GRADING OF THE AUSTRALIAN AND NEW ZEALAND RESEARCH BASED RECOMMENDATIONS FOR THE PREVENTION AND MANAGEMENT OF VENOUS LEG ULCERS

The Australian Wound Management Association Inc

The New Zealand Wound Care Society

Contents

1. INTRODUCTION

1.1 Process

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

The full recommendations, together with practice tips are available in *Australia and New Zealand clinical practice guideline for the prevention and management of venous leg ulcers*. This guideline is based on an evidence-based literature review conducted to NHMRC requirements.

Evidence statements

A systematic search for literature published from 1985 to 2009 was conducted and studies providing Level I evidence or Level II evidence on the NHMRC Levels of evidence scale[1] (see Table one) were considered for inclusion. Individual research papers that met the inclusion criteria were critically appraised using checklists developed by SIGN[2] and given an overall descriptive quality of high, moderate or low.

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

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

Table one – NHMRC levels of evidence[1]

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)

Recommendations

Each recommendation statement is supported by a grading from A to D (evidence based research) or EBO (expert based opinion) that reflects the strength of the recommendation and the trust or confidence health professionals can place in the recommendation when it is implemented in clinical practice. The recommendation grades are based on *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (2005)*[1] presented in Table two.

Table two: Recommendation grades[1]	
Evidence based research	
A	Excellent evidence - body of evidence can be trusted to guide practice
B	Good evidence - body of evidence can be trusted to guide practice in most situations
C	Some evidence - body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Weak evidence - body of evidence is weak and recommendation must be applied with caution
Expert based opinion	
EBO	Consensus evidence – there was insufficient evidence to make a graded recommendation due to insufficient or no evidence from systematic reviews or RCTs or the literature search not locating research addressing the field. The EBO recommendations are supported by all members of the Expert Working Committee.

The overall grade of each recommendation is based on a summation of an appraisal of individual components of the body of evidence on which the recommendation is based, including volume and consistency of the evidence. Table 3 shows the body of evidence assessment matrix, listing all the components that were considered when assessing the body of evidence, together with the grades used.[1]

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

The expert based opinion recommendations are available in *Australia and New Zealand clinical practice guideline for the prevention and management of venous leg ulcers*. As the research underpinning these recommendations has not been appraised and graded, they are not included in this grading document.

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

1.2 Commonly used abbreviations

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

1.3 Glossary

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

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

2. RESEARCH BASED RECOMMENDATIONS FOR PRIMARY PREVENTION OF VLUS

2.1 hlebotics

Evidence Summary		
A Cochrane review[3] investigated the effectiveness of oral and topical phlebotics for treating CVI. One of the primary outcomes of the SR was prevention of VLUs, which was reported in two trials. The trials, conducted in participants with moderate CVI, were of moderate to low quality and of short duration (1 to 3 months) and all participants used concurrent compression therapy. The trials compared the effectiveness of diosmine, hidrosmine or rutosides (n=80 over two trials) to placebo (n=80 over two trials). Pooled findings showed no statistically significant effect for phlebotics compared to placebo (59 ulcers vs. 60 ulcers, fixed effects model RR 0.95; 95% CI 0.80 to 1.13, p=0.56). When analysis was restricted to the higher quality trial, the effect for phlebotics in preventing VLU bordered on significance (39 ulcers vs. 46 ulcers; RR 0.83, 95% CI 0.69 to 1.00, p=0.056). The safety analysis included data from all trials included within the review, most of which did not report ulcer development as an outcome measure. Pooled data from 13 studies found no significant difference in the rate of adverse events between phlebotics and placebo. The reviewers concluded that there was insufficient evidence to suggest that phlebotonics are effective in treating CVI; and the findings regarding effect in preventing VLUs were inconsistent.[3]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
one good quality SR and meta-analysis[3]	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
One trial reported an effect and the other trial reported no effect.	**Some inconsistency, reflecting genuine uncertainty around question**	**C**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Pooled results showed no effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Participant characteristics were not reported in detail. Participants had moderate CVI.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted in France. There were no trials conducted in people from Aboriginal and Torres Straight Island or Maori backgrounds.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		

None
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***
There is inconsistent evidence on the effectiveness of phlebotics in preventing the development of VLUs in patients with venous disease. Body of evidence provides some support for recommendation(s) but care should be taken in its application **Grade C**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? Patients will need to be reviewed by a health professional who can prescribe medication. This may impact on the organisation of care in community clinics.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Patients who choose to take medications may have difficulty gaining access.	**YES**

3. RESEARCH BASED RECOMMENDATIONS FOR MANAGEMENT OF VLUS

3.1 Compression therapy

Evidence Summary *(an abridged version of the evidence detailed in the literature review)*

One good quality systematic review[4] reported the results from 7 moderate and low quality RCTs investigating the effect of compression bandaging compared to usual care (primary dressing). The trials used different methods and compression techniques over different periods of time and results were not suitable for pooling. In one trial (n=36) Unna's boot was found to be more effective than a polyurethane foam dressing for completed healed ulcers after 12 months (RR 2.30; 95% CI 1.29 to 4.10, p=0.0047). In one trial comparing four layer bandaging (4LB) to usual care (n=36) compression therapy was related to greater healing at three months (RR 4.0 95% CI 1.35 to 11.82, p=0.01). Another trial (n=36) found 4LB was no different to usual care for complete healing rate at 12 months (RR 1.18, 95% CI 0.96 to 1.47, p=0.12); however post-hoc analyses adjusting for patient age and baseline ulcer condition found healing was faster in the compression group. In a larger trial (n=200) comparing 4LB to standard care, there was significantly (p=0.06) faster healing in the participants receiving compression. A trial comparing short stretch bandage (SSB) to usual care (n=53) found greater numbers of complete healing at three months in those receiving compression (71% versus 25%). The other trials were small, had uneven groups and were at a high risk of bias.[4]

A second good quality systematic review and meta analysis[5] supported these findings. This earlier review[5] identified 8 trials, 5 of which are reported by O'Meara et al.[4] 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).[5]

One good quality cross-over RCT (n=81)[6] reported the effectiveness of two layer bandaging compression system compared to 4-layer bandaging in complete VLU healing. The trial was designed to measure the difference in bandage slippage. Although there was less bandage slippage for the two layer bandaging system there was no significant difference in ulcer healing rates. Patients preferred the two layer bandaging system. The trial was sponsored by a product manufacturer.[6]

One moderate quality RCT[7] (n=16) investigated the effectiveness of intermittent pump compression compared to compression bandaging. The researchers reported no significant difference between groups in ulcer size or leg volume, with both groups achieving a significant reduction (p<0.012) in ulcer size after 6 months. The trial was inadequately powered and did not report on adverse events.[7]

One low quality SR[8] reported on studies investigating training of nurses applying compression bandaging. The review included three pre-test post-test trials that assessed the amount of pressure applied. The three small studies reported that clinical bandaging skills can be improved through education programs however the effects may not be sustained beyond 10 weeks. None of the trials were randomised or adequately powered.[8]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*

Two good quality SRs[4, 5] reporting moderate and low quality trials. One additional SR[8] on education and 2 RCTs[6, 7] comparing different types of compression.	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**

Consistency		
Most trials showed compression was superior to usual care. In trials which showed no difference there were baseline differences between groups in size or duration of ulcers.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RR ranged from small to large. (RR 1.18 to 4.0)	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. In most trials patients were excluded if their limbs were oedematous, if they had diabetes, CV disease or arterial disease.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		
The majority of trials were conducted in Europe. There was no research on the effect/compliance of compression therapy in tropic or humid climates. Many clients may have limited access to the most appropriate compression intervention. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

There is good evidence that applying compression therapy is effective in promoting healing in VLUs.

Body of evidence can be trusted to guide practice in most situations **Grade B**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care currently includes compression therapy.	**NO**
Are there any resource implications associated with implementing this recommendation? There are resource implications related to this recommendation. Many patients do not have access to the most appropriate form of compression therapy, or are limited in the use of this intervention by financial constraints.	**YES**

Will the implementation of this recommendation require changes in the way care is currently organised? To implement this recommendation, more patients require referral to appropriate services where they can access the intervention, have compression applied on a regular basis and/or receive education in the importance of compression therapy and its application. There is a particular need for support for patients in rural and remote locations.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Many patients have limited access to the most appropriate healthcare services and compression products. Clinicians involved in wound management require appropriate training to apply compression therapy in a manner that achieves effective results.	**YES**

3.2 Dressings

Evidence Summary

One good quality SR[9] of 42 primarily low quality trials including 3001 participants with VLU. The review concluded that there is no evidence that any dressing product is superior to others. The reviewers suggest that in light of lack of evidence of superiority of any product, choice of dressing should be based on convenience, access and cost effectiveness. [9] Results are summarised below.

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

Pooled results from four RCTs (n=311) compared hydrocolloid dressings to foam dressings for 12 to 13 weeks showed no difference in complete healing at 12 weeks (RR 0.98 95% CI 0.79 to 1.22, p=0.87). Two RCTs (n=80) compared hydrocolloid dressings to alginate dressings. Pooled analysis showed a high heterogeneity and no significant difference in healing (RR 0.92 95% CI 0.48 to 1.69). Two RCTs (n=69) comparing different hydrocolloid products to each other were pooled in meta-analysis. There was high heterogeneity and no difference between products for complete healing over 8 weeks. (RR 1.56, 95% CI 0.67 to 3.63). Five additional small (n = 28 to 153) trials comparing hydrocolloid dressings to hydrogel, gauze, lyophilised collagen and magnesium sulphate paste beneath gauze showed no significant differences in complete ulcer healing. [9]

The results from two RCTs (n=203) comparing foam dressings to low adherent dressings for 12 and 17 weeks were pooled in meta-analysis and showed no significant difference in healing (RR RR 1.35 95% CI 0.93 to 1.94). Pooled results of two trials (n=136) found no significant difference in ulcer healing between products (RR 1.2, 95% CI 0.77 to 1.87, no heterogeneity). [9]

Five trials investigated hydrogel compared to low adherent dressings, a miscellaneous dressing and other hydrogel products. The trial on miscellaneous dressings (porcine skin and aluminium foil dressing) was small (n=53) and did not report total ulcers healed. There was two RCTs comparing different types of hydrogel; however meta-analysis was not possible due to incomplete data. Results reported in the systematic review state there was no significant difference between different hydrogels. Pooled data for two trials (n=151) comparing hydrogels to low adherent dressings for 12 weeks showed no significant difference between the products in complete ulcer healing (RR 1.53, 95% CI 0.96 to 2.42, no heterogeneity). [9]

One trial (n=60) comparing alginate to low adhesive dressings and another trial comparing two types of alginate dressings both showed no difference in healing rates. [9] One low quality RCT (n=95) compared cadoximer iodine powder to standard treatment. There was a 34% reduction in mean percentage of ulcer area cadoximer iodine group compared to a 5% increase in the standard therapy group after 6 weeks of treatment. One RCT (n=24 ulcers) compared a hyaluronan derivative fleece dressing to a paraffin gauze dressing used for 8 weeks. Individual ulcers were the end-point in the trial, with some participants (n=17) having more than one ulcer. The ITT analysis showed a significant reduction in the mean ulcer area ($p<0.002$) favouring the hyaluronan dressing; however comparability at baseline was not reported. One low quality RCT (n=40) compared a polyamide active charcoal dressing to a dressing applied according to the stage of healing showed no significant difference between the two dressing types over 6 weeks.[9]

Another good quality SR[10] supported the conclusions of the Palfreyman[9] 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[9] review, were generally of low to moderate quality. Nine RCTs compared hydrocolloid dressings to traditional dressings, of which one trial reported a significant result (hydrocolloids as superior to paraffin impregnated tulle); however the participants were not equivalent on baseline characteristics (ulcer size) in the trial. Eight of the trials provided data on ulcer healing and were pooled in a meta-analysis using a random effects model which showed significant heterogeneity. The pooled analysis showed no significant difference between hydrocolloids and traditional dressings (OR 1.4, 95% CI 0.83 to 2.34). Eleven RCTs made head-to-head comparisons of specific dressing types including collagen sponge dressing compared with dextranomer beads; lyophilised collagen dressing compared with hydrocolloid dressing; hydropolymer dressing compared with hydrocolloid dressing; hydrocolloid dressing compared to alginate dressing; four trials comparing different hydrocolloid types; and two trials comparing hydrocolloid to foam dressings. One trial (collagen sponge dressing compared with dextranomer beads) reported shorter healing times for hydrocolloid dressings, but results in the other trials were insignificant.[10]

A moderate quality SR[11] of low quality studies included 20 mostly low quality RCTs, of which five showed a statistically significant improvement in healing rate associated with the experimental dressing. Nine RCTs investigating semi-occlusive dressings were reported; however the trials were heterogeneous and results were unable to be pooled. Graphical reporting of the results from individual trials indicated that none of the 9 studies showed a statistically significant effect. Five RCTs investigating human skin equivalent (HSE) dressings were reported; however the trials heterogeneous and results were unable to be pooled in meta analysis. One of the trials showed a significant result in favour of HSE dressings. Eight trials investigated growth factor (GF) dressings, of which only two showed significant results. A pooled analysis from the eight RCTs using a random effects model favoured GF dressings over control dressings (eg. gauze pad, Adaptic™, hydrocolloid). GF dressings were superior for total healing, with a risk ratio of approximately 0.8 (reported graphically). Frequency of dressing changes and the control dressing varied between trials.[11]

A second moderate quality SR[12] 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.[11] Most of the trials excluded participants with ABPI < 0.80 and with chronic or serious disease including diabetes. Inclusion criteria for ulcers ranged between the trials, with some excluding ulcers greater than 10cm^2 and other trials limiting inclusion to ulcers less than 100cm^2. Some trials excluded infected ulcers. Although there was a range in the severity of ulcers being treated in these trials, there was no significant heterogeneity. Results from 8 RCTs (n=397) comparing hydrocolloid dressings to conventional dressings (e.g. gauze with paraffin or povidone iodine, non–adherent knitted viscose, paraffin–soaked gauze) for 10 weeks to 6 months were pooled. Most of the trials had non–significant results, and the pooled result for proportion of ulcers healed at completion also showed no significant difference (RR 0.99, 95% CI 0.85 to 1.15, p=0.90). Six RCTs compared hydrocolloid dressings to either polyurethane, another hydrocolloid or alginate dressings for 6 to 16 weeks. Pooled results showed no statistically significant difference in number of ulcers healed (RR 1.13, 95% CI 0.86 to 1.47, p=0.40). Results from 3 RCTs (n= 238) investigating polyurethane dressings compared to traditional dressing types (moist gauze, paraffin–soaked gauze, and non–adherent knitted viscose) for 12 weeks to 12 months were pooled. No significant difference in proportion of ulcers healed at the completion was found (RR 0.92; 95% CI 0.14 to 1.98, p=0.80).[12]

One low quality SR[13] included 16 trials that reported on the use of dressing products for managing VLUs. Papers ranged from experimental studies to case reports and the quality of evidence was indeterminable. The reviewers concluded that simple, non-adherent dressings that are of low cost and acceptable to the patient are the most appropriate type for treating VLU. Polyurethane foam, hydrocolloid and calcium alginate are recommended as the best options, with hydrofiber and calcium alginate dressings recommended for heavy exudate and either polyurethane foam for low to moderate exudate. However, these recommendations should be considered cautiously due to the poor quality of this review, and the

restriction of evidence to products available in Brazil in 2003.[13]

One low quality, unblinded RCT[14] investigated the efficacy of a biocellulose wound dressing (BWD XCELL®) compared to standard care of an Adaptic™ dressing in 24 patients diagnosed with CVI who had VLUs of at least 2 months duration that were considered to require debridement. After 12 weeks treatment with weekly dressing changes and concurrent compression therapy, the results showed no significant difference in wound healing time, oedema or exudate, and although pain was lower in those treated with the biocellulose wound dressing, this only reached significance at some time points.[14]

A low quality RCT[15] that failed to report methods of randomisation, allocation concealment or blinding or baseline comparability compared a lipidcolloid dressing (Urgotul®) to Duoderm® used in conjunction with compression for up to 8 weeks. Participants (n=91) had an ABPI of at least 0.8, ulcer duration of 2 to 18 months and ulcer size between 4 and 40cm^2. Ulcer area was measured weekly using wound tracings, photography and planimetry. At 8 weeks there was no significant difference in reduction of ulcer surface area (Urogtul 61.3 ± 39.7%versus Duoderm 52.1 ± 66.2%) or mean time to healing (Urgotul 33.3 ± 11.0 days versus Duoderm 29.8 ± 7.1 days).[15]

A low quality, unblinded RCT[16] compared the effectiveness of a lipidcolloid dressing impregnated with nano-oligosaccharide factor (NOSF) compared to an oxidised regenerated cellulose ***(ORC)*** dressing. Participants had an ABPI of at least 0.8 and had been compliant with compression therapy for at least 2 months, mean ulcer duration of 11 months, mean ulcer size at baseline of 10cm^2 and 61% of ulcers were recurrent. Wounds were redressed every 3 days following mechanical debridement as required for 12 weeks or until the wound was completely reepithelialised. More than 20% of participants withdrew from the trial, primarily due to local adverse events. The ITT analysis showed significantly greater reduction in wound area for the NOSF dressing compared to the ORC dressing (54.4% vs. 12.9%; p=0.00286). Complete wound healing was not significantly different between the two groups. Participants reported less difficulty in removing dressings and less pain during dressing changes in the NOSF group.[16]

A low quality, un-blinded RCT[17] investigated healing rate of VLUs treated with an oxidised regenerated cellulose collagen matrix dressing compared to a hydrocolloid dressing. The researchers did not provide a description of randomisation, allocation concealment or baseline comparability of participants. Participants were 27 patients with CVI who had a VLU of between 30 days and 3 months duration and no systemic inflammatory disease or malignancy. The trial lasted for 12 weeks and wounds were assessed on days 5, 14 and 28 for wound size (method not reported) and MMP-2, gelatinase, elastase and plasmin activity from exudates samples. It is unclear if any participants withdrew from the trial or if the analysis included all randomised participants and the trial was likely to be underpowered to measure a significant effect. The group treated with the oxidised regenerated cellulose collagen matrix dressing had a reduction in MMP-2, gelatinase, elastase and plasmin activity compared to the control group; however this did not translate to a significant difference in wound healing time. Adverse events were not reported.[17]

In a low quality RCT[18] researchers investigated the effectiveness of a hydrocellular foam dressing compared to composite foam dressing for managing VLUs. Participants had an ABPI of at least 0.8, no clinical signs of infection and a venous ulcer between 2 and 165 cm^2. Participants with diabetes were eligible if their condition was well controlled. In the experimental group VLUs were dressed with a foam composite dressing (Versiva; n=55) and control VLUs (n=52) received an adhesive hydrocellular dressing (Allevyn; n=52). Both groups wore compression bandaging and dressings were changed as required or every 7 days for 12 weeks or until complete ulcer healing was achieved. Wound tracing were performed every 14 days. There was no significant difference primary outcome measures related to wound healing including rate of healing (0.41cm^2 per week vs. 0.43 cm^2 per week, p=0.13); percentage change per week (median 7.3% vs. 6.1%, p= 0.27) or percentage of ulcers completely healed (38.2% vs. 38.5%; p= 0.96). Investigators reported significant preference for the hydrocellular foam dressing for some subjectively rated variables (e.g. conformability,

p=0.05; ease of application, p=0.01) but there was no difference in ratings for exudate absorption, protection of surrounding skin, non-traumatic dressing removal, and ease of removal.

A low quality RCT[19] compared the efficacy of two different foam dressings, Allevyn (n=81) and Mepilex (n=75), for the healing of VLUs. Participants were 156 adult patients with an ABPI of at least 0.8 and a VLU of between 2 and 52 weeks duration. Participants were concurrently randomised to receive one of two types of compression bandaging. The primary outcome measure was complete ulcer closure, defined as complete re-epithelialisation of the reference limb, and pain assessed using McGill pain questionnaire and a VAS was a secondary outcome measure. After 24 weeks of therapy, the hazard ratio favoured Mepilex but the result was not significant (HR 1.50, 95% CI 0.86 to 2.62, p=0.16). There was a high withdrawal rate (29.5%), primarily due to mild adverse events, and the definition of complete healing to refer to the entire limb rather than the reference ulcer may have influenced the findings. It is unlikely the study was sufficiently powered to measure an effect given the concurrent randomization of compression therapy. Participants in both groups reported improved pain levels after dressing changes and progressively throughout the trial, with no between group differences.

Trials investigating ability of dressings to handle exudate

A low quality RCT[20] investigated ability of a hydropolymer dressing to manage heavy wound exudate from VLUs compared to an alginate dressing. Participants were 113 patients with ulcers of venous origin confirmed by an ABPI of at least 0.8 on Doppler ultrasound and ulcers less than 1cm in depth and less than 11cm wide. Exclusion criteria included wound necrosis, clinical signs of infection and hypersensitivity to dressing products. Participants received either a hydropolymer dressing (n=54) or an alginate dressing with a clear film (n=22) or a swab dressing (n=37). The ITT analysis included the more than 20% of participants who withdrew from the trial due to adverse events. The results found a significantly longer wear time for the hydropolymer dressing compared to the pooled alginate dressing groups (p=0.001) and no significant difference in healing rates. The findings should be considered cautiously due to the dressing change protocol that allowed for dressing changes for reasons unrelated to the dressing ability to control exudates (eg. protocol included suspected infection, dressing displacement due to activity or dressing in place more than 7 days). Using subjective measures such as ease of application and removal, both investigators and participants (p<0.01 for both) were more likely to favour the hydropolymer dressing.[20]

A low quality RCT[21] compared an extra absorbent dressing, (n=10) to an alginate dressing (n=9) for the management of heavily exudating VLUs for a maximum of 6 weeks. Participants had an ABPI of 0.8 or higher, ulcers no larger than 28cm^2 and required dressing changes at least three times per week. The primary outcome measure was number of dressing changes required due to heavy exudate, subjectively assessed by a nurse. The researchers reported that 78% of ulcers dressed with kaltostat required dressing changes due to heavy exudate, compared to 8% of ulcers treated with the extra absorbent dressing. Due to a reduction in the bulkiness of dressings, the researchers proposed that extra absorption dressings may increase quality of life and decrease isolation for patients; however this was not formally assessed in the trial.[21]

A low quality RCT[22] compared the effectiveness of a hydrocapillary dressing to a hydropolymer dressing for healing VLUs. Participants were adults with an ABPI of at least 0.8 and a heavily exudating VLU of at least 4 weeks duration that had a maximum size of 8cm^2 who had no acute infection, severe eczema and disease or medications that may influence healing. Patients were treated with either the hydrocapillary dressing (Alione; n=49) or a hydropolymer (Tielle™ or Tielle™ Plus; n=48) until their ulcer healed, or for a maximum of 12 months. At the conclusion of the trial there were no significant differences for wound healing time, reduction in ulcer size, dressing wear time, or adverse events (infection, maceration or allergy). Subjective assessments from nurses significantly favoured the hydrocapillary dressing for absorptive capacity (p<0.05), although there was no significant difference noted in objective measures (numbers of times dressing leaked or estimates of absorption by weighing the dressing). Subjective ratings by patients of comfort favoured the hydrocapillary

dressing (p<0.001).

Adverse events

Only one of the SRs reported an analysis on adverse events associated with primary dressings. A moderate quality SR pooled results from all trials comparing a modern dressing to a traditional dressing to compare withdrawal rates and adverse events.[12] 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).[12]

A low quality RCT[15] reported significantly more (p=0.039) adverse events including eczema and infection were recorded in the group treated with Duoderm compared to those treated with Urgotul. (23 adverse events vs.10 adverse events).

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

A small, low quality RCT[18] investigating the effectiveness and tolerability of a hydrocellular foam dressing (Versiva®) compared to composite foam dressing (Allevyn*) reported on adverse events. Adverse events including maceration, erythema and eczema were experienced by 24% of participants treated with the hydrocellular foam dressing and 29% of those treated with the foam dressing, which was not statistically different between the groups.[18]

A low quality RCT[19] 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.

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Five SRs, [9, 11-14] of which two were good quality and included over 40 moderate and low quality trials for which results were not pooled. 10 additional low quality RCT comparing different primary dressings.	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
Most trials showed compression was superior to usual care. In trials which showed no difference there were baseline differences between groups in size or duration of ulcers.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Most reviews and trials established no effect between different types of primary dressings.	**Restricted**	**D**

Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Trials were sometimes restricted to certain populations (e.g. VLU of a certain size or duration, lack of complicating medical diagnoses). The majority of trials were conducted in patients with an ABPI of at least 0.8 and without disease that would complicate healing processes. Some trials included participants with well controlled diabetes.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		
Trials were conducted internationally. Access to certain dressing products is likely to be restricted by location, cost and other factors. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is excellent evidence that no specific primary dressing product is superior for reducing healing time in VLUs. Dressings should be selected based on clinical assessment of the wound, cost, access and client/practitioner preferences. Body of evidence can be trusted to guide practice **Grade A**		
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Usual care currently includes a large range of dressings.		**NO**
Are there any resource implications associated with implementing this recommendation? There are resource implications related to this recommendation. Many patients do not have access to an appropriate primary dressing, or are limited by financial constraints.		**YES**

Will the implementation of this recommendation require changes in the way care is currently organised? In most instances a qualified practitioner assesses VLUs and determines the most appropriate primary dressing product. Ensuring all patients with a VLU are referred to an appropriate clinician with experience in assessing and treating VLUs may increase the selection of the most appropriate dressing type.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Many patients have limited access to the most appropriate healthcare services and dressing products. Clinicians involved in wound management require appropriate training to assess VLUs and select the most appropriate dressing product.	**YES**

4.

3.3 Miscellaneous topical products

Evidence Summary		
A good quality trial[23] investigated the effectiveness of a topical PSSO for healing VLUs. Participants were adults with an ABPI over 0.8 and ulcer size of at least 3cm^2. Severe cardiac, respiratory, gastrointestinal, liver, or renal disease, malignancy, signs of wound infection and pregnancy or lactation were exclusion criteria. Participants were randomised to receive either 10% Leukichtan (a PSSO) (n=62) or a placebo gel (n=57) applied at 2 to 2.5 mm thickness under a non-adherent dressing and compression. Frequency of dressing changes was not reported. Patients were treated for 20 weeks, with wound assessments conducted every 2 weeks. At the final assessment after 20 weeks of treatment the group treated with PSSO achieved a significant reduction in overall ulcer area compared to the placebo group (mean 6.2cm^2 vs. 10.8cm^2, p<0.0005). Relative change in ulcer area was significantly greater in the treatment group (-72% vs. -18%, p<0.0001). There were no differences in complete epithelialisation (53% vs. 34%), fibrinous discharge, necrotic tissue or pain levels. Qualitative assessment of the overall treatment conducted by both patients and physicians favoured the PSSO (p<0.001 for both). Adverse events were equivalent between groups (12% vs. 11%). This trial provided good quality evidence that 10% Leukichtan (a PSSO) is more effective than placebo in promoting healing of VLUs if used in conjunction with compression for 12 weeks.[23] A low quality double blind RCT[24] investigated the effectiveness of *Mimosa tenuiflora* bark extract in healing VLUs. Forty participants with a mean VLU duration of 8.5 years who showed no clinical signs of infection were randomised to receive *Mimosa tenuiflora* bark extract 1.8g tannins/100g hydrogel or regular hydrogel daily for 12 weeks. Patients attended their own dressings on a daily basis and wore concurrent compression bandaging. Ulcers were measured weekly using digital photography and a data processing image analyser to determine ulcer area. The reliability of this measurement technique was not reported, nor was it clear whether mean ulcer size was equivalent between groups at baseline. Treatment effect became evidence after 3 weeks when 25% of the experimental group had at least 80% of VLU area healed compared to 0% in control group (p=0.001). By the study completion at 12 weeks 100% of the experimental group had at least 80% healed ulcer area compared to 18% in control group (p=0.0001). Almost half the control participants withdrew from the trial (11/20) and were not considered in the analysis. Only 1 participant withdrew from the *Mimosa tenuiflora* group. No adverse events or abnormal blood results were experienced during the trial. The results may have been influenced by the self-administration of treatment, including compression bandaging. Randomisation and allocation concealment methods were not reported. The results of this low quality trial suggested that topical *Mimosa tenuiflora* bark extract administered daily for 12 weeks may be more effective than regular hydrogel when used in conjunction with compression bandaging to treat VLUs.[24] This was considered insufficient evidence on which to make a recommendation on the products use for treating VLUs.		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality RCT[23] reporting the use of pale sulphonated shale oil	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**	**B**
Consistency		
Only one trial	**N/A**	
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		

Effect size was not reported. Significant reduction in overall ulcer size but no change to epithelialisation, fibrinous discharge, necrosis or pain.	**Slight**	**C**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Participants did not show clinical signs of infection in the VLU. Severe concurrent illnesses were excluded.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Conducted in a European country. Not investigated in Australian or NZ Indigenous populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is some evidence that topical pale sulphonated shale oil is more effective than standard care for promoting healing in VLUs. Body of evidence provides some support for recommendation(s) but care should be taken in its application		**Grade C**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? There is insufficient support for this product to recommend it in usual care.		**NO**
Are there any resource implications associated with implementing this recommendation? There may be financial barriers for patients who choose to use the product in the management of their VLUs.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO**

Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

3.4 Management of venous excema

Evidence Summary

A low quality trial[25] compared the effectiveness of Cavilon™ No Sting Barrier Film (NSBF) to a zinc compound paste as barrier preparations. Patients eligible for inclusion were those with VLUs with maceration or peri-wound irritation, a VLU of at least 4 week duration and an ABPI above 0.8. Exclusion criteria included insulin dependent diabetes, systemic therapy that may influence ulcer healing and ineligibility for compression therapy. Participants were randomly assigned to treatment for 12 weeks with either NSFB (n=18) or zinc paste (n=18) applied to peri-ulcer skin at each dressing change. The analysis at 12 weeks showed no significant difference in wound healing rates, exudate level or condition of peri-ulcer skin between the groups. Both products were deemed to be effective barrier creams to protect the skin around VLUs.[25]

A second low quality RCT[26] investigated the effect of Cavilon™ NSBF in controlling peri-wound erythema in 239 patients with heavily exudating VLUs. Participants had VLUs that had persisted for at least 2 years and were not clinically infected. Each VLU was treated with NSBF on one side of the wound and saline on the opposite side of the wound, with application of each performed. The NSBF and saline were applied daily for four days using applicators of different appearance and the patients and clinicians were not informed of which was the active treatment. Erythema was assessed using a chromometer that was reported to be a reliable measure of wound colour. The presented analysis for 200 of the participants showed the extent of erythema on the fourth day was 0% for parts of the VLU treated with NSBF and 99% for parts receiving saline. Statistical analysis was not performed. Participants who developed infection (n=12) were excluded from the analysis, as were those who did not respond to the NSBF. The trial provided low quality evidence that NSBF may contribute to a decrease in peri-wound erythema in patients with VLU.[26]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Two low quality RCTs[25, 26] investigating treatments for peri-wound skin to reduce irritation.	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
Trials showed an effect compared to placebo (saline).	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Difficult to ascertain. One trial found two products were equally efficient but did not compare to placebo. One trial comparing a product to placebo reported clinical impact with patients who did not respond excluded from the analysis.	**N/A**	
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Participants with complex illness were excluded.	**Evidence probably applicable to Australian healthcare context with few caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and*		

culture)		
Access to certain products is likely to be restricted by location, cost and other factors. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is weak evidence that topical barrier preparations reduce peri-wound erythema in patients with VLUs. Body of evidence is weak and recommendation must be applied with caution **Grade D**		
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Usual care often includes a peri-wound barrier preparation.		**NO**
Are there any resource implications associated with implementing this recommendation? Peri-wound barrier preparations increase the financial burden of VLU care.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Some patients may have limited access to appropriate products.		**YES**

3.5 Topical cadexomer iodine

Evidence Summary		
One good quality Cochrane review[27] reported the results of ten moderate quality RCTs investigating the use of the antimicrobial agent cadexomer iodine for the treatment of VLUs. Ten RCTs investigated the use of cadexomer iodine. Four trials compared cadexomer iodine to standard care, with none reporting baseline infection status. In one trial (n=28) patients received alternate day dressings. After 4 weeks there was no significant difference in number of ulcers healed (RR 4.33, 95% CI 0.56 to 33.53); however there was significantly greater reduction in ulcer area in the treatment group (33.6% vs. 4.2%, p<0.005). In a second trial (n=67) participants were admitted to hospital, maintained on bed rest for six weeks and had dressings changed daily. At 6 weeks there were significantly more ulcers healed in the cadexomer iodine group (RR 2.29, 95% CI 1.10 to 4.74) and a significantly greater reduction in ulcer area (71% vs. 54%, p<0.001); however, more than 10% of participants were excluded from the final analysis. In a third trial 61 participants treated with either cadexomer iodine or standard care showed no significant difference in numbers of ulcers healed at 12 weeks (RR 1.71, 95% CI 0.78 to 3.75). The fourth trial (n=75) did not report total healing rates. Results for rate of reduction in ulcer area were pooled with findings from the third trial and showed that ulcers treated with cadexomer iodine healed at a significantly faster rate (WMD 0.47cm^2 per week, 95% CI 0.26 to 0.69, p=0.00002).[27] Three trials compared cadexomer iodine with compression to compression alone. The first two trials (total n=132) reported complete healing at 4 and 6 weeks. Pooled results favoured cadexomer iodine (RR 6.72, 95% CI 1.56 to 28.95). The third trial did not report complete ulcer healing, but its analysis showed a significant decrease in colonization with *Staphylococcus aureus* in ulcers treated with cadexomer iodine (RR 31.31, 95% CI 1.95 to 503.29, p=0.015).[27] Two trials compared cadexomer iodine with dextranomer. Both trials were small, and although one had results for complete healing that bordered on significance (p=0.54) between groups, there was only 27 participants and 30% were excluded from the final analysis. One trial (n=153) compared cadexomer iodine to a hydrocolloid dressing for participants with non-infected VLUs. After 12 weeks there was no significant difference in complete healing (RR 1.37, 95% CI 0.48 to 3.91, p=0.55) or rate of ulcer reduction (WMD 1.00%, 95% CI -2.52 to 4.52, p=0.58); however, the mean reduction in ulcer area was larger in the cadexomer iodine group (WMD 20.90%, 95% CI 2.22 to 39.58, p=0.028). The same trial had a third arm treated with paraffin gauze. This group had no difference in complete healing to the cadexomer iodine group but cadexomer iodine was superior for mean reduction in ulcer area (WMD 37.70%, 95% CI 8.77 to 66.63, p=0.011) and rate of ulcer reduction (WMD 6.00%, 95% CI 1.56 to 10.44, p=0.0082).[27]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR[27] providing a narrative summary of 10 moderate quality RCTs	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
Studies generally reported an effect but inconsistencies were explained by trial size and methodology.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown*		

factors eg. not sample size or study quality)		
WMD 20.90% to 37.70% depending upon outcome.	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with varying sized VLUs of varying durations. Bacterial colonisation at baseline was not always reported.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were reported in international settings. Australian patients in some settings may have limited access to treatments. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Island or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is some evidence that cadexomer iodine is more effective than standard care in the treatment of VLUs. Body of evidence provides some support for recommendation(s) but care should be taken in its application		**Grade C**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Usual care involves a saline or water wash and application of a non-adherent dressing. This is sometimes accompanied by topical products.		**NO**
Are there any resource implications associated with implementing this recommendation? There may be financial constraints for patients.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? For patients who have their ulcer managed by a qualified practitioner, there should be no change in care. Qualified practitioners should have appropriate knowledge in assessing bacterial burden in a VLU.		**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Some patients do not have access to appropriate qualified wound care services.		**YES**

3.6 Topical silver

Evidence Summary

A good quality SR[28] investigating the effectiveness of silver products in treating VLUs identified nine RCTs meeting inclusion criteria for the review. The reviewers searched major databases, wound journals, conference proceedings and contacted manufacturers to identify literature. Six of the included studies investigated silver dressing products and three trials focused on topical silver treatment. All of the studies were of low quality.[28]

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

Six trials in this review compared silver-containing dressings to conventional dressings, a calcium alginate dressing or different types of silver dressings. One low quality study compared a silver foam dressing (n=65) to a hydrocellular foam (n=64) in patients with leg ulcers of mixed aetiology. Although the median relative reduction in ulcer area was significantly shorter in the group treated with the silver product (45 vs. 25% p=0.034) after 4 weeks, there was no difference in the proportion of ulcers that completely healed (silver 10%; control 9%; RR 1.10; 95% CI 0.34 to 3.57; p=0.88). In a follow-on study, 45 of the participants were then re-randomised and the results continued to show no significant difference in the proportion of ulcers that were completely healed (silver 8%; control 5%; RR 1.6; 95% CI 0.16 to 16.40; p=0.67). These results were supported in a third low quality trial (n=40) that compared a silver impregnated-activated charcoal dressing to a range of conventional therapies. No significant difference was shown for proportion of ulcer area healed or number of ulcers completely healed (RR 3.0; 95% CI 0.69 to 13.03; p=0.14). Pooled results from two of these trials using a fixed-effects model showed no significant difference in the proportion of ulcers completely healed (RR 1.66; 95% CI 0.68 to 4.05; p=0.27).[28]

One large trial (n=415) that compared the treatment of mixed aetiology ulcers with silver foam dressings compared to conventional treatment found the area of ulcer healed was significantly better for the silver dressing (45.5 vs. 28.8%, p=0.0001); however, the groups were not equivalent at baseline with respect to median ulcer sizes.[28]

Another low quality trial compared silver dressing (n=38) to a calcium alginate dressing (n=33) for treating VLUs for 4 weeks. No significant differences were found in either reduction of wound size (WMD –3.5; 95% CI 10.45 to 3.45, p=0.34) or healing rate (WMD 0.13; 95% CI 0.13 to 0.12; p=0.31).[28]

A moderate quality SR[29] reported findings from three RCTs investigated silver–based products. In one trial in which wounds were also debrided there was no significant difference between silver–impregnated activated charcoal dressing and dressings targeted at stage of wound healing. Silver sulphadiazine was not superior compared to saline cleansing and ulcers in the treatment group that were contaminated at baseline remained so throughout the 12 week trial. However, another trial investigating silver sulphazine reported it to be more effective for reducing mean ulcer area than both tripeptide–copper complex (ES 25.30 (95% CI 20.82 to 29.78, p=0.03) and placebo (ES 21.50, 95% CI 16.66 to 26.34, p=0.05). In the same trial there was no difference in treatments for complete ulcer healing.

In addition, a low quality RCT[30] investigated the effectiveness of a silver dressing compared to a regular foam. Participants had VLUs with clinical signs of infection and a mean size of 2cm^2. Patients with diabetes, taking systemic corticosteroids and with an ABPI less than 1.0 were excluded. Participants were randomised to receive a twice weekly dressing with either silver releasing foam (n=21) or a regular foam (n=21) covered in short stretch bandaging for 9 weeks. Randomisation and allocation concealment techniques were not reported and baseline equivalence for ulcer duration and concurrent medical conditions was unclear. After 9 weeks 81% of the treatment group compared to 48% of the control group (p=0.002) had achieved full ulcer healing (method of ulcer measurement was not reported). Patients treated with the silver releasing dressing achieved reduction in pain earlier in the trial period than the control group. No systemic or local effects were experienced. This low quality trial provided some evidence that silver dressing may be more effective at healing infected VLUs, although the trial was small and methods were not clearly reported.[30]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR[28] and meta analysis and an additional low quality RCT [30]	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
Most trails found non- significant results. Pooled meta-analysis supported this finding.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
No effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Trials often excluded patients with diabetes or taking systemic corticosteroids. Silver was generally used in conjunction with compression therapy.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted in international settings. Trials were not conducted in people from Aboriginal and Torres Strait Islander backgrounds or in people from New Zealand with a Maori background.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		

None

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

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

Body of evidence can be trusted to guide practice in most situations **Grade B**

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

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care currently consists of a saline or water wash and a non-adherent dressing	**NO**
Are there any resource implications associated with implementing this recommendation? The product is not recommended.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? The product is not recommended.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? The product is not recommended. This may be controversial amongst practitioners who regularly use topical silver.	**NO**

3.7 Topical honey

Evidence Summary		
A good quality Cochrane review[31] included trials investigating the effect of honey used to treat wounds. A search of major databases was conducted and studies were appraised by two reviewers. Appraisal included consideration of randomisation and allocation concealment methods, loss to follow up, blinding and use of ITT analysis. Complete healing at 12 weeks was the primary outcome measure for the review. Two good quality trials considering the use of honey for treating VLUs were included in the review. Pooling of results using a fixed effects method found no significant difference between honey and control therapy (regular dressings) for treating VLUs (RR 1.15, 95% CI 0.96 to 1.38, p=0.12). Pooling using a random effects model showed there was significantly more adverse events in participants treated with honey (111vs 84, RR 1.27, 95% CI 1.05 to 1.55, p=0.016) although one trial reported all adverse events including those that may not have been related to therapy. These findings were based on two trials with good methodological quality, one of which was a large study. In both trials honey was used in conjunction with compression. The results suggest there is no evidence suggesting honey used for between 4 and 12 weeks is more effective than standard care for treating VLUs.		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR and meta-analysis[31] of 2 moderate and good quality trials.	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
All good quality trials showed honey was not superior.	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
No effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Patients were excluded if their limbs were oedematous, if they had diabetes, CV disease or arterial disease.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted in Europe. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
The Expert Working Committee considered that although the evidence did not support the use of honey, the outcome measures may not have been the most appropriate and may have failed to capture evidence of some benefit of using honey. The Expert Working Committee recommends that in some circumstances honey may be used and this has been outlined in the guideline.		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
There is evidence that honey offers no benefit over standard care in reducing healing times for VLUs. Body of evidence can be trusted to guide practice **Grade A**	
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care does not include honey.	**NO**
Are there any resource implications associated with implementing this recommendation? The treatment is not recommended.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment is not recommended.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to implementation are known.	**NO**

3.8 Topical antimicrobials

Evidence Summary

One good quality Cochrane review[27] reported the results of 10 moderate quality RCTs investigating the use of a range of topical antimicrobial agents for the treatment of VLUs. When trials were clinically homogenous the results were pooled using appropriate techniques; however, for the most part differences in interventions and trial lengths precluded pooling and results were presented in a narrative summary.

Povidone iodine

Five trials reported the effectiveness of povidone iodine. Three trials compared povidone iodine plus compression to hyrocolloid dressing plus compression. In the first trial (n=200) participants were stratified according to ulcer size. For ulcers over 4cm in diameter, the hydrocolloid dressing was more effective for total healing than povidone iodine (p=0.02) and there was no significant difference in the rate of healing. Total healing was not reported for smaller ulcers. Thirty percent of participants withdrew from this trial. In the second trial (n=51) participants with more than one ulcer acted as their own controls. Ulcers treated with povidone iodine (17 patients) healed significantly faster (p<0.01). The third trial (n=74) compared povidone iodine with hyaluronic acid plus compression to either hydrocolloid or paraffin gauze and found no differences in rate of healing.[27]

One trial (n=100) compared povidone iodine to dextranomer in participants with ulcers colonised with bacteria at baseline. Mean time to healing was significantly shorter in those treated with dextanomer (4.4 weeks vs. 5.3 weeks, p<0.05) and time to eradicate *Staphylococcus aureus* was also shorter with dextranomer (14.7 days vs. 18.7 days, p<0.01). One low quality trial (n=63) compared povidone iodine and sugar ointment applied once or twice daily to recombinant tissue growth factor applied as a spray solution. After 4 weeks there was no significant difference in number of ulcer healed (RR 0.57, 96% CI 0.22 to 1.52, p=0.26).[27]

Peroxides

Three trials reported on the use of peroxides. One trial (n=31) had a three different arms comparing different concentrations of benzoyl peroxide with saline dressing in VLUs with unknown infection status at baseline. After 42 days, days, benzoyl peroxide lotion 10% was significantly more effective than saline in reducing ulcer area (WMD -30.40%, 95% CI -42.12 to -18.68) and benzoyl peroxide lotion 20% was also significantly more effective (WMD -34.10%, 95% CI -46.22 to -21.98). Two trials compared hydrogen peroxide plus compression to standard care plus compression. In both trials patients received systemic antibiotics prior to commencing the trial and were then randomised to receive hydrogen peroxide 1% cream or placebo cream for 10 days. In one of the trials (n=20) there was a significant reduction in ulcer are in those treated with peroxide (p<0.05) and the second trial also favoured peroxide (p<0.005).[27] Deaths associated with hydrogen peroxide used in wound care have been reported in the literature.[32-34]

Other treatments

One trial (n=253) investigated daily treatment with ethacridine lactate 0.1% lotion plus compression compared to placebo lotion plus compression and found ethacridine lactate was associated with significantly greater reduction in ulcer are after 21 days (RR 1.47, 95% CI 1.24 to 1.74, p<0.00001). Complete healing was not reported and the follow up period was short. Another trial compared of 2% mupirocin in paraffin tulle gras with vehicle (all participants also received compression). After 12 weeks there was no significant difference in complete ulcer healing (RR 1.14, 95% CI 0.56 to 2.35, p=0.72), rate of

healing or eradication of gram positive bacteria. The third trial compared chlorhexadine to hydrocolloid dressing, with all participants receiving compression and acting as their own controls. After 6 weeks there was no significant difference in time to healing.[27]

Overall, the SR provided evidence from moderate quality trials that most topical antimicrobial agents have no significant effect in the healing of VLUs. [27] 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.[27]

An additional moderate quality SR[29] investigated the effectiveness of antimicrobial agents. The critical appraisal suggested the included trials were not of high quality. Due to variations in populations, interventions and trial durations, results were not pooled. A narrative summary presented the findings.[29]

The review[29] reported seven small (less than 40 participants) trials in which topical antimicrobials were investigated, five of which were randomised and all of which were placebo controlled. Most trials excluded participants with clinical signs of infection and few reported wound colonization culture testing. In all trials, participants received concurrent compression therapy. There was no difference in healing rate and/or complete healing for polynoxylin paste, povidone iodine or mupirocin tulle gras compared to placebo or no therapy. Dimethyl sulphoxide powder and allopurinol powder were equivalent and both superior to placebo powder for complete healing (OR 10.67, 95% CI 2.30 to 49.39, p<0.01) when used in conjunction with compression therapy for at least 12 weeks in participants with VLUs less than 10cm^2. Withdrawals due to local irritation were similar between the groups (allopurinol=1, placebo=1, dimethyl sulphoxide=2).[29]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR[27] and an additional moderate quality SR[35] both providing narrative summaries of moderate quality RCTs	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
Inconsistencies explained by small studies, differences in populations and other methodological issues.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Studies generally showed no effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with varying sized VLUs of varying durations. Bacterial colonisation at baseline was not always reported.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were reported in international settings. Australian patients in some settings may have limited access to antimicrobial treatments. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Island or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		

None

Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*

The Expert Working Committee considered that although the evidence did not support the use of topical antimicrobials, the outcome measures may not have been the most appropriate and may have failed to capture evidence of some benefit. The Expert Working Committee recommends that in some circumstances, for example when there is a known increased microbial burden, topical antibiotics may be appropriate and this has been outlined in the guideline.

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

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION
Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

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

Body of evidence provides some support for recommendation(s) but care should be taken in its application **Grade C**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*

Will this recommendation result in changes in usual care? It is hoped that the recommendation will encourage clinicians to fully assess the need for antibiotic therapy, especially in older adults. Unwarranted antibiotic use may cause additional problems such as multi-resistance and topical sensitivities.	**YES**
Are there any resource implications associated with implementing this recommendation? No, it is not a practice that is recommended.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? It is hoped the recommendation will discourage the practice of using topical antimicrobials in inappropriate cases.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? There are no barriers to implementing the recommendation; however it may be seen as controversial by practitioners who use these products.	**NO**

3.9 Systemic antibiotics

Evidence Summary

One good quality Cochrane review[27] reported the results of 5 moderate and low quality RCTs investigating the use of systemic antibiotics for the treatment of VLUs. Only one trial selected antibiotics based on wound swabs and sensitivity testing. Wounds were not clinically infected at baseline.

In one RCT participants (n=48) received either co-trimoxazole, gentamicin or amikacin (according to sensitivities) for 10 days. At 20 day follow up there was no statistically significant difference in number of ulcers healed or mean ulcer area between those receiving standard care and those receiving antibiotics. There were more ulcers with bacterial eradication in the group receiving systemic antibiotics (RR 1.67, 95% CI 0.64 to 4.36, p=NS). [27]

Two trials compared ciprofloxacin to standard care or placebo. In the first trial, participants (n=26) were eligible if they had VLUs colonized by bacteria sensitive to ciprofloxacin. Participants were unevenly assigned between treatment and control groups and the treatment group had ulcers that were of significantly longer duration at baseline, possibly biasing the control group. At three months, more ulcers were completely healed in the group receiving antibiotics (RR 3.32, 95% CI 0.19 to 57.61, p=NS). There was no significant difference in number of patients with at least 10% reduction in ulcer length and width (p=0.08) and no significant reduction in bacterial eradication rates (p=0.32). The second trial compared ciprofloxacin (n=12) and placebo (n=10) for 12 weeks; however, those receiving the antibiotic therapy had larger ulcers of longer duration at baseline. At 16 weeks follow up there was no significant difference in number of ulcers healed (RR 1.39, 95% CI 0.44 to 4.43). Pooling of the data from these two studies found that antibiotic resistant strains of bacteria were more commonly seen in participants treated with ciprofloxacin compared to placebo (RR 8.65, 95% CI 1.76 to 42.60, p=0.008). [27]

One trial compared trimethoprim (n=12) to both placebo (n=10) over 16 weeks. Although there was no statistically significant difference (RR 1.25, 95% CI 0.40 to 3.91, p=0.70) between healing between the two antibiotic groups, those receiving ciprofloxacin had larger ulcers of longer duration at baseline. There was no difference between the groups in emergence of antibiotic resistant strains of bacteria. There was also no statistically significant difference between trimethoprim and placebo (RR 1.11, 95% CI 0.30 to 4.17, p=0.88) for complete healing, although the ulcers in the antibiotic group were of longer duration on entry into the trial. Difference in rates of development of antibiotic resistant bacteria strains bordered on significance (RR 6.67, 95% CI 0.98 to 45.29, p=0.052). [27]

One trial compared systemic amoxicillin to topical povidone iodine. In this three-arm trial, those receiving amoxicillin also received an undefined type of compression (n=21), a second group received povidone iodine and compression (n=21) and the third group were treated with povidone iodine alone. (n=21). There was no significant difference in complete healing rates between amoxicillin and either of the povidone iodine groups (with compression RR 1.06, 95% CI 0.81 to 1.39, p=0.68; without compression RR 1.38, 95% CI 0.95 to 2.02. p=0.092). [27]

One trial (n=59) compared levamisole two days per week for 20 weeks to placebo on the same regimen for the treatment of ulcers, the majority of which were venous in origin (baseline infection status not reported), There was a statistically significant greater rate of complete ulcer healing in the levamisole group compared to placebo (RR 1.31, 95% CI 1.06 to 1.62, p=0.012); however almost 20% of participants withdrew from the trial and were not included in the analysis. [27]

The SR[27] 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.		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR[27] reporting 5 moderate and low quality RCTs. Results for healing were not pooled	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
Most trials reported no effect for systemic antibiotics. One low quality trial reported a result but had a high risk of bias.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
No effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Wounds were not clinically infected.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted in internationally. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
Although the evidence did not support the use of systemic antibiotics, the VLUs in these trials were not clinically infected at baseline. The Expert Working Committee considered that there is a role for systemic antibiotics when clinical infection is confirmed. Appropriate use is outlined in the guideline.		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is some evidence that systemic antibiotics offer no advantage over standard care for reducing healing time of VLUs that show no clinical signs of infection. Body of evidence provides some support for recommendation(s) but care should be taken in its application		**Grade C**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care does not include systemic antibiotics.	**NO**
Are there any resource implications associated with implementing this recommendation? The treatment is generally not recommended.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment is generally not recommended.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to implementation are known.	**NO**

3.10 Wound debridement

Evidence Summary

One moderate quality RCT[36] investigated the effectiveness of an enzymatic debriding agent. Adults were eligible to participate if they had a chronic purulent and/or necrotic leg ulcer, did not have an illness likely to interfere with skin healing and were not taking systemic medication that would influence the study results. Eighty-four participants were randomised (stratified on ulcer size) to four groups receiving treatment with the assigned ointment and a non-stick dressing twice daily for three weeks. Group 1 received the full experimental ointment containing complete proteolytic ointment 1.28 U fibrinolysin/g with 1006 U of desoxyribonuclease/g. The second group received an ointment containing 1.15 U of fibrinolysin/g, the third group received 1027 U of desoxyribonuclease/g ointment and the fourth group received a placebo ointment. After three weeks all groups had achieved a small improvement for amount of purulent exudate, amount of necrotic tissue and an overall wound assessment (all assessed using a Likert scale). There were no significant differences between groups for any of the outcome measures. One participant (group not reported) experienced increased pain and inflammation deemed to be unrelated to the therapy.[36]

A low quality RCT[37] investigated the comparative effectiveness of an enzymatic debriding agent (n=27) to an autolytic debriding product (n=15). Participants were adults with CVI and a VLU of at least 6 week duration who were free from malignancy, arterial occlusion or disease that may inhibit healing. The primary outcome measure was a weekly subjective visual assessment of wound condition that was reported to be insufficient to determine an effect of the treatment over 14 days, leading to an extension of the trial for an additional 7 days. This reduced confidence in the finding that, for the patients who showed a response to treatment, both products produced a statistically significant decrease in slough and necrotic tissue and a significant increase in re-epithelialised tissue and granulated tissue in the first 14 days (p values ranged from 0.01 to 0.04) No between group comparisons was reported. Neither product was considered to have produced a statistically significant difference in wound condition when the full 21 days of therapy was considered. Patients performed their own dressings on a daily basis, which may have influenced the findings. Withdrawals from the trial were not reported and more than half of the participants in both groups did not respond to the treatment. The ethical approval process for this study was unclear and participants only consented verbally.[37]

In another low quality RCT,[38] the effectiveness of an enzymatic debriding agent, streptokinase-streptodornase, in cleansing ulcers of pus and debris was compared to saline. Participants were adult hospitalised patients without hard necrotic ulcer tissue who were randomised to receive either the enzymatic debriding agent (n=15) or saline (n=16) twice daily for 15 days. Ulcers were evaluated by a blinded observer using a 4 point scale to describe the level of pus and debris present in the ulcer and patient complaints of pain were noted. At day 10 there was significantly more ulcers in the treatment group that had small or no amounts of pus and debris compared to the control group (92% vs. 50%, $p<0.05$); however, patients who withdrew from the treatment group were not considered in the analysis and this is likely to have influenced the significance of the finding. There was no significant difference between group at day 15 and pain levels did not differ between groups. Side effects were not reported. The researchers did not report methods of randomisation, allocation concealment and blinding of patients. Participants were described as having chronic ulcers or wounds, and the origin of the ulcers was not reported.[38]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Three low[37, 38] and a moderate[36] quality RCT investigating enzymatic debriding agents.	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
Trials showed minimal to no effect for enzymatic debriding agents.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
No effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs or chronic leg ulcers of unknown aetiology. Participants with complex illness were excluded. In one trial participants were hospitalised.	**Evidence probably applicable to Australian healthcare context with some caveats**	**C**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Access to certain products is likely to be restricted by location, cost and other factors. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori and Pacific Island populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is some evidence that enzymatic debriding agents are not effective for promoting healing in VLUs.		
Body of evidence is weak and recommendation must be applied with caution		**Grade D**
There is insufficient evidence to make a recommendation on the effectiveness of other debriding methods for VLUs.		

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory inforrmation. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care does not include enzymatic debriding agents.	**NO**
Are there any resource implications associated with implementing this recommendation? The treatment is generally not recommended. Not all the products investigated in the research are available in Australia at this stage.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment is generally not recommended.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to implementation are known.	**NO**

3.11 Elevation

Evidence Summary		
In a small observational trial[39] the relationship between VLU healing and time spent elevating the leg was investigated. Participants (n=29) had VLUs of at least 6 weeks duration and an ABPI above 0.9. At baseline the median ulcer size for participants was 2.8cm^2. Exclusion criteria were vasculitis; renal hepatic or haematological disease; and those taking corticosteroids. Participants wore a validated data logging device that recorded time spent elevating limbs and the angle of elevation for 6 weeks. Ulcers were measured weekly using wound tracings. The median ulcer percentage reduction over 6 weeks for the 26 participants for whom useable data was recorded was 50%. Median elevation time was 352 minutes per 24 hours. The correlation between ulcer healing and elevation time was non-significant (p=0.616). The researchers suggested that lack of correlation may have related to elevation providing limited advantages above the concurrent 4-layer compression bandaging participants wore; or that the intermittent elevation regimen was insufficient to achieve benefit.[39] Another small prospective trial[40] investigated the effect on microcirculation of the skin of elevation of limbs by participants with VLUs. Participants (n=13) with VLUs of more than 2 years' duration and without concurrent systemic disease were hospitalised throughout the trial. Measurements of transcutaneous oxygen tension ($TcPO_2$) and laser Doppler fluximetry were made at baseline, 4 hours following elevation of limbs at 10° and after 24 hours of continuous elevation. Increase in laser Doppler fluximetry was significant, indicating that continuous elevation leads to changes in skin microcirculation. The trial did not investigate the correlation between skin microcirculatory changes and VLU healing.[40]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Two low quality trials[39, 40] that reported on effect of elevation on microcirculation.	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
Studies had consistent findings.	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
The trials did not report/were not relevant to clinical impact in healing VLUs.	**N/A**	
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. In one trial participants were hospitalised throughout	**Evidence not directly generalisable to the target population but could be sensibly applied**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted overseas. Australia has a different climate, however the effect on elevation and circulation is unlikely to be different. Studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**

Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
The trial was specific to microcirculation and did not report on VLU prevention or healing as an outcome measure. It is the Expert Working Committee's opinion that improvement in microcirculation and venous blood flow contributes to the healing of VLUs. An expert based opinion recommendation to this effect is included in the guideline.		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is evidence that the benefits of leg elevation are related to changes in microcirculation in patients with VLU. Body of evidence is weak and recommendation must be applied with caution **Grade D**		
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? This recommendation does not refer to any change in care. However, the related expert based opinion recommendation suggests that elevation should be recommended to patients with VLUs. This recommendation may increase the number of patients who receive education about the benefit of elevation.		**YES**
Are there any resource implications associated with implementing this recommendation?		**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?		**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Some patients may have difficulties implementing the recommendation due to lifestyle issues.		**YES**

3.12 Exercise

Evidence Summary		
A low quality RCT[41] evaluated the effects of short term supervised calf exercise on calf muscle pump function and venous haemodynamics in limbs with a VLU. Participants with VLUs, impaired calf muscle function (ejection fraction <60%) and full ankle joint movement were randomised to either an exercise therapy group (n=10) or to a non-exercise group (n=11). Exclusion criteria included mixed origin ulcers, ABPI above 1.0, vasculitis, collagen diseases, steroid therapy, immunosuppression, venous outflow obstruction, pregnancy, cancer, congestive cardiac failure and uncontrolled diabetes. The exercise group participated in a supervised program with active planter flexions using standardised 4 kg resistance pedal ergometer for three sets of 6 minutes daily for 7 days. Both groups received concurrent ulcer dressings twice weekly and inelastic (short stretch) bandaging. Ejected venous volume and ejection fraction was measured using air plethysmography. On day eight the exercise group had significantly better ejected venous volume ($p<0.001$) and ejection fraction ($p<0.001$) than the control group. The venous filling index and venous volume did not change ($p>0.5$) in either study group. Calf muscle endurance in the exercise group increased 135% from a median 153 planter flexions at baseline to 360 daily on day 7 ($p=0.001$). This study provided low quality evidence that active exercise in patients with VLUs promotes muscular endurance and the power and efficacy of calf muscle function.[41]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One low quality trial[41] that reported on effect of exercise in improving strength.	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
There was only one study.	**N/A**	
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RCTs indicated an approximate 35% improvement in muscle strength. Effect in improving VLUs was not an outcome.	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs and/or CVI.	**Evidence not directly generalisable to the target population but could be sensibly applied**	**C**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trial was conducted in Europe. Although the climate varied, the type of exercise would not be significantly influenced by location. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
The trial was specific to improving calf pump function and did not report on VLU prevention or healing as an outcome measure. It is the Expert Working Committee's opinion that improvement in calf pump function and venous blood flow contributes to the healing of VLUs. An expert based opinion recommendation to this effect is included in the guideline.		

Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*	
None	
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
There is evidence that exercise improves calf muscle function and venous ejection fraction in patients with VLU. Body of evidence is weak and recommendation must be applied with caution **Grade D**	
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Yes, it is hoped more health professionals managing VLUs will develop holistic management plans that include exercise recommendations. It may also increase referral to appropriate exercise-based health services (eg. physiotherapy).	**YES**
Are there any resource implications associated with implementing this recommendation? There may be financial constraints for patients accessing specialised services; however, appropriate exercise can be conducted in the patient's home without supervision at no cost.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? It may increase referral to exercise physiologists, physiotherapy and other exercise-related specialists.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Exercise services may not be available in all locations. However, education regarding exercise can be provided by wound specialists.	**YES**

3.13 Skin grafting

Evidence Summary

A Cochrane review[42] investigated the effectiveness of different types of skin grafting in healing VLUs. Seventeen trials compared skin grafts to standard therapy (generally a non-adherent dressing) or other skin graft types. All trials were conducted in participants with hard to heal ulcers (persisting more than 6 months) and were of moderate to low methodological quality.[42]

Autografts compared to hydrocolloid dressings

Two trials investigated effectiveness of split thickness autografts to hydrocolloid dressings, whilst one trial (n=102) found no significant differences between the two treatments the other trial reported a large significant effect for skin grafting. The difference in healing in the control groups was large between the two trials, although both used populations with difficult to heal dressings and conducted a 6 month follow up. The findings were insufficient to make a recommendation on effectiveness of autografts compared to hydrocolloid dressings.[42]

Allografts compared to standard care

Three trials (n=80) compared frozen allografts to standard care (with a non adherent dressing or hydrocolloid dressing). The trials were small and of low methodological quality. Pooled results indicated no effect of allografts above standard therapy. Three trials (n=45) investigated fresh allografts compared to standard care (non-adherent dressings) and pooled results showed no significant differences in healing. However, pooling of the results from trials comparing eith frozen or fresh allografts to standard care (n=125) showed a significant improvement in healing in ulcers treated with grafting (RR 2.00, 95% CI 1.04 to 3.84, p=0.038).[42]

Human skin equivalent compared to standard care

Two trials (n=345) compared bi-layered (dermal thickness) grafting to simple dressings with compression in participants with hard to heal ulcers. Both trials reported superior healing in VLUs treated with the bilayered grafts. (RR 1.51, 95% CI 1.22 to 1.88, p=0.0002). Clinical effect was large, with healing improving by 40 to 60%. Two trials (n=71) compared single thickness grafting using skin replacements to standard therapy. None of the individual trials reported significant results after 12 weeks. Results were not pooled due to differences in treatment regimens, primarily the number of pieces of dermal skin replacements.[42]

Comparison of different graft types

Five trials compared different graft types to each other and none of the trials provided strong evidence for a superior effect of a specific type of graft product.[42]

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.[42]

One good quality SR[43] reported the results from nine trials investigating BSSs used to treat VLUs. Most of the trials were also reported in the Cochrane review.[42] Nine trials of moderate and low quality met the review inclusion criteria. Participant and ulcer characteristics were not reported. In all trials the group receiving a BSS was treated with concurrent compression therapy. One moderate quality trial (n=275) investigated Apligraf® compared to Unna's boot. At six months significantly more patients treated with Apligraf had

complete ulcer closer (absolute risk difference 0.14; 95% CI 0.03 to 0.26); however the power of the study to measure this effect was not reported. There was no difference in recurrence rates after wound closure. Two blinded trials investigated Dermagraft® compared to compression alone. Neither trial showed a significant difference between treatment and control groups at 12 weeks; however pooled results showed a small significant effect (OR 4.48, 95% CI 1.01 to 19.8, p=0.05). One moderate quality trial investigated OASIS® Wound Matrix (n=120) compared to compression alone. At 12 weeks significantly more patients in the treatment group achieved complete wound healing (absolute risk difference 0.20, 95% CI 0.03 to 0.38). One low quality trial investigated Promogran™ (n=73) compared to compression with petroleum gauze. There was no significant difference in complete wound healing at 12 weeks; however, more participants treated with Promogran reported severe pain. One low quality trial investigated EpiDex® (n=77) compared to compression with split-thickness skin graft. There was no significant difference in healing at 12 weeks or 6 months. Two trials compared cytopreserved cultured allografts to a hydrocolloid. One (n=27) was of low quality, and the second (n=43) was of moderate quality. Neither study showed significant differences in healing between treatment and control groups. One low quality trial (n=22) investigating cultured keratinocyte allografts compared to placebo and compression reported no significant difference in healing after 6 weeks. In trials reporting adverse effects (n=7) such as infection and cellulitis there was no significant difference between treatment and control groups. In one trial nine deaths occurred; however these were not different between groups and no cause was reported. This good quality systematic review concluded that BSS products that had a dermal matrix component showed efficacy above standard therapy for healing of ulcers. However, the trials were not of high quality, patient and ulcer characteristics are unknown and description of the comparative treatments was lacking.[43]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Two good quality SR[42, 43] reporting moderate and low quality RCTs in meta analysis and narrative summary.	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
Inconsistency appeared to relate to the layer of the skin the product incorporated into.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Effect size was moderate to large for bilayered grafting	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
The trial was conducted with participants with VLUs that were hard to heal. Participants were generally outpatients. Concurrent illness was not reported.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
One review was conducted in Australia by the Commonwealth Government. Trials were not conducted in Australia. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence probably applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		

Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*	
None	
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
There is some evidence that bi-layered bioengineered skin grafts are more effective than standard care in promoting healing in persistent VLUs. Body of evidence can be trusted to guide practice in most situations	**Grade B**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Skin grafting is already considered when usual care is ineffective.	**NO**
Are there any resource implications associated with implementing this recommendation? Yes, the products are more costly than usual care. However, the grafting products shown to be most effective do not require skin harvesting and this would reduce resources and surgery.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? It may reduce the use of autografting and reduce surgery time and risk of mortality.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Potential financial barrier to patients and potential difficulty accessing products.	**YES**

3.14 Pain management: EMLA cream

Evidence Summary		
A good quality meta-analysis[44] investigating the management of chronic VLU pain identified six RCTs for inclusion, all of which investigated the effectiveness of EMLA 5% cream in reducing pain during debridement. All trials were of good methodological quality. The six RCTs were conducted in patients with VLU less than 50 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 VAS was administered during the procedure, leading to significantly higher pain scores. A limitation of all the trials was a lack of recording of baseline pain assessments prior to the procedure.[44] A total of 159 participants were treated with EMLA 5 % cream 30 minutes prior to debridement and 158 participants were randomly allocated to receive a placebo cream. The results were pooled in a meta-analysis for the outcome measure of pain on VAS during debridement. Mean difference in pain score using a random effects model favoured the treatment group, with a WMD -20.65 (95% CI -29.11 to -12.19, p<0.000001). This correlates to a mean reduction of 20.65 mm on VAS. Meta-analysis was conducted using a fixed effects model for the results of three trials that reported adverse events. The findings indicated no significant differences between the EMLA 5% cream groups and the control groups for either burning when cream removed (OR 1.72, 95% CI 0.74 to 4.01, p=0.21) or itching when cream removed (OR 1.68, 95% CI 0.64, 4.38, p=0.29).[44]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality meta-analysis of 6 RCTS.[44]	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
All studies in the review found an effect for EMLA	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RCTs indicated a decrease in pain of 20% more than placebo.	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLU smaller than 50cm². Trials included participants with complex disease including diabetes.	**Evidence directly generalisable to the target population**	**A**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trial was conducted internationally. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		

Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*	
None	
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
There is excellent evidence that EMLA® cream is effective in reducing pain associated with the debridement of VLUs. Body of evidence can be trusted to guide practice **Grade A**	
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Yes, more professionals will recommend EMLA cream to patients experiencing pain during VLU dressing changes.	**YES**
Are there any resource implications associated with implementing this recommendation? There may be financial constraints for patients. If EMLA cream is applied by the practitioner it will increase treatment time as EMLA cream should be applied 30 minutes prior to dressing attendance.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Wound services may need to change the way care is delivered in order to apply EMLA cream prior to dressings. However, for some patients it may be appropriate that they apply EMLA cream prior to attending the wound service. Local guidelines may need to be developed by service providers.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? EMLA cream may not be available to all patients.	**YES**

3.15 Pain management: Ibuprofen dressing

Evidence Summary		
One moderate quality trial[45] investigated the effect of a dressing impregnated with slow release ibuprofen in relieving pain from VLUs. Adults aged over 65 years with painful chronic venous leg ulcers of more than 8 weeks with a baseline pain described as at least moderate on a 5-point verbal rating scale who had an ABPI above 0.8 were eligible following a 2 week run in period in which the ulcer was treated with compression. Patients were ineligible if they had experienced an analgesic-resistant ulcer in the preceding 6 months, had an allergy to NSAIDs, asthma, urticaria, clinical infection, were pregnant or lactating, diagnosed with diabetes, or taken unscheduled analgesia in the 3 days before trial commencement. The participants had ulcers ranging in size, with a minimum length of 1.6cm and maximum area of 50 cm^2. Participants were randomised to receive either a dressing containing 112.5 mg of ibuprofen releasing over 7 days (n=62) or a comparator foam dressing (n=60), with treatment continuing for 47 days. In the last five days of the trial, the ibuprofen dressing group received the control dressing. Outcomes were assessed daily in the first and last 5 days of the trial. Significantly more participants in the ibuprofen dressing group had pain relief in the first five days of the trial (74% vs. 58%, $p<0.05$). Wound pain intensity in the first 5 days was significantly greater for the ibuprofen dressing group (40% reduction vs 30% reduction, $p < 0.003$) and decreased for all patients over time ($p < 0.001$). In the last 5 days of the trial, when the treatment group received the control dressing, this group experienced a significant increase ($p<0.05$) in wound pain but the control group pain intensity remained stable. There was no significant difference in rate of ulcer healing, no serious adverse events and the minor adverse events (primarily skin reactions) occurred at a comparable rate between the groups. This trial provided moderate quality evidence for the effect of an ibuprofen impregnated dressing in reducing pain, with a moderate clinical impact of at least 2 points on a 10 point pain scale.[45]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One moderate quality RCT[45]	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
There was only one trial.	**N/A**	
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RCTs indicated a decrease in pain of 10% more than placebo.	**Slight**	**C**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with painful VLU and without concurrent complex disease eg. diabetes and clinically infected VLUs.).	**Evidence directly generalisable to the target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trial was conducted in Europe. Not all patients may have access to the product in Australia, The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations	**Evidence applicable to Australian healthcare context with few caveats**	**B**

Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*
None
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*
None
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***
There is some evidence that an ibuprofen impregnated dressing reduces pain associated with VLUs. Body of evidence provides some support for recommendation(s) but care should be taken in its application **Grade C**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Yes, more professionals will consider the appopriateness of offering patients an ibuprofen-impregnated dressing if they have a particularly painful VLU.	**YES**
Are there any resource implications associated with implementing this recommendation? There may be financial constraints for patients. Practitioners may require education in use of the product.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Services may need to develop local guidelines regarding the use of the dressing product.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Ibuprofen dressings may not be available to all patients.	**YES**

3.16 Pain management: Electrotherapy

Evidence Summary		
A low quality RCT[46] reported the effectiveness of electrotherapy for reduction of pain and promotion of healing in 39 patients with chronic VLU of average 42 months duration. Details of the trials are reported under electrotherapy. The electrotherapy group had achieved significant reduction in pain by the end of the first treatment month and this remained significant until 4 month follow up (p=0.01) and was also significant compared to the sham therapy group (p=0.049). However, 59% of participants took concurrent analgesia, and it was unclear if this was equivalent between groups. This trial provided low quality evidence that electrotherapy may be associated in a reduction of pain.[46] A low quality trial[47] with 35 participants investigated the treatment of VLUs with frequency rhythmic electrical modulation system (FREMS). The trial is reported in more detail under electrotherapy. At 8 week follow up FREMS was associated with a significant decrease in pain scores measured on VAS. However, the groups were non-equivalent at baseline, with the control group having ulcers of significantly longer duration. Participants treated with FREMs experienced slight burning at electrode sites.[47]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Two low quality RCTs[46, 47]	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
Results were consistent, with both trials showing an effect.	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Unable to determine. The effect size was not reported.	**N/A**	
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLU and without concurrent complex disease eg. diabetes).	**Evidence directly generalisable to the target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trial was conducted in Europe. Not all patients may have access to the product in Australia, The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
There is weak evidence that electrotherapy may have an effect in reducing pain from VLUs. Body of evidence is weak and recommendation must be applied with caution	**Grade D**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care does not include electrotherapy. If practitioners choose to try electrotherapy to manage pain, there would be a change to usual care.	**YES**
Are there any resource implications associated with implementing this recommendation? Patients who choose to use electrotherapy may be constrained by cost.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? If used, it is likely this therapy would be restricted to specialist clinics. It may require change to local guidelines.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Not all patients will have access to this treatment.	**YES**

3.17 Therapeutic ultrasound

Evidence Summary		
A good quality Cochrane review[48] reported on the effectiveness of ultrasound therapy for the treatment of VLUs. The review was of good quality; however the trials included were of a generally low methodological quality and included small numbers of participants. Ultrasound therapy compared to sham ultrasound The results of five low and moderate quality trials were pooled using a fixed effect model where the same outcome measures were reported. Two of the trials included participants with VLUs at least 2 cm^2 in size and had persisted for at least 2 to 3 months. Follow up periods used in the trials were between 8 and 12 weeks. In all trials, both groups received either compression or support bandaging, ultrasound treatment regimens investigated were: a) 3 MHz at 1 W/cm^2 3 times per week for 4 weeks in two trials b) 1 MHz at 0.5 W/cm^2 3 times per week in the first month, twice weekly in the second month and weekly for the final month c) 1 MHz at 1.0 W/cm^2 twice per week for 8 weeks Findings in individual trials varied, with some establishing a significant effect on specific outcome measures at some time periods. In the meta-analysis, there was no statistically significant difference in total number of ulcers healed (RR 1.41; 95% CI 0.83 to 2.39, p=0.20); however, the results favoured ultrasound therapy for percentage of ulcer area remaining (WMD -4.75%, 95% CI -8.24 to -1.26, p=0.0076). It was unclear how healing was defined in individual trials or how area of the wound was measured. [48] Ultrasound therapy compared to standard therapy Three trials compared ultrasound therapy to different standard therapies that consisted of various dressing products, antibiotics, fibrinolyic agents and support bandaging. Participants receiving ultrasound were also treated with the same standard therapies in all trials. Follow up varied from 3 weeks to 12 weeks. One trial used ultrasound at 30 kHz administered in water and the other two used pulsed ultrasound at 0.5 to 1 MHz, 0.5 W/cm^2. The results of these three trails were pooled using a fixed effects model and showed no statistically significant difference between the groups for number of ulcers totally healed (RR 1.55, 95% CI 1.00 to 2.40). [48] 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.[48] A low quality SR[35] 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[48] were pooled in a meta-analysis and the results concurred that ultrasound compared to sham ultrasound is associated with an improvement in percentage of ulcer area healed but not total number of ulcers healed.[35]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR and meta-analysis[48] and an additional low quality SR[35]	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
Results varied for ulcer healing.	**All studies consistent**	**A**

Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Both SRs showed that there was no benefit of ultrasound for total number of healed ulcers but some benefit on percentage of healed ulcer area	**Slight**	**C**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Some trials restricted participants to those with ulcers over 2cm^2 and persisting for at least 2 months.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Access to services is likely to be restricted. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is good evidence that therapeutic ultrasound therapy is not related to an improvement in total ulcer healing but may slightly improve the percentage of healed ulcer area when used in combination with compression therapy. Body of evidence can be trusted to guide practice in most situations **B**		**Grade**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Usual care does not require therapeutic ultrasound.		**NO**
Are there any resource implications associated with implementing this recommendation? There may be financial constraints for patients wishing to access therapeutic ultrasound		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment may be restricted to specialist clinics.		**NO**

Are the guideline development group aware of any barriers to the implementation of this recommendation? There are no known barriers to implementation.	**NO**

3.18 Health professional education

Evidence Summary

One low quality RCT[49] provided evidence that community nurses' knowledge of VLUs improves as a result of education specific to the nurses' requirements. Thirty-eight nurses with patients suffering from VLUs were recruited into the trial after volunteering and attending intensive information sessions. After completing a validated pre-test to determine baseline knowledge on VLU diagnosis, assessment, physiology and care, nurses were randomised (method not reported) to regular a group where participants maintained work conditions (no specific support) or to a second group receiving tele-advice from an expert when required. Nurses receiving the intervention took digital photos of the patients' wounds and received personalised feedback via telephone regarding the most appropriate care. After 12 weeks the participants all completed a post-test to detect changes in knowledge levels. Those in the intervention group had significant improvements from baseline in overall average score (p=0.022) and score for both dressing and management of wound care questions (p=0.05) but did not improve on questions related to physiology (p=0.23) or those classified as most the difficult questions. The control group showed no significant improvement in any category, a significant decrease on scores for most difficult questions (p=0.006) and for weighted average score (p=0.008). The trial was too small to make inter-group comparisons. Although the study suggested that this form of education may improve nursing knowledge, there was numerous limitations. There was no control for nursing staff completing their own research to improve scores; it was unclear if advice was received from the same expert for all participants; and those who participated were likely to have been highly motivated to perform well. The contribution that improved knowledge may make to the overall care and healing rate of the patient's VLU was not addressed in this trial, although follow on studies were inferred.[49]

Lower level evidence

One quasi-experimental, non-randomised trial[50] conducted in Hong Kong investigated the ability of an ulcer specific education program in improving the knowledge and skills in caring for patients with VLU of 42 enrolled and registered nurses working in community settings and had varying baseline knowledge levels. The education program administered to the nurses included didactic teaching, open discussion, multi-media presentation and skill demonstration. Content of the program included epidemiology, pathology, ulcer assessment and management and QOL issues. Participants demonstrated improvements in knowledge after participating in the program, with identification of ulcer aetiology being an area in which nurses made significant improvement in their knowledge.[50]

Another quasi-experimental, non-randomised trial[51] conducted with 264 community nurses in the UK investigated the effect on knowledge of an education program consisting of an open learning pack, two day study period, a visit to a VLU clinic and multi-media presentations. The 224 nurses who participated in the education program achieved greater improvement on a knowledge questionnaire following the education than did 40 control nurses who were not exposed to targeted education.[51]

However, a second non-randomised quasi-experimental study[52] conducted in the UK to compare the effects of a 4-hour educational program designed to incorporate different learning styles and needs to those of a standardised program found no significant differences between the knowledge improvements of participants. The experimental learning program was designed to address needs identified through participant performance at hands-on and enquiry stations. It consisted of didactic learning, instruction in group and individual settings, discussion groups, case studies and group debate and problem solving. The program was as effective as a regular didactic lecture in improving knowledge of VLUs.[52]

One quasi-experimental study[53] investigated the relationship between a nurse education program and

improving patient adherence to treatment and ulcer recurrence. Patients from various district nursing programs were followed for 52 weeks. Nurses working in the districts receiving the experimental education program participated in a 3 hour education session focused on improving patient compliance with therapy. Patients in this group received educational pamphlets describing strategies to prevent VLU recurrence. The control group of nurses received a one hour education session on VLU guidelines and patients received standard care. At 52 weeks, the experimental group patients had a significantly lower rate of VLU recurrence (p=0.004) compared to the patients in the control group, although there was no significant differences between the two groups for time spent wearing compression. The experimental group performed greater leg elevation. The trial suggested that nurse education may be a factor in improving patient adherence to therapy and reduction of VLU recurrence.[53]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One low quality RCT[49] and four level III quasi-experiments.[50-53]	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
	Most studies consistent and inconsistency can be explained	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
	Slight	**C**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted in nurses caring for patients with VLU. In one trial, nurses had access to digital photography and internet services.	**Evidence directly generalisable to the target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
One trial was conducted in Australia, The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context**	**A**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
Health professionals benefit from appropriate education on VLUs and their management. Body of evidence provides some support for recommendation(s) but care should be taken in its application **Grade C** **Patient outcomes may be superior when ulcer care is conducted by an appropriately trained health professional.**	
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? It is likely that many practitioners access both formal and informal education. It is hoped that more education will be provided to practitioners as a result of this recommendation. The guideline itself serves an educative purpose.	**YES**
Are there any resource implications associated with implementing this recommendation? Education must be designed and made available. Education has financial and time constraints for practitioners and services.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Services may need to develop education programs and/or develop strategies to promote practitioners accessing education.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Education services may not be available in all areas of Australia. However, increasingly education is provided in online contexts.	**YES**

3.19 Patient education

Evidence Summary		
A low quality RCT[54] investigated the effectiveness of written information material in improving the knowledge patients with VLU have regarding their disease and its management. The researchers recruited 20 participants who took a baseline knowledge questionnaire before receiving verbal information from the doctor together with written supportive information (n-10) or no written information (n=10). Patients repeated the questionnaire 4 to 6 weeks later. The result indicated no significant differences between patients who did or did not receive reinforcing written educational material. Participants in both groups had significant improvement in knowledge, particularly regarding exercise and compression for VLUs. The study did not investigate if improved education translated into implementation of appropriate intervention. The study was small, participants had a low level of education (65% had no formal education beyond primary schooling) and confounding issues such as cognitive illness, sensory deficits, non-English speaking backgrounds, emotional status, support from carers, other access to educational material and ability to read were either not discussed or not considered in the trial design. The results that written material is not beneficial should be considered cautiously given the study design, patient selection and small size of the trial.[54] A moderate quality SR[55] reported on the effectiveness of different programs in improving patient concordance with therapy. The majority of papers compared different types of compression therapy; however, three of the included papers addressed educational and psychosocial interventions. One paper reported on the development of "leg ulcer clubs" focused on social interaction, patient participation, role modeling and interactive education (early detection and prevention). Although methods of assessment were not reported, failure of patients to initaite or continue with recommended therapies reduced from 17% at commencement of the clubs to 5% after 11 months. Of those who failed to concord with recommeded therapy by the end of the trial, the majority had concurrent diagnosis of dementia. An audit of similar clinics reported only 3 out of 10 patients who had attended a "leg club" failed to implement recommendations reagrding maintenance of dressings. Two studies reported educational interventions to improve concordance with VLU treatments. In one quasi-experiment a program comprising combinations of behavioural, educational and affective strategies was shown to have a positive effect. Participants (n=51) exposed to the educational intervention elevated their legs for more than 12 hours per day, whilst the control group spent less than 10 hours with legs elevated. However, time spent wearing compression bandaging did not change and the groups were not comparable at baseline. In the second trial, education in the form of oral and written information and a quiz achieved 91% concordance with therapy in VLU patients. Both studies were of low quality and confounding factors (eg. patient selection) seem likely to have influenced the results.[55]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One low quality RCT[54]	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
There was only one study.	**N/A**	
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Unable to determine. The effect size was not reported.	**Restricted**	**D**

Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLU who were primarily from low socioeconomic and educational backgrounds.	**Evidence directly generalisable to the target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trial was conducted in the UK. Similar education may not be available in Australia, The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
Although this trial found that written material did not provide additional educational value over verbal education from a health practitioner, it is the Expert Working Committee's opinion that written material reinforces education material provided verbally. Patients often seek out written education material (eg on the internet) and it is important to provide education that is from reliable sources.		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is weak evidence that patients with VLUs benefit from appropriate education on their condition and its management. Body of evidence is weak and recommendation must be applied with caution **Grade D**		
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Yes, it is hoped practitioners will increase the amount of education with which patients are provided.		**YES**
Are there any resource implications associated with implementing this recommendation? Providing patients with education increases time involve din consultation. However, education can increase patient implementation of appropriate interventions and increase healing time. Written education would need to be developed.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? It may increase time taken in a consultation.		**YES**

Are the guideline development group aware of any barriers to the implementation of this recommendation? Patient factors (eg. sensory and communication deficits, socioeconomic background) can influence the effectiveness of education and willingness of patients to participate. Practitioners require support from their service to implement this recommendation.	**YES**

3.20 Pentoxifylline

Evidence Summary		
A good quality Cochrane SR[56] included 12 RCTs published up to 2009 that investigated the effectiveness of pentoxifylline 400mg (twice or three times daily) for the treatment of VLUs. Of the trials included in the review, quality ranged from moderate to low. Results from eleven trials (n=841) comparing pentoxifylline to placebo pooled using a random effects model showed that participants receiving pentoxifylline were more likely to heal than those receiving placebo (RR 1.70, 95% CI 1.30 to 2.24, p=0.00013); however, the trials were heterogeneous. The reviewers conducted a number of sensitivity analyses (eg. published vs unpublished trials, based on duration, based on primary outcome measure). The only sensitivity analysis without significant heterogeneity was that in which studies that specifically recruited hard-to-heal patients were excluded. In this analysis, participants treated with pentoxifylline were more likely to have ulcer healing than those receiving placebo (RR 1.30; 95% CI 1.10 to 1.54, p=0.0019). This translated to an absolute increase in healing of 21% (95% CI 8% to 34%) and a NNT ranging from 3 (95%CI 2 to 12) to 11 (95%CI 6 to 43) for pentoxifylline compared to placebo.[56] Pooled results from seven trials comparing pentoxifylline to compression plus placebo using a random effects model showed that participants receiving pentoxifylline were more likely to have ulcer healing than those receiving compression and a placebo (RR 1.56, 95% CI 1.14 to 2.13, p=0.005). Once again, there was significant heterogeneity. When results from the three trials that recruited hard-to-heal patients were combined using a fixed effects model, the results were homogeneous and showed that participants treated with pentoxifylline were more likely to have ulcer healing than those who received compression plus placebo (RR 2.36; 95% CI 1.74 to 3.19, p<0.00001). This translated to an absolute increase in healing of 23% (95% CI 4% to 43%) and a NNT ranging from 3 (95%CI 2 to 8) to 4 (95%CI 2 to 9) for pentoxifylline without concurrent compression therapy.[56] Nine trials (n-549) reported on side effects. These trials were combined using a fixed effects model and the analysis showed that participants treated with pentoxifylline were significantly more likely to experience side effects than those receiving placebo (RR 1.56; 95% CI 1.10 to 2.22, p=0.014). Gastrointestinal side effects were the most experienced adverse event.[56]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR and meta analysis of 12 trials of varying quality ranging from moderate to low.[56]	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**B**
Consistency		
RCTs included in the SR generally showed a positive effect. Pooled analyses were heterogeneous. The result were homogenous when RCTs conducted in hard-to-heal populations were removed from the analysis	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RR 1.30 translating to an increase in healing of 21% (95% CI 8% to 34%) and a NNT ranging from 3 (95%CI 2 to 12) to 11 (95%CI 6 to 43) for pentoxifylline compared to placebo.	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by*		

guideline)		
Trials were conducted with participants with VLUs. Trials had heterogenous results on pooling, however this was explained with consideration of whether the trials recruited participants with hard-to-heal ulcers.	**Evidence directly generalisable to the target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted in Europe. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is good evidence that pentoxifylline is effective in promoting healing in VLUs. Body of evidence can be trusted to guide practice in most situations **Grade B**		
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care?		**NO**
Are there any resource implications associated with implementing this recommendation? Yes, patients would have increased pharmaceutical costs.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? A script is required so nurse-led clinical would require medical professional's support.		**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No		**NO**

3.21 Micronised purified flavanoid fraction

Evidence Summary		
One moderate quality systematic review[57, 58] investigated the effect of micronised purified flavonoid fraction (MPFF) on VLU healing. The SR included five trials. Participants (n=723) had clinical signs of VLU, a previous history of varicose veins or post-thrombotic syndrome. In all trials, VLUs were present for at least three months. Participants across the five included trials had a mean ulcer area of 10.4 cm^2 (range 1 to 108 cm^2); mean ulcer duration of was 19.6 months (range 1 to 237 months); and average ulcer disease duration of average 13.5 years (range 0 to 58 years). Trials compared MPFF 1 g daily as an adjunct therapy to compression bandaging at a minimum of 30 mm Hg at the ankle. Pooled data from four trials for complete healing at six months showed a relative risk reduction (RRR) of 32% (95% CI 3% to 70%) for MPFF. However, there was significant heterogeneity (p=0.014). Exclusion of one trial that had a large proportion of ulcers that were less than 5cm^2 and of shorter duration created homogeneity and showed a RRR of 45% (95% CI 23% to 71%). A sub group analysis of participants with ulcers more than 5cm^2 in area (4 trials) showed a RRR of 53% (95% CI 15 to 103%) for complete healing in six months with MPFF. Results from five trials showed a RRR 44% (95% CI 7 to94%; p=0.015) of complete healing in two months for MPFF, but the results for healing at four months were not significant. The results of this systematic review should be considered within the context of the methodological limitations of the trials included in the analysis. Of the included trials, only two used a placebo control.[57, 58] One of these did not report complete healing at six months so was excluded from the primary analysis leaving open the possibility that the findings are influenced by the placebo effect. In addition, only two of the trials in this review were double blinded, with no blinding in the other three. Once again, the two double blinded trials were those not included in the primary analysis. The issues related to methodological flaws within the included trials, along with potential bias from the involvement of the product manufacturer in providing funding this review, suggest that the outcome should be considered cautiously until further good quality placebo-controlled, blinded RCTs investigating the role of MPFF in ulcer-healing provide further evidence.		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One moderate quality SR of 5 RCTs[57, 58]	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
Findings from studies varied and the meta-analysis produced different results depending upon which trials were included.	**Evidence is inconsistent**	**D**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RR between 32-53%	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Participants with complex co morbidities were excluded from some trials. Participants had VLUs of varied sizes and duration.	**Evidence directly generalisable to the target population with some caveats**	**B**

Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trials were conducted internationally. There were no trials conducted in people from Aboriginal and Torres Straight Island or Maori backgrounds.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is weak evidence that micronised purified flavanoid fraction may decrease healing time for VLUs. Body of evidence is weak and recommendation must be applied with caution		**Grade D**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Possibly health professionals will consider using MPFF in non-healing VLUs.		**YES**
Are there any resource implications associated with implementing this recommendation? If health professionals prescribed medication it would increase pharmaceutical expenses for patients.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? Patients would need review by a medical practitioner for prescribing. This would have implications for patients treated by community health nurses.		**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No.		**NO**

4 RESEARCH BASED RECOMMENDATIONS FOR PREVENTING RECURRENCE OF VLUS

4.1 Ongoing compression therapy

Evidence Summary		
One good quality Cochrane review[59] reported secondary outcome measures from moderate to low quality RCTs sponsored by product manufacturers. In one trial, 32% of participants who were non-compliant with stocking compression had recurrence of an ulcer within the five year trial period, compared with 19% of participants who wore stockings on a daily basis. In the second trial a post hoc analysis found that the participants who were excluded from the trial due to inability to apply stockings experienced significantly greater recurrence of ulcers compared to those who participated in the trial (RR 2.58, 95% CI 1.33 to 5.01).[59] A second good quality Cochrane review[4] reported one moderate to low quality RCT (n=233) comparing compression to no compression for preventing recurrence of VLUs. There were no significant differences in likelihood of ulcer recurrence or time to reoccurrence over 12 months (p=0.38) between a four layer bandage system and usual care. The trial was under powered to detect a significant result. In another trial (n=30) there was no cases of recurrence within 6 months in VLUs treated for 12 weeks with single layer elastic bandaging, four layer bandaging or a four component compression with paste bandaging. There was no non-compression comparison group.[4] One good quality RCT[60] reported re-ulceration as a secondary outcome. Participants who had healed from a VLU were randomised to receive either no compression or below knee compression stockings (35 to 45 mmHG graduated pressure) for up to 12 months. The group wearing stockings had a lower rate of reulceration (22.36% vs. 54.3%, p=not reported). However, 22% of participants in the compression stocking group withdrew from the trial due to undefined stocking-related events.[60]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Two good quality SRs[4, 59] with low risk of bias reporting evidence from Level II studies at moderate risk of bias (results not pooled). One good quality RCT.[60]	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
Inconsistencies explained by small studies, of moderate to low quality and underpowered to measure significant effect.	**Most studies consistent and inconsistency can be explained**	**B**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Effect size not reported; Recurrence rates ranged from 19 to 53%.	**Moderate**	**B**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. In most trials patients were excluded if their limbs were oedematous, if they had diabetes, CV disease or arterial disease.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		

The majority of trials were conducted in Europe. There was no research on the effect/compliance of compression therapy in tropic or humid climates. Many clients may have limited access to the most appropriate compression intervention. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**

Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*

None

Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*

None

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

There is some evidence that compression systems are effective in reducing the risk of recurrence of venous leg ulcers.

Body of evidence provides some support for recommendation(s) but care should be taken in its application **Grade C**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*

Will this recommendation result in changes in usual care? Usual care currently includes compression therapy.	**NO**
Are there any resource implications associated with implementing this recommendation? There are resource implications related to this recommendation. Many patients do not have access to the most appropriate form of compression therapy, or are limited in the use of this intervention by financial constraints.	**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? To implement this recommendation, more patients require referral to appropriate services where they can access the intervention, have compression applied on a regular basis and/or receive education in the importance of compression therapy and its application. There is a particular need for support for patients in rural and remote locations.	**YES**
Are the guideline development group aware of any barriers to the implementation of this recommendation? Many patients have limited access to the most appropriate healthcare services and compression products. Clinicians involved in wound management require appropriate training to apply compression therapy in a manner that achieves effective results.	**YES**

5 TREATMENTS NOT CURRENTLY RECOMMENDED

5.1 Electromagnetic therapy

Evidence Summary

A good quality Cochrane review[61] investigated electromagnetic therapy for treating VLUs. After a comprehensive literature search only 3 RCTs meeting the well-defined inclusion criteria were identified. The trials were subjected to critical appraisal and reported to be of varying quality. Due to variations in the type of treatments, the outcomes of the studies were not appropriate for pooling in meta-analysis and were reported in a discursive format. All the studies in the review were small and likely to be underpowered. [61]

Two of the RCTs compared PEMT to sham therapy. The first was a moderate quality double-blind RCT included 44 people with VLU. Participants were randomised to receive either electromagnetic therapy at 75 Hz, 2.7 mT, with an impulse width 1.3ms (n = 22) or sham stimulation (n = 22) for four hours per day for 3 months. The two groups were not comparable with respect to ulcer size at the commencement of the trial. Using data from participants who completed the trial, at 90 days there was significantly greater proportion of people with healed ulcers in the PEMT group compared to those receiving sham therapy (97% vs. 32%, RR 2.11, 95% CI 1.01 to 4.42, p=0.47). When the participants who dropped out of the trial were included in analysis, there were no significant differences (RR 2.0, 95% CI 0.92 to 4.37). In a good quality but small RCT participants were randomised to receive PEMT at 0.06 mV/cm, with a signal of 3.5 ms total width (n=18) or to sham therapy (n=13) for 3 hours for 12 weeks. The groups were comparable at baseline, there was blinded outcome measurement and the researchers conducted ITT analysis for the primary outcome measure. At 8 weeks, participants in the PEMT group had a 47% reduction in the size of ulcers, whilst those in the sham therapy group had a 49% increase in size of ulcers. The third trial was a low quality double blind RCT comparing PEMT with standard topical treatments. Participants (n=19) were randomly assigned one of three groups. The first group received electromagnetic therapy at 600 Hz electric field and 25 mTesla magnetic field. The second received electromagnetic therapy at 600 Hz on the first five days followed by 800 Hz and a 25 mTesla magnetic field for the remainder of the trial. The third group received sham therapy. Therapy was administered for 5 days a week for 30 days along with regular dressings. There was no significant difference between the two groups in the number of ulcers healed (20% vs. 22%, RR 0.90, 95% CI 0.16 to 5.13, p=0.91). The review concluded there was no reliable evidence supporting the effectiveness of PEMT in treating VLU.[61]

A second good quality SR[62] reported the results from 6 RCTs investigating PEMT. The review reported that 4 of the RCTs were of strong methodological designs and 2 were low quality studies. Three of the trials were reported in the Cochrane review.[61] Pooling of results was not performed due to heterogeneous treatment regimens. Four of the six trials reported a significant improvement in ulcers exposed to PEMT. There were inconsistencies in the findings between studies regarding the ability of PEMT to heal ulcers within a specific time frame. Studies reportedly included participants with different sized VLUs and the reviewers noted a pattern for smaller VLUs (<15cm^2) having the most significant rates of healing. Although the review concluded that there is strong evidence for a significant effect of PEMT on healing VLUs,[62] there are inconsistencies reported between studies within the review and between this review and a Cochrane review[61] reporting some of the same studies.

A low quality RCT[63] investigating the effectiveness of static electromagnetic therapy for healing VLUs. The intervention of interest, Ulcer Care, was described as containing 4 neodynamic magnets and was used for 12 weeks on the participants randomised to the treatment group (n=16), although the regimen was not reported. The placebo group (n=12) received sham treatment. Similarities between groups at baseline

were unclear, but it appeared the intervention group had small ulcers. intervention group achieved significantly greater healing after 12 weeks on outcome measures of change in ulcer area, change in and ulcer width, perimeter and length. There was no difference between the magnetic and the sham therapies for pain intensity, QOL and overall measures of health. Patients who withdrew or had missing data were not considered in the analysis and were not equivalent between groups. Due to methodological short comings the results of this trial were unconvincing.[63]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Two good quality SRs[61, 62] reporting moderate and good quality trials.	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
Results varied and trials were too small to be confident.	**Some inconsistency, reflecting genuine uncertainty around question**	**C**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Some trials reported significant results.	**Slight**	**C**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		
Trials were conducted in Europe. Access to services is likely to be restricted. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

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

Body of evidence provides some support for recommendation(s) but care should be taken in its application

Grade C

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care does not include electromagnetic therapy.	**NO**
Are there any resource implications associated with implementing this recommendation? The treatment is generally not used and there was no compelling reason to recommend the therapy. Patients who chose to use electromagnetic therapy may be constrained by cost.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment is generally not recommended.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

5.2 Electrotherapy

Evidence Summary		
A low quality RCT[46] reported the effectiveness of electrotherapy for reduction of pain and promotion of healing in 39 patients with chronic VLU of average 42 months duration. Participants were treated for a 3 month run-in period with compression then randomised to receive electrotherapy at a pulse of 128 Hz and average strength of 300 µA or sham electrotherapy. Electrotherapy was applied under compression twice daily for 30 minutes using a treatment cycle of 7 days of negative polarity followed by 3 days of positive polarity. Treatment continued for an average of 100 days (ie 10 cycles). After 4 months the electrotherapy group had achieved a significant reduction in ulcer surface area (p=0.03) but this was not significant compared to the sham treatment group. Equivalence of baseline demographic and ulcer characteristics was also not reported and there was no discussion of adverse events. This trial provided low quality evidence that electrotherapy does not promote ulcer healing.[46] A low quality trial[64] investigated the effect of electrotherapy in healing VLUs. Randomisation was by alternate admission to two different hospital wards. Thirty-three participants in one ward were treated with electrotherapy consisting at 100 Hz frequency and approximately 100 V depending on patient response for 50 minutes, 6 days per week for a total of 7 weeks. Participants were treated with negative polarity until pus coverage of the VLU cleared (between 1 and 3 weeks), then treatment was conducted with positive polarity. The second group of participants (n=32) were treated with various different topical dressings for a period of 6 weeks. Both groups received concurrent compression therapy. A third group of 14 participants being treated as outpatients were also recruited and treated with Unna's boot for 5.5 weeks. Baseline comparisons are poorly reported; however the community group had ulcers of shorter duration and smaller in size and the topically-treated group had VLUs with a greater coverage of pus at baseline. At the trial completion all groups had significantly improved VLUs and there was no significant difference between the groups in rate of healing. The group treated with electrotherapy had significantly faster resolution of supporative ulcer area; however this group had less pus at commencement of the trial.[64] A low quality trial[47] investigated the treatment of VLUs with frequency rhythmic electrical modulation system (FREMS). Participants were 35 patients with primarily VLUs. All participants were treated with a range of dressings and topical treatments but no compression. Conventional analgesics were also prescribed. The intervention group (n=20) received FREMS 5 days per week for 3 weeks for 40 minutes at pulse amplitudes from 0 to 300 V and intensity from 100 to 170 µA. It was unclear if the control participants (n=19) received a placebo/sham treatment. At 8 week follow up FREMS was associated with a significant decrease in ulcer surface area measured using a digital imaging technique and overall ulcer condition using subjective Likert scales. However, the groups were non-equivalent at baseline, with the control group having ulcers of significantly longer duration. Participants treated with FREMs experienced slight burning at electrode sites.[47]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
Three low quality RCTs[46, 47, 64]	**Level IV studies or Level I to III studies/SRs with high risk of bias**	**D**
Consistency		
Results varied for ulcer healing.	**Evidence is inconsistent**	**D**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Some trials reported significant results but effects were small and inconistent.	**Restricted**	**D**

Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Participants with diabetes were excluded from some trials.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
Trials were conducted in Europe. Access to services is likely to be restricted. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is weak evidence that electrotherapy offers no benefit over standard care in promoting healing in VLUs.		
Body of evidence is weak and recommendation must be applied with caution		**Grade D**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Usual care does not include electrotherapy.		**NO**
Are there any resource implications associated with implementing this recommendation? The treatment is not recommended. Patients who chose to use electrotherapy may be constrained by cost.		**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment is generally not recommended. If used, it would be restricted to specialist clinics.		**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No barriers to implementation are known.		**NO**

5.3 Low level laser therapy

Evidence Summary

A good quality Cochrane SR[65] reported two RCTs comparing LLLT to sham laser therapy. One RCT (reported to have adequate methodology) compared helium neon laser used at an energy level of 4 Joules/cm² (n=23) to sham laser therapy (n=23). Participants also received standard treatment of saline cleansing, paste and support bandages and were encouraged to perform exercise. LLLT was conducted twice weekly for 12 weeks. There was no significant difference in proportion of ulcers healed after 12 weeks (LLLT 17%, placebo 13%). The second RCT (also of adequate methodology) investigated a gallium arsenide laser at an energy level of 1.96 Joules/cm². Participants also received standard treatment of saline cleansing, paste and support bandage and an exercise program. Laser (n=21) or sham laser (n=21) was administered twice weekly for 12 weeks. In contrast to the first trial, in this trial there was a large proportion of healing observed in both the LLLT group (62%) and the sham therapy group (52%). Comparison between groups showed no statistically significant difference in proportion of ulcers healed at 12 weeks. The results of these two trials were pooled and no heterogeneity was found. There was no statistically significant difference between treatment with any type of laser compared to sham laser (RR 1.21; 85% CI 0.73 to 2.03, p=0.46).[65]

A moderate quality RCT[66] investigated the effectiveness of LLLT in healing VLUs. Patients with VLUs were eligible for inclusion if they had an ulcer 1–8cm in diameter and between 3 months and 3 years duration that had previously been treated with compression. Exclusion criteria included malignancy, insulin dependent diabetes mellitus and arterial dysfunction. Participants were randomised to LLLT (n=17), placebo laser (n=17) or standard treatment (n=10). The laser therapy consisting of a continuous red light wave of 685nm at a fluence of 200mW producing 4J/cm² administered for 6 to18 minutes depending upon ulcer size, daily for 14 days then alternate days for 14 days. All groups received enzymatic debridement of the ulcer in the first week of therapy and daily (first 2 weeks) then alternate day hydrofiber dressings and compression. At the end of the treatment phase (day 28), there was no significant difference between the three groups for reduction in mean ulcer size measured by wound tracings and planimetry. The placebo laser group achieved a significant reduction in mean ulcer size between commencement and day 28 (median reduction approximately 2cm², p=0.023), as did the control group (mean reduction approximately 5cm², p=0.047). There was no change in the median size of ulcers in the laser group (p= 0.492). At 90 days follow up there remained no significant between group difference and only the placebo laser group had a significant reduction in ulcer size from baseline (p=0.011). Lack of treatment effect may have been due to insufficient laser dosage, the smaller size of the ulcers in the treatment group at baseline (although the difference was not significant between groups), or the lack of ITT analysis.[66]

Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR[65] reporting 2 moderate quality trials and an additional moderate quality trial. [66]	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
All moderate quality trials showed LLLT was not superior to usual care.	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RR not significant.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		

Trials were conducted with participants with VLUs.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		
Access to services is likely to be restricted. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context with few caveats**	**B**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		
RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***		
There is some evidence that low level laser therapy offers no benefit over standard care in promoting healing in VLUs. Body of evidence provides some support for recommendation(s) but care should be taken in its application		**Grade C**
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*		
Will this recommendation result in changes in usual care? Usual care does not require LLLT and there is no overwhelming reason to recommend its use		**NO**
Are there any resource implications associated with implementing this recommendation? There may be financial constraints for patients wishing to access LLLT.		**YES**
Will the implementation of this recommendation require changes in the way care is currently organised? The treatment may be restricted to specialist clinics. Using this therapy would involve increased time and require appointments to be spaced appropriately.		**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? The treatment is not recommended, however if it is used, the therapy would involve increased time and require appointments to be spaced appropriately.		**NO**

5.4 Topical phenytoin

Evidence Summary		
A moderate quality SR[67] provided a narrative report of three RCTs at moderate risk of bias that reported the use of topical phenytoin for treating VLUs. One good quality RCT compared phenytoin to placebo in 30 patients, reporting on the primary outcome measure of decrease in ulcer size after 13 weeks. At follow up, the ulcers in the phenytoin group had decreased in size compared with deterioration in condition observed in the control group VLUs. Some patients treated with phenytoin experienced ataxia and dizziness. The second RCT was a non-blinded trial comparing phenytoin with honey to honey alone in 50 patients with VLUS. After 4 weeks of treatment there was significantly greater healing in the phenytoin group compared to the group treated with honey alone (22% vs. 0%, $p<0.05$). No adverse events were reported. The third RCT compared phenytoin (n=50) to EUSOL (n=52) in managing VLUs over 4 weeks. In this trial there was a significant increase in healthy granulation in the VLUs in the phenytoin group compared to the control ($p<0.001$). Both VLU surface area ($p<0.01$) and subjectively measured pain levels ($p<0.05$) improved significantly for the phenytoin group. No adverse events were reported. The reviewers conclude there is moderate evidence to support the use of phenytoin in treating VLUs for 4 to 13 weeks.[67]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One moderate quality SR[67] providing a narrative summary of 3 moderate quality RCTs	**One or two Level III studies with low risk of bias or Level I or II studies with moderate risk of bias**	**C**
Consistency		
The trials all showed an effect for topical phenytoin compared with placebo or standard therapies. In one trial, honey was used in combination with phenytoin.	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
Effect size not reported.	**Unable to determine**	
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs. Other characteristics of participants were not reported.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		
Details of the intervention and population was not reported; however there it is likely that it would be relevant to the Australian and NZ health care context.	**Evidence probably applicable to Australian healthcare context with some caveats**	**C**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
In vitro studies have shown that topical phenytoin has cytotoxic effects on skin cells[68, 69] 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.		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

There is some evidence that topical phenytoin is more effective than standard care for promoting healing in VLUs venous leg ulcers.

Body of evidence provides some support for recommendation(s) but care should be taken in its application **Grade C**

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

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*

Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation?	**NO**

5.5 Oral zinc

Evidence Summary		
A Cochrane review[70] included four moderate quality RCTs investigating the effect of oral zinc for improving healing of VLUs. All trials were randomised and double blinded, although methods were not always reported within the trials. In two of the trials the groups were not comparable at baseline with respect to the size of ulcers. Intention to treat analysis was not used in one trial. The trials were all small (between 10 and 42 participants) and used a regimen of oral zinc 200 to 220mg, three times daily for the period of the trial, which ranged from 3 to 10 months. Comparison groups were assigned placebos. In all trials, ulcers had persisted beyond 4 weeks, and in two of the trials participation was restricted to people with ulcers of between 10 and 100 cm^2. In two trials baseline measures of serum zinc were conducted; however, it is unclear if group assignment was stratified by baseline serum zinc levels and whether this would influence the findings. Concomitant therapies included a variety of dressing types and in one trial participants also received compression therapy. All trials reported the number of ulcer healed at the trial end point as the primary outcome measure. No individual trials reported a significant effect for oral zinc compared to placebo for healing venous leg ulcers. In one trial a sub-group analysis was conducted to determine if an effect existed in participants with low serum zinc levels (less than 110mcg/100ml) and this analysis also showed no effect above placebo. Pooled results from the 4 RCTs found no significant effect above placebo for oral zinc in the treatment of venous leg ulcers (RR 1.22; 95% CI 0.88 to 1.68, p=0.24). The results should be considered cautiously due to the methodological flaws in these trials and the low number of participants in individual trials, which likely meant these studies were underpowered to measure an effect. The unclear contribution of serum zinc levels of participants at baseline and the restriction to ulcers of at least 4 weeks duration may also have influenced findings.[70]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality SR[70] and meta analysis of 4 moderate quality trials	**One or more level I studies with low risk of bias or several level II studies with low risk of bias**	**A**
Consistency		
RCTs included in the SR all showed no effect.	**All studies consistent**	**A**
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RCTs included in the SR all showed no effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLUs and in some trials were restricted to VLUs of moderate to large sizes. Some trials excluded participants with complex concurrent disease.	**Evidence directly generalisable to target population with some caveats**	**B**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and cuture)*		
Trials were conducted internationally. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori	**Evidence applicable to Australian healthcare context with few caveats**	**B**

populations.		

Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*

None

Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*

None

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION

Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence. ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***

There is excellent evidence that oral zinc offers no benefit over standard care in improving healing in VLUs.

Body of evidence can be trusted to guide practice **Grade A**

Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*

Will this recommendation result in changes in usual care?	**NO**
Are there any resource implications associated with implementing this recommendation?	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? This may be controversial among practitioners that recommend zinc supplements for wound healing.	**NO**

5.6 Horsechestnut seed extract

Evidence Summary		
A good quality, double blind RCT[71] investigated the effectiveness of horse chestnut see extract (HCSE) for healing VLUs. Participants were recruited from an Australian ulcer clinic and randomised to receive either 375 mg daily HCSE (n=27) or a daily placebo (n=27) for 12 weeks or until the VLU healed. Participants had a mean age of 77 years, a mean ABPI of 1.05 and had ulcers of at least 4 weeks duration that were between 1 cm and 20 cms in diameter. The participants were treated with either a low adherent dressing, absorbent dressing or zing impregnated past bandage with either high, moderate or low pressure compression. Selection of concurrent dressing was considered in the final analysis. Ulcers were assessed at baseline and every 4 weeks using a validated digital photography method and computerized planimetry. At 12 weeks both groups showed a significant improvement in wound surface area. However, there were no between group differences for percentage of ulcers healed at 12 weeks, rate of wound healing, wound surface area or ulcer recurrence. The HCSE group had a reduction in frequency of dressing changes over the trial period compared to an increase in dressing changes for the placebo group (p=0.009); however, the researchers did not report how the decision to change a dressing was made. The HCSE group had a significantly greater number of adverse events (p=0.014), reported to be primarily gastrointestinal symptoms lasting less than 24 hours. Although the trial had insufficient participants to meet the a-priori power calculation requirements, it was a well conducted trial that provided good evidence for a lack of effect of HCSE 375 mg daily in improving the healing of VLUs over 12 weeks.[71]		
Evidence base *(volume of studies, level of evidence and risk of bias of included studies)*		
One good quality trial[71]	**One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias**	**B**
Consistency		
There was only one trial	**N/A**	
Clinical impact *(indicate if impact is indeterminable due to study results varying according to unknown factors eg. not sample size or study quality)*		
RCT showed no effect.	**Restricted**	**D**
Generalisability *(how well does body of evidence match the population and clinical setting targeted by guideline)*		
Trials were conducted with participants with VLU including those with concurrent complex disease (eg. diabetes).	**Evidence directly generalisable to the target population.**	**A**
Applicability *(body of evidence relevant to Australian health care context in terms of service delivery and culture)*		
The trial was conducted in Australia. The studies did not include, or did not report, data specific to Aboriginal and Torres Strait Islander or Maori populations.	**Evidence applicable to Australian healthcare context**	**A**
Other factors *(Indicate other factors that were taken into account when assessing the evidence that may have caused a downgrade or upgrade in the recommendation)*		
None		
Dissenting opinion *(Indicate any dissenting opinion within the guideline development group)*		
None		

RECOMMENDATION STATEMENT AND OVERALL GRADE OF RECOMMENDATION *Determine the overall grade of the recommendation based on a summation of the rating for each individual component of the body of evidence.* ***A recommendation cannot be graded A or B unless the evidence base and consistency of the evidence are both rated A or B.***	
There is good evidence that horse chestnut seed extract is not more effective than standard care in promoting healing in VLUs Body of evidence can be trusted to guide practice in most situations **Grade B**	
Implementation of the recommendation *(Indicate yes or no to the following questions and provide explanatory information. This information is used to develop the implementation plan for the Guideline)*	
Will this recommendation result in changes in usual care? Usual care does not include HCSE.	**NO**
Are there any resource implications associated with implementing this recommendation? No, the treatment is not recommended.	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised? No, the treatment is not recommended.	**NO**
Are the guideline development group aware of any barriers to the implementation of this recommendation? No, the treatment is not recommended. This may be controversial amongst practitioners who recommend its use for managing VLU.	**NO**

5.

6. REFERENCES

1. Coleman K, Norris S, Weston A, Grimmer K, Hillier S, Merlin T, Middleton P, Tooher R & Salisbury J, 2005. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: pilot program 2005 - 2007. NHMRC: Canberra.
2. Scottish Intercollegiate Guidelines Network, 2001-2009. Critical apprasisal: notes and checklists, in http://www.sign.ac.uk/methodology/checklists.html, SIGN, Editor.
3. Martinez M, Bonfill X, Moreno R, Vargas E & Capella D. 2005. Phlebotonics for venous insufficiency. Cochrane Database of Systematic Reviews. **Issue 3**.
4. O'Meara S, Cullum N & Nelson E. 2009. Compression for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.
5. Palfreyman S, Lochiel R & Michaels J. 1998. A systematic review of compression therapy for venous leg ulcers. Vascular Medicine. **3**(4): p. 301-313.
6. Moffatt C, Edwards L, Collier M, Treadwell T, Miller M, Shafer L, Sibbald G, Brassard A, McIntosh A, Reyzelman A, Price P, Kraus S, Walters S & Harding K. 2008. A randomised controlled 8-week crossover clinical evaluation of the 3M Coban 2 Layer Compression System versus Profore to evaluate the product performance in patients with venous leg ulcers. International Wound Journal. **5**(2): p. 267-79.
7. Rowland J. 2000 Intermittent pump versus compression bandages in the treatment of venous leg ulcers. Australian & New Zealand Journal of Surgery. **70**(2): p. 110-3.
8. Feben K. 2003 How effective is training in compression bandaging techniques? British Journal of Community Nursing. **8**(2): p. 80-4.
9. Palfreyman S, Nelson EA & Michaels JA. 2007. Dressings for venous leg ulcers: systematic review and meta-analysis. BMJ. **335**(7613): p. 244-256.
10. Bradley M, Cullum N, Nelson E, Petticrew M, Sheldon T & Torgerson D. 1999. Systematic reviews of wound care management: (2) dressings and topical agents used in the healing of chronic wounds. Health Technology Assessment. **3**(17 II): p. iii-126.
11. O'Donnell TF & Lau J. 2006. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. Journal of Vascular Surgery. **44**(5): p. 1118-25.
12. Bouza C, Munoz A & Amate JM. 2005. Efficacy of modern dressings in the treatment of leg ulcers: A systematic review Wound Repair and Regeneration. **13**(3): p. 218-229.
13. Borges EL, Caliri MHL & Haas VJ. 2007. Systematic review of topic treatment for venous ulcers. Revista Latino-Americana de Enfermagem. **15**(6): p. 1163-70.
14. Alvarez O, Patel M, Booker J & Markowitz L. 2004. Effectiveness of a biocellulose wound dressing for the treatment of chronic venous leg ulcers: results of a single center randomized study involving 24 patients. . Wounds: A Compendium of Clinical Research and Practice. **16**(7): p. 224-33.

15. Meaume S, Ourabah Z, Cartier H, Granel-Brocard F, Combemale P, Bressieux J & Bohbot S. 2005. Evaluation of a lipidocolloid wound dressing in the local management of leg ulcers. Journal of Wound Care. **14**(7): p. 329-34.

16. Schmutz J, Meaume S, Fays S, Ourabah Z, Guillot B, Thirion V, Collier M, Barrett S, Smith J, Bohbot S & Dompmartin A. 2008. Evaluation of the nano-oligosaccharide factor lipido-colloid matrix in the local management of venous leg ulcers: results of a randomised, controlled trial. International Wound Journal. **5**(2): p. 172-82.

17. Smeets R, Ulrich D, Unglaub F, Woltje M & Pallua N. 2008 Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. International Wound Journal. **5**(2): p. 195-203.

18. Vanscheidt W, Sibbald R & Eager C. 2004. Comparing a foam composite to a hydrocellular foam dressing in the management of venous leg ulcers: a controlled clinical study. . Ostomy Wound Management. **50**(11): p. 42-55.

19. Franks P, Moody M, Moffatt C, Hiskett G, Gatto P, Davies C, Furlong W, Barrow E & Thomas H. 2007. Wound Healing Nursing Research Group. Randomized trial of two foam dressings in the management of chronic venous ulceration. . Wound Repair & Regeneration. **15**(2): p. 197-202.

20. Schulze H, Lane C, Charles H, Ballard K, Hampton S & Moll I. 2001. Evaluating a superabsorbent hydropolymer dressing for exuding venous leg ulcers. Journal of Wound Care. **10**(1): p. 511-8.

21. Rainey J. 1993. A comparison of two dressings in the treatment of heavily exuding leg ulcers. Journal of Wound Care. **2**(4): p. 199-200.

22. Norkus A, Dargis V, Thomsen J, Harding K, Ivins N, Serra N, Torres de Castro O, Galindo A, Andersen K, Roed-Petersen J, Gottrup F, Blanco J, de Mena M, Hauschild A, Moll I, Svensson A & Carter K. 2005. Use of a hydrocapillary dressing in the management of highly exuding ulcers: a comparative study. Journal of Wound Care. **14**(9): p. 429-32.

23. Beckert S, Warnecke J, Zelenkov aH, Kovnerystyy O, Stege H, Cholcha W, Konigsrainer A & Coerper S. 2006. Efficacy of topical pale sulfonated shale oil in the treatment of venous leg ulcers: a randomized, controlled, multicenter study. Journal of Vascular Surgery. **43**(1): p. 94-100.

24. Rivera-Arce E, Chavez-Soto M, Herrera-Arellano A, Arzate S, Aguero J, Feria-Romero I, Cruz-Guzman A & Lozoya X. 2007 Therapeutic effectiveness of a Mimosa tenuiflora cortex extract in venous leg ulceration treatment. . Journal of Ethnopharmacology. **109**(3): p. 523-8.

25. Cameron J, Hoffman D, Wilson J & Cherry G. 2005. Comparison of two peri-wound skin protectants in venous leg ulcers: a randomised controlled trial. Journal of Wound Care. **14**(5): p. 233-6.

26. Neander K & Hesse F. 2003. The protective effects of a new preparation on wound edges. Journal of Wound Care. **12**(10): p. 369-71.

27. O'Meara S, Al-Kurdi D & Ovington L. 2010. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.

28. Chambers H, Dumville J & Cullum N. 2007. Silver treatments for leg ulcers: A systematic review. Wound Repair and Regeneration. **15**(2): p. 165-173.

29. O'Meara S, Cullum N, Majid M & Sheldon T. 2001 Systematic review of antimicrobial agents used for chronic wounds British Journal of Surgery. **88**(1): p. 4-21.

30. Dimakakos E, Katsenis K, Kalemikerakis J, Arkadopoulos N, Mylonas S, Arapoglou V & et al. 2009. Infected venous leg ulcers: management with silver-releasing foam dressing. Wounds: A Compendium of Clinical Research and Practice. **21**(1): p. 4-8.

31. Jull A, Rodgers A & Walker N. 2008. Honey as a topical treatment for wounds Cochrane Database of Systematic Reviews. **Issue 4**.

32. Haller G, Faltin-Traub E, Faltin D & Kern C. 2002. Oxygen embolism after hydrogen peroxide irrigation of a vulvar abscess. Br J Anaesth. **88**: p. 597-9

33. Henley N, A. D, Kaehr D & Clements B. 2004. Air Embolism associated with irrigation of external fixator pin sites with hydrogen peroxide. The Journal of Bone and Joint Surgery. **86**: p. 821-822.

34. Sleigh J & Linter S. 1985. Hazards of hydrogen peroxide. British Medical Journal. **291**(6510): p. 1706.

35. Johannsen F, Gam A & Karlsmark T. 1998. Ultrasound therapy in chronic leg ulceration: a meta-analysis. Wound Repair and Regeneration. **6**(2): p. 121-126.

36. Falabella A, Carson P, Eaglstein W & Falanga V. 1998. The safety and efficacy of a proteolytic ointment in the treatment of chronic ulcers of the lower extremity. Journal of the American Academy of Dermatology. **39**(5 Pt 1): p. 737-40.

37. Konig M, Vanscheidt W, Augustin M & Kapp H. 2005. Enzymatic versus autolytic debridement of chronic leg ulcers: a prospective randomised trial. Journal of Wound Care. **14**(7): p. 320-3.

38. Forsling E. 1988. Comparison of saline and streptokinase-streptodornase in the treatment of leg ulcers. European Journal of Clinical Pharmacology. **33**(6): p. 637-8.

39. Dix F, Reilly B, David M, Simon D, Dowding E, Ivers L, Bhowmick A & McCollum C. 2005. Effect of leg elevation on healing, venous velocity and ambulatory venous pressure in venous ulceration. Phlebology. **20**(2): p. 87-94.

40. Barnes M, Mani R, Barret D & White J. 1992. Changes in skin microcirculation at periulcerous sites in patients with chronic venous ulcers during leg elevation. Phlebology. **7**: p. 36-39.

41. Kan Y & Delis K. 2001. Hemodynamic effects of supervised calf muscle exercise in patients with venous leg ulceration: a prospective controlled study. Archives of Surgery. **136**(12): p. 1364-9.

42. Jones J & Nelson E. 2007. Skin grafting for venous leg ulcers. Cochrane Database of Systematic Reviews. **2:CD001737**.

43. Barber C, Watt A, Pham C, Humphreys K, Penington A, Mutimer K, Edwards M & Maddern G. 2008 Influence of bioengineered skin substitutes on diabetic foot ulcer and venous leg ulcer outcomes. Journal of Wound Care. **17**(12): p. 517-27

44. Briggs M & Nelson E. 2003. Topical agents or dressings for pain in venous leg ulcers. . Cochrane Database of Systematic Reviews. **Issue 1**.

45. Gottrup F, Jorgensen B, Karlsmark T, Sibbald R, Rimdeika R, Harding K, Price P, Venning V, Vowden P, Junger M, Wortmann S, Sulcaite R, Vilkevicius G, Ahokas T, Ettler K & Arenbergerova M. 2008. Reducing wound pain in venous leg ulcers with Biatain Ibu: a randomized, controlled double-blind clinical investigation on the performance and safety. Wound Repair & Regeneration. **16**(5): p. 615-25.

46. Junger M, Arnold A, Zuder D, Stahl H & Heising S. 2008. Local therapy and treatment costs of chronic, venous leg ulcers with electrical stimulation (Dermapulse): a prospective, placebo controlled, double blind trial. Wound Repair & Regeneration. **16**(4): p. 480-7.

47. Jankovic A & Binic I. 2008. Frequency rhythmic electrical modulation system in the treatment of chronic painful leg ulcers. Archives of Dermatological Research. **300**(7): p. 377-83.

48. Al-Kurdi D, Bell-Syer SE & Flemming K. 2008. Therapeutic ultrasound for venous leg ulcers. Cochrane Database of Systematic Reviews. **1:CD001180**.

49. Ameen J, Coll A & Peters M. 2005. Impact of tele-advice on community nurses' knowledge of venous leg ulcer care. Journal of Advanced Nursing. **50**(6): p. 583-94.

50. Wong I. 2003. Assessing the value of a leg ulcer education programme in Hong Kong. Journal of Wound Care. **12**(1): p. 17-9.

51. Jones J & Nelson E. 1997 Evaluation of an education package in leg ulcer management. Journal of Wound Care. **6**(7): p. 342-3.

52. Seeley M & Harding K. 2008. The effects of education and training on clinical practice in wound healing. International Wound Journal. **5**(5): p. 660-4.

53. Brooks J, Ersser S, Lloyd A & Ryan T. 2004 Nurse-led education sets out to improve patient concordance and prevent recurrence of leg ulcers. Journal of Wound Care. **11**(3): p. 111-6.

54. Clarke Moloney M, Moore A, Adelola O, Burke P, McGee H & Grace P. 2005. Information leaflets for venous leg ulcer patients: are they effective? Journal of Wound Care. **14**(2): p. 75-7.

55. Van Hecke A, Grypdonck M & Defloor T. 2008 Interventions to enhance patient compliance with leg ulcer treatment: a review of the literature. Journal of Clinical Nursing. **17**(1): p. 29-39.

56. Jull A, Arroll B, Parag V & Waters J. 2007. Pentoxifylline for treating venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 3**.

57. Coleridge-Smith P. 2005. Daflon 500 mg and venous leg ulcer: New results from a meta-analysis. Angiology. **56**(1): p. S33-S39.

58. Coleridge-Smith P, Lok C & Ramelet A. 2005. Venous Leg Ulcer: A Meta-analysis of Adjunctive Therapy with Micronized Purified Flavonoid Fraction. Eur J Vasc Endovasc Surg. **30**: p. 198-208.

59. Nelson A, Bell-Syer S & Cullum NA. 2000 Compression for preventing recurrence of venous ulcers. Cochrane Database of Systematic Reviews. **Issue 4**.

60. Vandongen Y & Stacey M. 2000. Graduated compression elastic stockings reduce lipodermatosclerosis and ulcer recurrence. Phlebology. **15**(1): p. 33-37.

61. Ravaghi H, Flemming K, Cullum N & Olyaee Manesh A. 2006. Electromagnetic therapy for treating venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 2**.

62. McGaughey H, Dhamija S, Oliver L, Porter-Armstrong A & McDonough S. 2009. Pulsed electromagnetic energy in management of chronic wounds: a systematic review. Physical Therapy Reviews. **14**(2): p. 132-46.

63. Eccles N & Hollinworth H. 2005. A pilot study to determine whether a static magnetic device can promote chronic leg ulcer healing. Journal of Wound Care. **14**(2): p. 64-7.

64. Franek A, Polak A & Kucharzewski M. 2000. Modern application of high voltage stimulation for enhanced healing of venous crural ulceration. . Medical Engineering & Physics. **22**(9): p. 647-55.

65. Flemming K & Cullum N. 1999. Laser therapy for venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 1**.

66. Kopera D, Kokol R, Berger C & Haas J. 2005. Does the use of low-level laser influence wound healing in chronic venous leg ulcers? Journal of Wound Care. **14**(8): p. 391-4.

67. Shaw J, Hughes C, Lagan K & Bell P. 2007. The clinical effect of topical phenytoin on wound healing: A systematic review. British Journal of Dermatology. **157**(5): p. 997-1004.

68. Scheinfeld N. 2003. Phenytoin in cutaneous medicine: Its uses, mechanisms and side effects. Dermatology Online Journal. **9**(3): p. 6.

69. Bhatia A & Prakash S. 2004. Topical phenytoin for wound healing. Dermatology Online Journal. **10**(1): p. 5.

70. Wilkinson E & Hawke C. 1998 Oral zinc for arterial and venous leg ulcers. Cochrane Database of Systematic Reviews. **Issue 4**.

71. Leach M, Pincombe J & Foster G. 2006 Clinical efficacy of horsechestnut seed extract in the treatment of venous ulceration. Journal of Wound Care. . **15**(4): p. 159-67.

APPENDIX ONE EXPERT WORKING COMMITTEE

1. Membership of the Expert Working Committee

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

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

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

1. Conflicts of Interest

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

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

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

APPENDIX TWO PROCESS REPORT

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

The project consisted of the following phases:

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

1 Identification, appraisal and synthesis of new evidence

Search strategy

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

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

Search strategy for systematic reviews

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

Search strategy randomised controlled trials

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

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

Inclusion/exclusion criteria

Types of studies

Studies that provide Level I evidence or Level II evidence on the National Health and Medical Research Council (NHMRC) Levels of evidence scale[1] (see Table one) were considered for inclusion. For intervention studies, RCTs (or systematic reviews of RCTs) that compared a single or combination intervention to placebo, sham-intervention, no treatment or another active intervention were included. For questions related to aetiology, diagnosis and assessment of leg ulcers, there was limited level I or II evidence available, therefore the search was expanded to include relevant level III and level IV research, as well as expert opinion and consensus guidelines. Randomised controlled trials that were reported in systematic reviews that were included were not subjected to individual critical appraisal to prevent replication of data.

Table one – NHMRC levels of evidence[1]

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	Analysis of prognostic factors amongst persons in a single arm of a randomised	A comparison with reference standard that does not meet the criteria for Level II or Level III-1 evidence

	series with a control group	controlled trial	
III –3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group	A retrospective cohort study	Diagnostic case–control evidence
IV	Evidence obtained from case series, either post-test or pre-test and post-test	Case series, or cohort study of persons at different stages of disease	Study of diagnostic yield (no reference standard)

Types of participants

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

Types of interventions

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

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

Types of outcomes

Outcome measures of interest included:

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

Critical appraisal

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

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

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

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

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

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

Data extraction

The primary reviewer systematically extracted the data from all studies using a data extraction tool that combined NHMRC data extraction[1] suggestions with information collected using the SIGN checklist tools. A second reviewer checked data extraction for 100% of systematic review papers and 30% of the additional research. Data from included studies was presented in evidence summary statements.

Special Populations

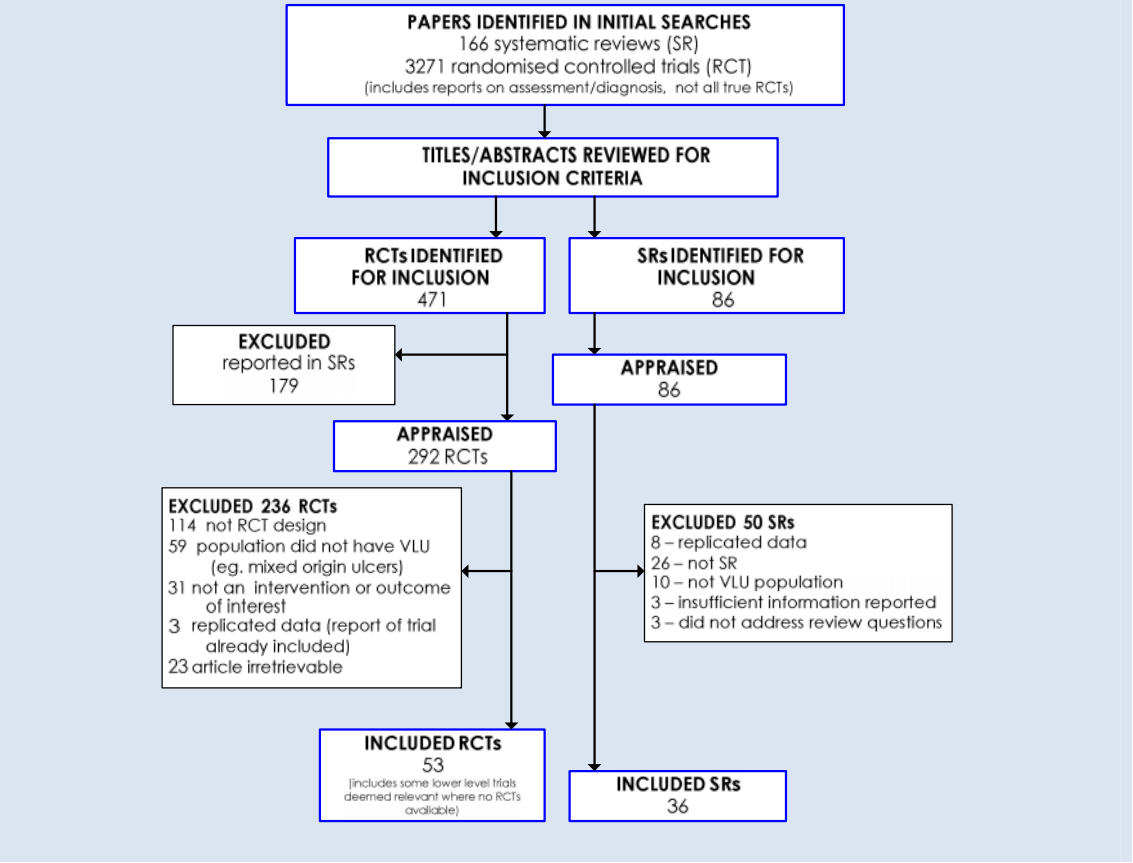
The search strategy was designed to retrieve all available evidence meeting the inclusion criteria, including research specific to special populations including Aboriginal and Torres Strait Islander people; New Zealand Maori people; rural and remote communities; and people from culturally and linguistically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

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

Identified research

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

Figure 1 – Review process



2 Development and grading of the recommendations

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

The evidence was summarised into evidence statements. A body of evidence assessment matrix developed by the NHMRC[1] (Table two) was used to assess the volume and consistency of evidence supporting each recommendation; as well as the clinical impact, generalisability and applicability of the recommendation.

Table two - Body of evidence assessment matrix[1]

Component	A	B	C	D
	Excellent	**Good**	**Satisfactory**	**Poor**
Volume of evidence	Several level I or level II studies with low risk of bias	One or two level II studies with low risk of bias or a SR of multiple level III	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

		studies with low risk of bias		
Consistency	All studies consistent	Most studies consistent and inconsistencies may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical Impact	Very large	Substantial	Moderate	Slight or restricted
Generalis-ability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence different to the target population for the guideline but it is clinically sensible to apply this evidence to the target population (e.g. results in adults that are clinically sensible to apply to children)	Population/s studied in the body of evidence different to the target population for the guideline and hard to judge whether it is sensible to generalise to the target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

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

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

Table one: Recommendation grades[1]	
Evidence based research	
A	Excellent evidence - body of evidence can be trusted to guide practice

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