks in one trial and eight weeks in the other) neither trial showed an increased healing rate for participants treated with ultrasound. Pooled results (total n=61, two studies) showed a relative risk of 3.91 (95% CI 0.47 to 32.85, p=0.21).[51]

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.[51]

Another low-quality SR[158] 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[51] were pooled in a meta-analysis and the results concurred that ultrasound compared with sham ultrasound is associated with an improvement in percentage of ulcer area healed but not total number of ulcers healed.[158]

12.3 Electromagnetic therapy

Information about how electrotherapy is applied is available in section 7.

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.

Recommendation

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 two months ago, congenital pathology of central nervous system or kidney disease or in pregnant women.[160,161]

Evidence summary

A good-quality Cochrane review[54] investigated electromagnetic therapy for treating VLUs. After a comprehensive literature search, only three 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.[54]

Two of the RCTs compared pulsed electromagnetic therapy (PEMT) with sham therapy. The first was a moderate-quality, double-blind RCT that included 44 people with VLUs. Participants were randomised to receive either electromagnetic therapy at 75 Hz, 2.7 mT, with an impulse width 1.3 ms (n=22) or sham stimulation (n=22) for four hours per day for three 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 a significantly greater proportion of people with healed ulcers in the PEMT group compared with 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 three 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 eight 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 to 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 25 mTesla magnetic field for the remainder of the trial. The third group received sham therapy. Therapy was administered for five 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.[54]

A second, good-quality SR[53] reported the results from six RCTs investigating PEMT. The review reported that four of the RCTs were of strong methodological design and two were low-quality studies. Three of the trials were reported in the Cochrane review.[54] 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 (<15 cm^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,[53] there are inconsistencies reported between studies within the review and between this review and a Cochrane review[54] reporting some of the same studies.

A low-quality RCT[162] investigated the effectiveness of static electromagnetic therapy for healing VLUs. The intervention of interest was described as containing four neodynamic magnets that were 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 the 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 and change in 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 shortcomings, the results of this trial were unconvincing.[162]

12.4 Electrotherapy

Electrotherapy is proposed as a therapy for accelerating natural wound healing processes. The trials reviewed in the literature used a range of different therapy regimens. One trial specifically investigated high voltage therapy[163] 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 three to six 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.[57] Two trials[57,163] 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 trial reporting a slight increase in healing rates, although there was significant methodological inconsistency. The effect of electrotherapy on pain is reported under pain management.

Recommendation

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.[55] Electrotherapy is contraindicated in patients with electrical implants (for example, pacemakers), epilepsy, malignancy or who are pregnant. Electrotherapy should be used with caution in patients with impaired circulation.[56]

Evidence summary

A low-quality RCT[57] 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 three-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 seven days of negative polarity, followed by three days of positive polarity. Treatment continued for an average of 100 days (that is, 10 cycles). After four months, the electrotherapy group had achieved a significant reduction in ulcer surface area (p=0.03) but this was not significant compared with 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.[57]

A low-quality trial[163] 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, six days per week for a total of seven weeks. Participants were treated with negative polarity until pus coverage of the VLU cleared (between one and three 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 six weeks. Both groups received concurrent compression therapy. A third group of 14 participants being treated as out-patients 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 suppurative ulcer area; however, this group had less pus at commencement of the trial.[163]

A low-quality trial[55] investigated the treatment of VLUs with FREMS. Participants were 35 patients with 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 five days per week for three 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 eight-week follow-up, FREMS was associated with a significant decrease in ulcer surface area (measured using a digital imaging technique) and with overall ulcer condition (measured 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.[55]

12.5 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.[164] There is currently little evidence that LLLT has these effects or, if it does, these effects 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.

Recommendation

Low-level laser therapy should not be used to promote healing in VLUs. (Grade A)

Caution

No adverse events were reported for trials investigating LLLT.[164,165] Participants in trials investigating the use of LLLT for other conditions have not experienced adverse events.[166,167]

Evidence summary

A good-quality Cochrane SR[165] reported two RCTs comparing LLLT with 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) with sham laser therapy (n=23). Participants also received standard treatment of saline cleansing, paste and support bandages and were encouraged to perform exercise and 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 with sham laser (RR 1.21, 85% CI 0.73 to 2.03, p=0.46).[165]

A moderate-quality RCT[164] investigated the effectiveness of LLLT in healing VLUs. Patients with VLUs were eligible for inclusion if they had an ulcer 1–8 cm in diameter and between three months' and three years' duration, which 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 685 nm at a fluence of 200 mW producing 4J/cm², was administered for six to18 minutes depending upon ulcer size, daily for 14 days then on alternate days for 14 days. All groups received enzymatic debridement of the ulcer in the first week of therapy and daily (first two weeks) then alternate day hydrofibre 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 2 cm², p=0.023), as did the control group (mean reduction approximately 5 cm², p=0.047). There was no change in the median size of ulcers in the laser group (p=0.492). At the 90-day 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.[164]

12.6 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 management.[168] 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.[168,169]

Topical phenytoin formulations include gel, cream, phenytoin sodium powder and phenytoin powder.[168,169] 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[168,170] 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.

Recommendation

Topical phenytoin may be more effective than standard care for promoting healing in VLUs; however, it should not be used due to the risk of serious adverse events that outweigh the benefits. (Grade C)

Caution

Skin sensitivity may result from topical products used for extended periods. Burning sensation,[168] gingivial hyperplasia[170] and hirsuitism[170] 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. Phenytoin should not be used in pregnancy due to the risks of foetal damage.[170]

Evidence summary

A moderate-quality SR[169] 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 with 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 four weeks of treatment there was significantly greater healing in the phenytoin group compared with the group treated with honey alone (22% vs 0%, $p<0.05$). No adverse events were reported. The third RCT compared phenytoin (n=50) with EUSOL (n=52) in managing VLUs over four weeks. In this trial there was a significant increase in healthy granulation in the VLUs in the phenytoin group compared with 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 four to 13 weeks.[169]

12.7 Ibuprofen dressings for pain management

Ibuprofen-impregnated dressings are designed for management of painful, 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.[171]

The recommendation that ibuprofen dressings have no effect in reducing pain associated with VLUs is underpinned by a good-quality meta-analysis of two trials at moderate risk of bias that had consistent findings.

Recommendation

Ibuprofen dressings should not be used to relieve pain associated with VLUs. (Grade A)

Evidence summary

Two RCTs (total n=185) at moderate to high risk of bias investigating the effect of ibuprofen dressings were pooled in a good-quality meta-analysis.[172] Both trials compared the reduction in pain achieved on the first evening of dressing administration. In one trial, participants were adults aged over 65 years with painful chronic VLUs of varying sizes and of duration longer than eight weeks with a baseline pain described as at least moderate. The second trial included adults with exudating VLUs of at least 1 cm^2. In both trials, participants were randomised to receive either ibuprofen-impregnated foam dressings or a control treatment (local best practice or a regular foam dressing). Outcome measures in both trials included pain relief on the first evening as measured on a five-point pain scale. Both trials reported only a small reduction in pain relief associated with ibuprofen dressing. Results were pooled in a meta-analysis using a random-effects model and showed an RR of some pain relief of 1.15 (95% CI 0.91 to 1.44, p=0.24), corresponding to a non-significant reduction in pain levels of 9%. In one of the trials, 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. The Cochrane review concluded that the current evidence suggests no significant reduction of pain is achieved from ibuprofen foam dressings.[172]

12.8 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 SR underpinning this recommendation tested the effect of zinc in high doses (200 to 220 mg daily) to promote healing.[173]

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 three to 10 months. The meta-analysis concurred with these findings.

Recommendation

Oral zinc should not be used to improve healing of VLUs where there is no nutritional deficit. (Grade A)

Caution

Zinc is a safe supplement when taken at recommended daily doses. It should not be taken during pregnancy or lactation.[174] No adverse events were reported in the trials reported in the literature. Product information recommends that zinc is taken on a full stomach and the only reported side effect is mild epigastric discomfort, which occurs rarely.[174]

Evidence summary

A Cochrane review[173] 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. ITT 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 220 mg, three times daily for the period of the trial, which ranged from three to 10 months. Comparison groups were assigned placebos. In all trials, ulcers had persisted beyond four 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 ulcers healed at the trial end point as the primary outcome measure. No individual trials reported a significant effect for oral zinc compared with placebo for healing VLUs. In one trial a subgroup analysis was conducted to determine if an effect existed in participants with low serum zinc levels (less than 110 mcg/100 ml) and this analysis also showed no effect above placebo. Pooled results from the four 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 four weeks' duration may also have influenced findings.[173]

12.9 Horse chestnut seed extract

Horse chestnut seed extract (HCSE) (*Aesculus 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 action of aescin are not fully understood, it has an enzyme-inhibiting action and potential prevention of leukocyte activation.[175,176]

Good-quality SRs 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.[175,176]

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

Recommendation

Horse chestnut seed extract is not effective in promoting healing in VLUs. (Grade C)

Caution

Adverse events associated with HCSE include GIT signs and symptoms (diarrhoea and vomiting), enlarged pupils and visual disturbance, dizziness, flushing, fatigue, headaches and pruritus.[175-177] An SR of trials investigating the use of HCSE in patients with CVI reported the adverse event rate to vary between 1% and 36% of participants.[175] HCSE may increase the risk of bleeding; therefore, it is not recommended for patients with bleeding disorders or patients taking anticoagulants.[177]

Evidence summary

A good-quality, double-blind RCT[178] investigated the effectiveness of 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 four weeks' duration that were between 1 cm and 20 cm in diameter. The participants were treated with either a low-adherent dressing, absorbent dressing or zinc-impregnated paste 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 four weeks using a validated digital photography method and computerised 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 with 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 GIT 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 375 mg HCSE administered daily in improving the healing of VLUs over 12 weeks.[178]

13. INTERVENTIONS WITH INSUFFICIENT EVIDENCE

Recommendation

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

- **balneotherapy**
- **aspirin**
- **hyperbaric oxygen**
- **topical negative pressure therapy**
- **herbal therapy and bark extract**
- **topical pawpaw-derived products**

The Expert Working Committee considered one low-quality study to be insufficient evidence on which to make a graded recommendation on the effectiveness of an intervention.

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.[179]

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 reported a significant reduction in ulcer surface area and an increase in ulcer healing compared with placebo. No adverse events were experienced.[180]

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 therapy achieves increased arterial oxygenation that improves fibroblast activity, regulates the inflammatory response and has antibacterial effects.[181] 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.[181]

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.[182] One small, low-quality trial reported that this therapy was effective in reducing healing times for chronic leg ulcers.[183]

Herbal therapy includes over-the-counter preparations containing plant and herb extracts. The use of products containing *Calendulae off., Symphytum off., Achilea millefolium*, *Salvia off., Aesculus hipp., Melilotus off., Rosmarini* and *Lavandulae*. is reported in one small RCT. The pilot trial found an effect for two herbal preparations in reducing bacterial proliferation and promoting healing in VLUs.[184]

Topical pawpaw-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 summary

Balneotherapy

One low-quality, single-blinded RCT[179] investigated the effectiveness of balneotherapy in treating CVI. Although not the primary outcome measure of the trial, of interest to this SR was the occurrence of VLUs at 12 months. Other outcome measures include change in skin pigmentation, QOL 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 three weeks, with participants receiving four sessions daily on six days per week. The therapy 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 with 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 three-week retreat, the increased interaction with care staff or concurrent therapies (for example, 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 no evidence that balneotherapy reduces the risk of VLU over 12 months.[179]

Aspirin

One low-quality trial[180] reported on the effectiveness of aspirin for treating VLUs. Twenty participants (average age less than 65 years) with ulcers larger than 2 cm^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 out-patient clinic. At baseline the groups were reported to be equivalent with respect to biochemical and haematological indices and lower limb characteristics (for example, 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 300 mg daily or a placebo for four months. Wound healing rate was measured using duplicate tracings and wound planimetry to determine wound surface area. At four 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 the healing of VLUs.[180]

HBOT

A moderate-quality SR[181] 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 and VLUs of at least one year's 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 the 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.[181]

Topical negative pressure therapy

One low-quality, non-blinded RCT[183] reported the effectiveness of vacuum-assisted closure (VAC) in patients with a leg ulcer (not all ulcers were of venous origin) that had been treated with a split-thickness skin graft. Following grafting, participants (n=45) were randomly assigned to receive 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 wound pressure may increase healing in ulcers following skin grafting.[183]

Herbal therapy

A low-quality, non-blinded RCT[184] that did not report methods of randomisation or allocation concealment investigated the effect of a herbal therapy on healing VLUs. Inclusion criteria were a VLU, ABI above 0.8, ulcer duration not longer than two months, no recurrent VLUs in the preceding six months, and no previous herbal therapy or alternative therapies (including electrotherapy, LLLT or light therapy). Exclusion criteria were a VLU above 10 cm^2, clinical signs of infection, thrombophlebitis, hyperglycaemia, renal disease and malignancy. All participants' ulcers showed signs of colonisation at baseline. Participants were randomised to receive either herbal therapy (n=17) or control care (n=15). There were no significant differences between the group at baseline for demographics or ulcer duration (mean 5.80 weeks). Participants in the phytotherapy group had their VLUs treated twice daily with Plantoderm® ointment containing alcohol extracts of *Calendulae off., Symphytum off., Achilea millefolium* and *Salvia off*. applied to the ulcer and Fitoven® herbal gel containing alcohol extracts of *Aesculus hipp., Melilotus off., Rosmarini* and *Lavandulae*. applied to the lower leg. The control group had their VLUs washed daily and treated with a wide range of topical anti-inflammatory, anti-exudative and/or disinfectant dressings, selected according to wound swab results. Wounds of all participants were swabbed at baseline and every second week for the duration of the seven-week trial. The primary outcome was rate of healing reported in cm^2 and percentage change. Wound size was estimated using wound tracings and a formula based on an elliptical-shaped wound. After the first week of the trial the herbal therapy group had a mean reduction in ulcer size of 15.21%, which increased to a 32.92% reduction in size by week five and 42.68% ulcer size reduction in week seven. This compared with a 13.53% reduction in ulcer size in the first week and a 35.65% reduction by week seven for the control group. The difference between groups was significant ($p<0.05$) and favoured the herbal therapy group. The number of different bacteria isolated in the VLUs of the herbal therapy group was significantly less than the control group by the end of the trial. This was a small trial and was not powered to measure the effect on VLU healing. No adverse events were seen in the herbal therapy group. There was a small increase in ulceration in the control group, but this was not reported in detail. Further research on the effect of herbal therapies is required before this therapy could be recommended.[184]

Bark extract

A low-quality double-blind RCT[185] 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 1.8 g tannins/100 g 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 evident after three weeks when 25% of the experimental group had at least 80% of VLU area healed compared with 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 with 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 one 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 to treat VLUs when used in conjunction with compression bandaging.[185] This was considered insufficient evidence on which to make a recommendation on the product's use for treating VLUs. *(Level II evidence)*

14. EMERGING TREATMENTS

14.1 Protein-derived 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.[186] A tissue plasminogen activator is a topical product containing proteins that assist in the breakdown of blood clots.[187]

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

Evidence summary

A moderate-quality, single-blinded RCT[188] 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 15 and 25 cm^2 that had persisted for at least six months, and who had been treated with compression therapy for at least one month without an improvement in ulcer condition before 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), which was applied weekly as a 0.5 mm 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 the groups in the rate of ulcer healing in either the ITT or per protocol analysis, in a subanalysis of participants with ulcers greater than 10 cm^2 or in participants with ulcers of 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.[188]

A second trial investigated the same product. This low-quality RCT[189,190] investigated Xelma® used in conjunction with compression, compared with compression alone for the management of VLUs. Participants were adults with an ABPI of at least 0.8 and an ulcer between 8 cm^2 and 36 cm^2 that was at least six 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, this group 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 with the control 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 11-point VAS, although this is likely to be 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.[189,190]

A low-quality trial[187] 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 to 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 four weeks, with final follow-up at six weeks. At six 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, prothrombin 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.[187]

14.2 Growth factor treatments

Growth factors are naturally occurring proteins or hormones that stimulate cell growth. They are not currently used in Australia or New Zealand. Keratinocyte growth factor stimulates epithelialisation.[191] Granulocyte-macrophage colony-stimulating factor (GM-CSF) reportedly stimulates neutrophils, macrophages and keratinocytes, all of which promote wound healing.[192,193] 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 that investigated growth factor preparations reported significant improvements in healing, others found no effect above standard care. Further research is required on these emerging treatments.

Evidence summary

GM-CSF

A good-quality RCT[193] 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 three months' duration with an ABPI above 0.8 and without diabetes, clinical infection or complex disease. The mean ulcer size of participants was 4.7 cm^2 to 6.1 cm^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 (totalling 5 ml) subcutaneously at peri-wound sites weekly for four weeks. Before administration, ulcers were debrided and cleansed with povidone iodine. A gauze dressing and compression bandaging was applied. Wounds were cleansed every second day. At the 12- to 14-week 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 groups compared with the placebo group $p<0.05$). 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.[193]

A good-quality trial[194] 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) titrated doses up to 2 ng/kg/minute over six hours daily for five days followed by two rest days repeated weekly for three weeks or a placebo saline infusion (n=45) on the same regimen. During infusion therapy, all patients received local therapy consisting of debridement, topical antiseptics, compression bandaging and leg elevation. 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 with 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 the treatment was not reported). The small trial provided some evidence that six-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.[194]

In a small, low-quality trial[192] 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 six weeks' duration (average greater than one year) with a surface area between 1 and 30 cm^2 (average 10 cm^2). Patients with diabetes, clinical infection, neoplasms or complex comorbidities 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 with day eight 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 eight weeks, about half the ulcers in the treatment group had healed. The only reported adverse event occurring more frequently in the treatment group compared with placebo was wound itching. This trial provided low-quality evidence and was too small to provide any indication of the effectiveness of this therapy.[192]

Keratinocyte growth factor

A moderate- to good-quality trial[191] investigated repifermin, a keratinocyte growth factor, applied topically for the treatment of VLUs. Participants were adults with CVI with ulcers up to 30 cm^2 and between three 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 group received 20 $\mu g/cm^2$ of repifermen (n=31), the second group received 60 $\mu g/cm^2$ of repifermen (n=32) and the third group received a topical placebo (n=31). Treatment and placebo were sprayed onto the ulcer from approximately 30 cm away starting from the perimeter and moving inward. After administration, the ulcer was covered with a non-adherent dressing and compression. Treatment was administered twice weekly for 12 weeks. At the 12-week 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 groups. Treatment effect appeared greater for wounds less than 15 cm^2 or less than 18 months' duration. Adverse events including pruritus, rash, leg pain and reopening of leg ulcer did not occur more frequently in the treatment groups 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 the usefulness of repifermin in promoting VLU healing.[191]

Protein-derived growth factor

A moderate-quality RCT[195] 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. Participants had ulcers with a mean size of 2 cm^2 that had persisted for a mean duration of three 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, and the gauze delivered 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 (maximum follow-up was nine months). Participants who did not display a response to treatment after three 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.[195]

Adverse events

Protein-derived growth factor increases the risk of cancer mortality[195].

14.3 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.[196] In trials included in the literature, prostaglandin E1 was administered intravenously daily for between 20 and 120 days. Intravenous infusion was administered over six hours.[196,197]

The evidence that intravenous prostaglandin E1 is effective in improving healing in hard-to-heal ulcers was provided by one good-quality and one 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 the effect of intravenous prostaglandin E1 in conjunction with compression for improving VLUs, this therapy is currently not available in Australia or New Zealand.

Evidence summary

A good-quality, double-blind RCT[197] 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's duration and between 5 and 30 cm^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 60 mg 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 hospitalised for six 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 per cent 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 to hypotension, headache and 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.[197]

A low-quality trial[196] investigated the use of intravenous prostaglandin E1 on a daily basis for six weeks for healing VLUs. Participants with VLUs of at least four months' duration and at least 0.5 cm 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 washout period and were randomised to receive either 60 µg prostaglandin E1 (n=22) or placebo (n=22) by daily intravenous infusion over three hours. Treatment continued for six 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 E, 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 per cent of the treatment group had completely healed ulcers and 85% had resolution of oedema compared with 9.1% and 35%, respectively 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.[196]

Adverse events

In trials conducted in patients with VLUs, adverse events occurred more frequently than placebo, and included headache, hypotension and GIT effects.[197]

15. IMPLICATIONS FOR FUTURE RESEARCH

The development of this guideline highlighted the paucity of research at low risk of bias investigating the management of VLUs. Much of the research appraised in this guideline was at a moderate to high risk of bias. The Expert Working Committee recommends that future research related to VLUs focus on:

- Implementation of study designs and processes that are at low risk of bias.
- Research specific to Aboriginal and Torres Strait Islander, New Zealand Maori and Pacific Islander populations.
- Research on the cost-effectiveness of interventions to manage VLUs.
- Further research into the implication of venous surgery and its role in management and prevention of VLU recurrence.
- Further research into areas with limited, existing, consistent, good-quality evidence including:
  - the most effective degree of compression to prevent the initial development and recurrence of VLUs, and the most effective degree of compression to heal VLUs
  - the effectiveness of topical antimicrobial agents (for example, honey and silver)
  - the role of exercise in the management of VLUs
  - effectiveness of various debriding agents in VLU management
  - the role of psychosocial and educational support groups in Australia and New Zealand.

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17. APPENDICES

APPENDICES	
A	Expert Working Committee
B	Process report
C	Excluded studies
D	Venous Leg Ulcer Guideline Development Committee Disclosure of Interest and Confidentiality
E	Search strategies

APPENDIX A: EXPERT WORKING COMMITTEE

1. Membership of the Expert Working Committee

The Expert Working Committee that has overseen the development of the guideline consisted of a vascular surgeon, geriatrician, nurse practitioners, registered nurses, three consumer representatives, a medical research consultant and an NHMRC GAR consultant. The Expert Working Committee comprised:

Committee member	Speciality and qualifications	Location and setting of clinical practice	Types of populations
Donna Angel	Nurse practitioner (wound management) RN; BN; NP; PGradDip(Clin Spec); MSc(Nurs); MRCNA	Perth and surrounds, WA • Hospital setting • Telehealth	• Urban • Rural • Remote • Maori and Pacific Island communities
Judith Barker, Vice-Chair	Nurse practitioner (wound management) RN; NP; STN; BHlthSc(Nurs); MN(NP)	ACT • Community care • Out-patient clinics • Residential care	• Urban • Multicultural populations
Debbie Blanchfield	Clinical nurse consultant: wound care RN; M Wound Care	Illawarra and Shoalhaven region, NSW • Hospital setting • Community care	• Urban • Rural • Multicultural populations
Keryln Carville	A/Professor RN; STN(Cred); PhD	Perth, WA • Community care • Education • Research • Telehealth • Residential care	• Urban • Rural • Remote • Australian Indigenous communities
Roy Cochrane	Consumer representative	Melbourne, Vic	N/A
Emily Haesler	Methodologist and researcher BN; PGradDip(AdvNsg)	Canberra, ACT	N/A
Catherine Hammond	Clinical nurse specialist: wound care RN; MN	Christchurch, New Zealand • Hospital setting • Residential care	• Urban • Rural • Maori and Pacific Island communities
David Hardman, Chair	Vascular surgeon A/ Professor MBBS(Hons); LLB(Hons); GradCertHE; FRACS; FACLM	ACT Rural region, NSW • Private and public practice • Out-patient clinics • Surgery	• Urban • Rural • Multicultural populations
Susan Hillier	NHMRC GAR consultant BAppSc(Physiotherapy); PhD	Adelaide, SA	N/A
Suzanne Kapp	Clinical nurse consultant BN; PGradDip(AdvNsg); MSc(Nurs)	Melbourne, Vic • Community care • Education • Research	• Urban • Rural
Deane Larkman	Consumer representative BSc(Hons); GradDipCompStud; MIT	Canberra, ACT	N/A
Judith Manning	Clinical nurse (wound management) RN; MA; BEd	Adelaide, SA • Residential care • Education	• Urban • Multicultural populations

Bill McGuiness	AWMA President; A/ Professor RN; DipT; BN; MNS; PhD	Melbourne, Vic • Hospital setting • Community care • Residential care • Tertiary education	• Urban • Multicultural populations
Robyn Rayner	Clinical nurse (wound management) RN; BSc(Nursing); PGrad Health Admin; M Wound Care	Bunbury, WA • Community care Perth, WA • Education	• Urban • Rural • Remote • Australian Indigenous communities
Jan Rice	Clinical nurse educator RN; M Wound Care; MRCNA; Cert. Plastic & Reconstructive Surgery; FAWMA	Melbourne, Vic • Community care • Out-patient clinics • General Practice • Residential care • Education	• Urban • Rural • Remote • Australian Indigenous communities • 3rd World countries
Pip Rutherford	Nurse practitioner RGON; BN; GDCM; GradCert Wound Care; MN	Hawkes Bay, New Zealand • Hospital setting • Community care • Out-patient clinics • Residential care • Teleconference	• Urban • Rural • Remote • Maori and Pacific Island communities
Juliet Scott	Clinical nurse consultant/ Endorsed NP BAppSci(Prim Hlth); Grad Cert; GradDipDN; MN	Tasmania • Primary health/community • Hospital setting • Rural • Out-patient clinics • Education • Residential • Telehealth	• Urban • Rural • Remote • Multicultural populations
Jill Sparks	Clinical nurse consultant (wound management) RN; DipNsg; GradDipMdwfy; MN	Western Sydney & Nepean Blue Mountains Local Health Networks, HSW • Hospital clinics • Community care • Telehealth	• Urban • Multicultural populations
Sue Templeton	Nurse practitioner (wound management) RN; BN; MNSci(NP)	Adelaide, SA • Community Care	• Urban • Multicultural populations
Carolina Weller	PhD scholar RN; BN; MEd(Research); GradCert Higher Education	Melbourne, Vic • Hospital setting • General practice • Out-patient clinics • Education and research	• Urban • Rural
Peter Wilkins	Consumer representative	Canberra, ACT	N/A
Michael Woodward	A/Professor MB; BS; MD; FRACP	Melbourne, Vic • Hospital setting • Out-patient clinics	• Urban • Multicultural populations

2. Conflicts of Interest

Members of the Expert Working Committee completed an AWMA declaration of conflict of interest and confidentiality statement (Appendix D) 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
Emily Haesler	No conflicts to declare
Catherine 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	Sponsorship from ArjoHuntleigh to attend a conference
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	Education grant from Sutherland Medical
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 B: PROCESS REPORT

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

The project consisted of the following phases:

- formation of a multidisciplinary Expert Working Committee (see Appendix A)
- development of a scoping document providing an overview of the objectives and process for the development of the guideline that was registered with the NHMRC
- regular reporting to the NHMRC on the process and progress via the NHMRC GAR consultant
- 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
- response to feedback and completion of final guideline.

1 Identification, appraisal and synthesis of new evidence

Search strategy

Searches were conducted for papers on the diagnosis and management of VLUs. The main search was performed in MEDLINE, Embase, CINAHL, The Cochrane Library including the CENTRAL Cochrane Controlled Trial Register, The WHO International Clinical Trials Registry Platform Search Portal, the Australian Wound Management Association journal, Wound Practcie and Research 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 SRs and RCTs to limit the identified evidence to that of a high level. An additional search was conducted to identify different types of studies (for example, cohort trials, case-control studies) related to assessment of VLUs, in order to inform the body of evidence. This search combined terms related to assessment and prognosis combined with VLU terms.

In January 2011 an additional abridged search was conducted in MEDLINE and The Cochrane Library using search terms describing venous ulceration to identify new research published during the development time frame of this guideline. Studies that met the review criteria and substantially added to the body of evidence were appraised and included in the guideline.

Although the initial searches were 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 VLUs with terms to describe Indigenous populations. No papers that met the review inclusion criteria were identified in this search. The search strategies are provided in full in Appendix E.

Inclusion/exclusion criteria

Types of studies

Table B.1: NHMRC levels of evidence[15]

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 allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised, controlled trial	A comparison with reference standard that does not meet the criteria 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)

Studies that provide Level I or Level II evidence on the NHMRC Levels of evidence scale[15] (see Table B.1) were considered for inclusion. For intervention studies, RCTs (or systematic reviews of RCTs) that compared a single or combination intervention with placebo, sham-intervention, no treatment or another active intervention were included. RCTs that were reported in SRs that were included were not subjected to individual critical appraisal to prevent replication of data.

Types of participants

The review included research conducted in participants with VLUs and participants at risk of developing VLUs. There were no age restrictions.

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, social/education groups.
- Diagnosis and assessment: Doppler studies — measurements of 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 (for example, number of new ulcers developed in trial period).

- Other outcomes related to the intervention: QOL and global assessments, functional outcomes, venous ulcer specific QOL, 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 GAR consultant recommended 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 all the research. 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 SRs 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 RCTs was assessed against key criteria on the SIGN assessment tool. The SIGN tool includes critical appraisal of all components suggested by the NHMRC[198] including:

- randomisation and allocation concealment methods
- similarity of study groups at baseline regarding prognostic indicators
- blinding of subjects, therapists/researchers and assessors of the outcomes
- measurement of outcome measurements in a standard, valid and reliable manner
- follow-up of subjects
- all subjects 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"
- clear reporting of potential conflicts of interest.

Cohort trials and case studies were also appraised using critical appraisal tools available at the SIGN website. These tools assist in the critical appraisal of all components identified by the NHMRC.[198]

SRs and RCTs considered to at low risk of bias after assessing the above factors are referred to throughout the guideline as being of high quality, and those assessed as being at high risk of bias are referred to as being low quality.

Data extraction

The primary reviewer systematically extracted the data from all studies using a data extraction tool that combined NHMRC data extraction[15] suggestions with information collected using the SIGN checklist tools. A second reviewer checked data extraction for 100% of SR papers and 30% of the additional research. Data from included studies was presented in evidence summaries.

Special populations

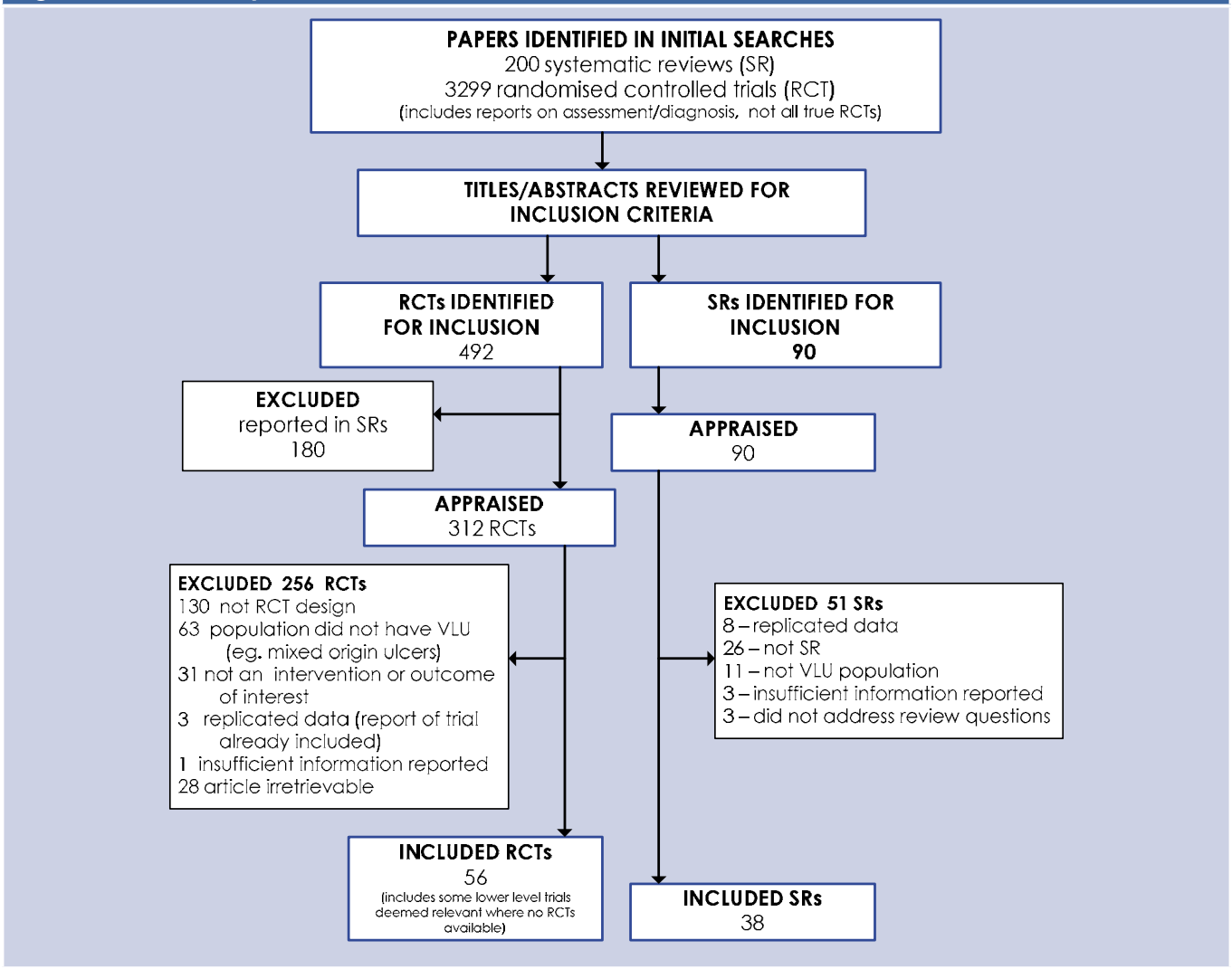
The search strategy was designed to retrieve all available evidence meeting the inclusion criteria, including research specific to special populations including Aboriginal and Torres Strait Islander people; rural and remote communities; and people from CALD backgrounds.

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

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 B.1, a total of 553 papers were identified for retrieval, of which 86 were SRs. 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 C.

Figure B.1: Review process



2 Development and grading of 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 collated into evidence summaries. A body of evidence assessment matrix outlined in *NHMRC levels of evidence and grades for recommendations for developers of guidelines* (2009)[15] (Table B.2) was used to assess the volume and consistency of evidence supporting each recommendation; as

well as the clinical impact, generalisability and applicability. The Expert Working Committee considered one low-quality study as insufficient evidence on which a graded recommendation could be made and also considered it inappropriate to make recommendations for interventions not currently available in Australia or New Zealand.

Table B.2: Body of evidence assessment matrix[15]

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several Level I or Level II studies with low risk of bias	One or two Level II studies with low risk of bias or an 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 health care context	Applicable to Australian health care context with few caveats	Probably applicable to Australian health care context with some caveats	Not applicable to Australian health care context

****Applicability to the New Zealand context was also considered***

Each recommendation was given a final grading (Table B.3) 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 A or B unless the volume and consistency of evidence components were both graded either A or B.

Table B.3: Recommendation grades[15]

Evidence-based recommendations	
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
Consensus-based recommendations (CBR)	
CBR	Consensus evidence — a graded recommendation could not be made due to a lack of evidence from SRs or RCTs in populations with VLUs. The CBRs are supported by all members of the Expert Working Committee.

Process for expert opinion recommendations (grade CBR)

Consensus-based recommendations (CBRs) have been made for areas in which no research conducted in populations with VLUs was identified in the literature search. These recommendations address topics considered important by the Expert Working Committee. CBRs were developed through group discussion and email. Discussion continued until consensus was reached.

The NHMRC grading system does not recognise non-analytical studies, discussion, case studies or opinion of experts; therefore, fields for which this is the best available evidence fall outside the grading system. A full search for these lower levels of evidence was not conducted; however, other evidence-based guidelines or reviews conducted in similar populations (for example, patients with chronic wounds) have been used to support the expert opinion recommendations.

3 Consultation phase

Draft versions of the *Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers* and *Grading of the Australian and New Zealand recommendations for prevention and management of venous leg ulcers* were presented to the AWMA committee and NZWCS membership for comment and feedback. These groups consist of professionals representing all major fields of health care including general practice, specialist medical and surgical fields, nursing, physiotherapy, podiatry, education and wound care.

In October 2010 draft versions of the *Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers* and *Grading of the Australian and New Zealand recommendations for 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. In October 2010 the AWMA and NZWCS also solicited feedback and comment directly from peak bodies and groups representing health professionals.

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

- Pharmacy Guild of Australia
- Australasian Lymphology Association, Compression Garment Subcommittee, Queensland, Australia
- Marianne Cutler, Kylie Elder, Megan Gibbs, Suzanne Kapp, Raquel Kempster, Sally Kime, Linda Mills, Jenny Pilgrim, Jane Piper, Carmen Pout, Wound Management Clinical Leadership Group, Royal District Nursing Service Royal District Nursing Service St Kilda, Victoria, Australia
- Annette Finlay, Quality & Risk Coordinator, Christchurch, New Zealand
- Adrian Te Patu, Maori Cultural Advisor, Christchurch, New Zealand
- Juliet Bentin, Pacific Registered Nurse, New Zealand
- Christine Cumming, Nurse Educator, New Zealand
- Desley Johnson, Clinical Nurse Specialist in Wound Care, New Zealand
- Julie Vickery, Charge Nurse of District Nursing, New Zealand
- Karen Huxtable, Clinical Nurse Specialist in Wound Care, New Zealand
- Julie Betts, Nurse Practitioner Wound Care, Waikato, New Zealand
- Kate Gray, Clinical Nurse Specialist — Wound Care, Hitt Valley DHB, New Zealand
- Amanda Pagan, Clinical Nurse Specialist — Wound Care, Southern Region DHB, New Zealand
- A/Professor David Lewis, Vascular Surgeon Christchurch Hospital & University of Otago, Christchurch School of Medicine, New Zealand
- Rimi Statkus, Diabetes Specialist Podiatrist, Tasmania, Australia
- Deb Geard, Community Nurse, Tasmania, Australia
- Dr Andrew Jull, Associate Professor, School of Nursing, University of Auckland, New Zealand
- Marianne Cullen, Clinical Nurse Consultant — Wound Management, Victoria, Australia
- Jane Gallagher, Community Care Policy, DVA, Canberra, Australia
- Dr David Huber, Chair Section of Vascular Surgery, Wollongong Hospital, Australia

- Catherine Sharp, Founder and CEO The Wound Centre, Sydney, Australia
- Dr Hugo Partsch, Professor of Dermatology, Medical University of Vienna, Austria
- Dr Laurie Foley, Podiatrist, Perth, Australia
- Sheralee Sandison, Australian and New Zealand Society of Vascular Nurses
- Christine Gruys, Clinical Nurse Specialist — Wound Care, Taranaki, New Zealand
- Marina Boogaerts, Clinical Nurse Consultant, Continuing Care Program, ACT Health, Australia
- Ann Marie Dunk, Clinical Nurse Consultant Wound Management, ACT Health, Australia
- Dr Violeta Lopez, Professor and Director, Research Centre for Nursing and Midwifery Medical School, CMBE, Australian National University, Australia
- Wendy White, Wound Care Consultant, Woongarrah, NSW, Australia
- Angela Carter, District Nurse, New Zealand
- Desley Rosevear, District Nurse, New Zealand
- Vanessa Witt, RN, New Zealand
- Mary Cleland, New Zealand
- Betty Hassell
- Felicity Wilson, New Zealand
- Sheena Crabb, District Nurse, New Zealand

4 Dissemination

Final versions of the *Australian and New Zealand clinical practice guideline for prevention and management of venous leg ulcers* and *Grading of the Australian and New Zealand recommendations for prevention and management of venous leg ulcers* will be publicly available on the AWMA website, http://www.awma.com.au/ and the NZWCS website, http://www.nzwcs.org.nz

The AWMA and NZWCS intend to develop and distribute appropriate resources related to the guideline 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. Consumer-appropriate versions of the guideline and an abridged version of the guideline will also be developed.

APPENDIX C: EXCLUDED STUDIES

Reasons for exclusion of SRs	
1	replicated data
2	not an 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 SRs	Reason
Al-Kurdi D, Bell-Syer SE & Flemming K. Therapeutic ultrasound for venous leg ulcers. Cochrane Database of Systematic Reviews 2008; 1.	1
Amsler F & Blattler W. Compression Therapy for Occupational Leg Symptoms and Chronic Venous Disorders — a Meta-analysis of Randomised Controlled Trials. European Journal of Vascular and Endovascular Surgery 2008; 35(3):366–372.	3
Anand S, Dean C, Nettleton R & Praburaj D. Health-related quality of life tools for venous-ulcerated patients. British Journal of Nursing 2003; 12(1):48–59.	2
Berliner E, Ozbilgin B & Zarin D. A systematic review of pneumatic compression for treatment of chronic venous insufficiency and venous ulcers. Journal of Vascular Surgery 2003; 37(3):539–44.	4
Briggs M & Flemming K. Living with leg ulceration: a synthesis of qualitative research. Journal of Advanced Nursing 2007; 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. Leg ulcer treatment. Journal of Vascular Surgery 2009; 49(3):804–808.	2
Crowe T & Brockbank C. Nutrition therapy in the prevention and treatment of pressure ulcers. Wound Practice and Research 2009; 17(2).	2
Curran M & Plosker G. Bilayered bioengineered skin substitute (Apligraf): a review of its use in the treatment of venous leg ulcers and diabetic foot ulcers. Biodrugs 2002; 16(6):439–55.	2
Duncan G & Brooks M. Chronic wound pain: a literature review. Wound Practice and Research 2009; 17(3).	3
Duprez D. Ultrasound diagnostics of lower limb venous diseases. International Angiology 1993; 12(3 Suppl 1):45.	2
Ernst E. Ultrasound for cutaneous wound healing. Phlebology 1995; 10(1):2–4.	2
Flemming L, Cullum N & Nelson E. A systematic review of laser therapy for venous leg ulcers. Journal of Wound Care 1999; 8(3):111–4.	1
Fletcher A, Cullum N & Sheldon T. A systematic review of compression treatment for venous leg ulcers. British Medical Journal 1997; 315(7108):576–580.	1
Franks P & Morgan P. Health-related quality of life with chronic leg ulceration. Expert Review of Pharmacoeconomics and Outcomes Research 2003; 3(5):611–622.	2
Gray M. Does oral supplementation with vitamins A or E promote healing of chronic wounds Journal of Wound Ostomy and Continence Nursing 2003; 30(6):290–294.	2
Green J & Jester R. Health-related quality of life and chronic venous leg ulceration: Part 2. British Journal of Community Nursing 2010; 15(3):S4–6, S8, S10.	6
Green J & Jester R. Health-related quality of life and chronic venous leg ulceration: part 1. British Journal of Community Nursing 2009; 14(12):ss12,14,16–7.	6
Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F & Lange S. Negative pressure wound therapy: A vacuum of evidence? Archives of Surgery 2008; 143(2):189–196.	3
Heinen M, van Achterberg T, op Reimer W, van de Kerkhof P & de Laat E. Venous leg ulcer patients: a review of the literature on lifestyle and pain-related interventions. Journal of Clinical Nursing 2004; 13(3):355–66.	4
Herber O, Schnepp W & Rieger M. A systematic review on the impact of leg ulceration on patients' quality of life. Health and Quality of Life Outcomes 2007; 5.	5
Howell-Jones R, Wilson M, Hill K, Howard A, Price P & Thomas D. A review of the microbiology, antibiotic usage and resistance in chronic skin wounds. Journal of Antimicrobial Chemotherapy 2005; 55(2):143–149.	2
Jull A, Waters J & Arroll B. Pentoxifylline for treatment of venous leg ulcers: A systematic review. Lancet 2002; 359(9317):1550–1554.	1

Excluded SRs	Reason
Khan M & Davies C. Advances in the management of leg ulcers — The potential role of growth factors. International Wound Journal 2006; 3(2):113–120.	2
Kranke P, Bennett M, Debus S, Roeckl-Wiedmann I & Schnabel Alexander. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database of Systematic Reviews 2004; 1.	1
Lazarides M & Giannoukas A. The role of hemodynamic measurements in the management of venous and ischemic ulcers. International Journal of Lower Extremity Wounds 2007; 6(4):254–261.	2
Machet L, Couhe C, Perrinaud A, Hoarau C, Lorette G & Vaillant L. 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 2004; 150(5):929–35.	2
McCann M. Toe bandaging for lymphoedema and venous ulceration. British Journal of Nursing 2008; 17(7):428, 430–3.	2
Nelson E, Cullum N & Jones J. Venous leg ulcers. American Family Physician 2005; 71(7):1365–1366.	2
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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

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APPENDIX D

Venous Leg Ulcer Guideline Development Committee

Disclosure of Interest and Confidentiality

Committee Members' Responsibilities regarding 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 conflicts of interest can be addressed in a transparent and appropriate manner.

The guidelines are designed to guide the committee and co-opted 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 VLUGDC.

*All other persons appointed, engaged or co-opted to assist the work of the AWMA VLUGDC.

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 VLUGDC or who is co-opted 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 include 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 (for example, a hospital or higher education institution) in circumstances where the member will benefit financially from their involvement.

- 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, for example, 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 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 VLUGDC 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 the project is completed forwarded to the 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 VLUGDC 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-chairperson. 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 nor 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.

APPENDIX E: SEARCH STRATEGIES

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 randomised controlled trial.pt.
2 controlled clinical trial.pt.
3 randomised.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

Search strategy for diagnosis/assessment

1 exp Leg Ulcer/
2 Varicose Ulcer/
3 Venous Insufficiency/
4 Venous ulceration.mp.
5 Varicose eczema.mp.
6 1 or 2 or 3 or 4 or 5
7 Sensitivity and specificity/

8 Diagnosis/
9 Diagnosis, Differential/
10 sensitivity.mp
11 specificity.mp
12 assessment.mp
14 predictive.mp
15 Nursing Assessment/
15 assessment tool.mp
16 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17 6 and 16

Additional search strategy for Australian Indigenous populations

1 Oceanic Ancestry Group/
2 Aboriginal.mp
3. Indigenous.mp
4. 1 or 2 or 3
5. exp Leg Ulcer/
2 Varicose Ulcer/
3 Venous Insufficiency/
4 Venous ulceration.mp.
5 Varicose eczema.mp.
6 1 or 2 or 3 or 4 or 5
7 4 and 6

Search strategy for updated research

1 exp Leg Ulcer/
2 Varicose Ulcer/
3 Venous Insufficiency/
4 Venous ulceration.mp.
5 Varicose eczema.mp.
6 1 or 2 or 3 or 4 or 5
7 limit 7 to (english language and humans and yr=»2009 -Current»)

NOTES

NOTES

The Australian Wound Management Association Inc.

New Zealand Wound Care Society Inc.