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Antibiotics and antiseptics for venous leg ulcers

Susan O'Meara , Deyaa Al-Kurdi, Yemisi Ologun, Liza G Ovington, Marrissa Martyn-St James, Rachel Richardson

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Abstract

Background

Venous leg ulcers are a type of chronic wound affecting up to 1% of adults in developed countries at some point during their lives. Many of these wounds are colonised by bacteria or show signs of clinical infection. The presence of infection may delay ulcer healing. Two main strategies are used to prevent and treat clinical infection in venous leg ulcers: systemic antibiotics and topical antibiotics or antiseptics.

Objectives

The objective of this review was to determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers.

Search methods

In May 2013, for this second update, we searched the Cochrane Wounds Group Specialised Register (searched 24 May 2013); the Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 4); Ovid MEDLINE (1948 to Week 3 May 2013); Ovid MEDLINE (In-Process & Other Non-indexed Citations, 22 May 2013); Ovid EMBASE (1980 to Week 20 2013); and EBSCO CINAHL (1982 to 17 May 2013). No language or publication date restrictions were applied.

Selection criteria

Randomised controlled trials (RCTs) recruiting people with venous leg ulceration, evaluating at least one systemic antibiotic, topical antibiotic or topical antiseptic that reported an objective assessment of wound healing (e.g. time to complete healing, frequency of complete healing, change in ulcer surface area) were eligible for inclusion. Selection decisions were made by two review authors while working independently.

Data collection and analysis

Information on the characteristics of participants, interventions and outcomes was recorded on a standardised data extraction form. In addition, aspects of trial methods were extracted, including randomisation, allocation concealment, blinding of participants and outcome assessors, incomplete outcome data and study group comparability at baseline. Data extraction and validity assessment were conducted by one review author and were checked by a second. Data were pooled when appropriate.

Main results

Forty-five RCTs reporting 53 comparisons and recruiting a total of 4486 participants were included, Many RCTs were small, and most were at high or unclear risk of bias. Ulcer infection status at baseline and duration of follow-up varied across RCTs. Five RCTs reported eight comparisons of systemic antibiotics, and the remainder evaluated topical preparations: cadexomer iodine (11 RCTs reporting 12 comparisons); povidone-iodine (six RCTs reporting seven comparisons); peroxide-based preparations (four RCTs reporting four comparisons); honey-based preparations (two RCTs reporting two comparisons); silver-based preparations (12 RCTs reporting 13 comparisons); other topical antibiotics (three RCTs reporting five comparisons); and other topical antiseptics (two RCTs reporting two comparisons). Few RCTs provided a reliable estimate of time to healing; most reported the proportion of participants with complete healing during the trial period.

Systemic antibiotics

More participants were healed when they were prescribed levamisole (normally used to treat roundworm infection) compared with placebo: risk ratio (RR) 1.31 (95% CI 1.06 to 1.62). No between-group differences were detected in terms of complete healing for other comparisons: antibiotics given according to antibiogram versus usual care; ciprofloxacin versus standard care/placebo; trimethoprim versus placebo; ciprofloxacin versus trimethoprim; and amoxicillin versus topical povidone-iodine.

Topical antibiotics and antiseptics

Cadexomer iodine: more participants were healed when given cadexomer iodine compared with standard care. The pooled estimate from four RCTs for complete healing at four to 12 weeks was RR 2.17 (95% CI 1.30 to 3.60). No between-group differences in complete healing were detected when cadexomer iodine was compared with the following: hydrocolloid dressing; paraffin gauze dressing; dextranomer; and silver-impregnated dressings.

Povidone iodine: no between-group differences in complete healing were detected when povidone-iodine was compared with the following: hydrocolloid; moist or foam dressings according to wound status; and growth factor. Time to healing estimates for povidone-iodine versus dextranomer, and for povidone-iodine versus hydrocolloid, were likely to be unreliable.

Peroxide-based preparations: four RCTs reported findings in favour of peroxide-based preparations when compared with usual care for surrogate healing outcomes (change in ulcer area). There was no report of complete healing.

Honey-based preparations: no between-group difference in time to healing or complete healing was detected for honey-based products when compared with usual care.

Silver-based preparations: no between-group differences in complete healing were detected when 1% silver sulphadiazine ointment was compared with standard care/placebo and tripeptide copper complex; or when different brands of silver-impregnated dressings were compared; or when silver-impregnated dressings were compared with non-antimicrobial dressings.

Other topical antibiotics: data from one RCT suggested that more participants healed at four weeks when treated with an enzymatic cleanser (a non-antibiotic preparation) compared with a chloramphenicol-containing ointment (additional active ingredients also included in the ointment): RR 0.13 (95% CI 0.02 to 0.99). No between-group differences in complete healing were detected for framycetin sulphate ointment versus enzymatic cleanser; chloramphenicol ointment versus framycetin sulphate ointment; mupirocin ointment versus vehicle; and topical antibiotics given according to antibiogram versus an herbal ointment.

Other topical antiseptics: data from one RCT suggested that more participants receiving an antiseptic ointment (ethacridine lactate) had responsive ulcers (defined as > 20% reduction in area) at four weeks when compared with placebo: RR 1.45 (95% CI 1.21 to 1.73). Complete healing was not reported. No between-group difference was detected between chlorhexidine solution and usual care.

Authors' conclusions

At present, no evidence is available to support the routine use of systemic antibiotics in promoting healing of venous leg ulcers. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed. In terms of topical preparations, some evidence supports the use of cadexomer iodine. Current evidence does not support the routine use of honey- or silver-based products. Further good quality research is required before definitive conclusions can be drawn about the effectiveness of povidone-iodine, peroxide-based preparations, ethacridine

lactate, chloramphenicol, framycetin, mupirocin, ethacridine or chlorhexidine in healing venous leg ulceration. In light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not for bacterial colonisation.

Plain language summary

English

Antibiotics and antiseptics to help healing venous leg ulcers

Venous leg ulcers are a type of wound that can take a long time to heal. These ulcers can become infected, and this might cause further delay to healing. Two types of treatment are available to treat infection: systemic antibiotics (i.e. antibiotics taken by mouth or by injection) and topical preparations (i.e. treatments applied directly to the wound). Whether systemic or topical preparations are used, patients will also usually have a wound dressing and bandage over the wound. This review was undertaken to find out whether using antibiotics and antiseptics works better than usual care in healing venous leg ulcers, and if so, to find out which antibiotic and antiseptic preparations are better than others. In terms of topical preparations, some evidence is available to support the use of cadexomer iodine (a topical agent thought to have cleansing and antibacterial effects). Current evidence does not support the use of honey- or silver-based products. Further good quality research is required before definitive conclusions can be drawn about the effectiveness of antibiotic tablets and topical agents such as povidone-iodine, peroxide-based products and other topical antibiotics and antiseptics in healing venous leg ulceration.

Background

Description of the condition

Venous leg ulcers are a common and recurring type of chronic, or complex, wound. They are usually caused by venous insufficiency (impaired venous blood flow) brought about by venous hypertension (Doughty 2007). The duration of venous leg ulceration ranges from a matter of weeks to longer than 10 years, and in some people these wounds never heal (Moffatt 1995; Ruckley 1998; Vowden 2009a). Older patient age, longer wound duration and larger ulcer surface area have been reported as independent risk factors for delayed ulcer healing (Margolis 2004; Gohel 2005).

Reported prevalence rates for leg ulceration are variable. A systematic review of the epidemiological literature from developed countries reported prevalence rates for any aetiology of open lower limb ulceration ranging from 0.1% to 1.1% (cases validated) (Graham 2003). Another review of 11 venous leg ulceration prevalence studies conducted in Australia and Europe estimated point prevalence as 0.1% to 0.3% (Nelzen 2008). Surveys undertaken in the UK estimated prevalence of venous leg ulceration as 0.023% in Wandsworth, London (Moffatt 2004); 0.044% in Hull and East Yorkshire (Srinivasaiah 2007); and 0.039% in Bradford and Airedale (Vowden 2009a; Vowden 2009b). The lower estimates reported in the UK surveys relative to the worldwide literature might be explained by differences in disease

management or case definition, or both. We were unable to identify contemporary prevalence data for non-Western countries during the latest review update. The epidemiological data have consistently suggested that prevalence increases with age and is higher among women (Margolis 2002; Graham 2003; Lorimer 2003a; Moffatt 2004; Vowden 2009a).

Diagnosis of venous leg ulceration can be made according to the appearance and location of the ulcer. Clinical practice guidelines recommend the use of clinical history, physical examination, laboratory tests and haemodynamic assessment (RCN 2006; SIGN 2010). The latter often includes an assessment of arterial blood supply to the leg using the ankle-brachial pressure index (ABPI), measured by using a hand-held Doppler ultrasound device. An ABPI measurement greater than 0.8 is generally used to rule out the co-existence of clinically significant peripheral arterial disease in a leg ulcer that has been diagnosed as due to venous insufficiency (Moffatt 2007).

Leg ulcers are associated with considerable cost to patients and to healthcare providers. Two systematic reviews summarised the literature on health-related quality of life in patients with leg ulcers (Persoon 2004; Herber 2007). Both included qualitative and quantitative evaluations and reported that the presence of leg ulceration was associated with pain, restriction of work and leisure activities, impaired mobility, sleep disturbance, reduced psychological well-being and social isolation.

The cost of treating an unhealed leg ulcer in the UK has been estimated to be around GBP 1300 per year at 2001 prices (Iglesias 2004). Another evaluation estimated the average cost of treating a venous leg ulcer in the UK (based on costs for material for dressing changes) as falling between EUR 814 and EUR 1994, and, in Sweden as lying between EUR 1332 and EUR 2585 (price year 2002), with higher costs associated with larger and more chronic wounds (Ragnarson Tennvall 2005). These data reflect findings from a more recent evaluation conducted in Germany, which estimated the total mean annual cost of illness for leg ulcers as EUR 9060 per patient (price year 2006), taking account of direct, indirect and intangible costs from a societal perspective. Estimates ranged from zero cost (i.e. no treatment) to EUR 44,462, with higher costs associated with arterial aetiology of the ulcer, larger wound size and no history of wound closure (Augustin 2012). In Bradford, in the UK, GBP 1.69 million was spent on dressings and compression bandages, and GBP 3.08 million on nursing time (estimates derived from resource use data for all wound types, not just venous leg ulcers) during the financial year 2006 to 2007 (Vowden 2009c). We were not able to identify further contemporary international cost data during the latest review update.

The burden of venous leg ulceration may be aggravated by the presence of wound infection. Moist, chronic skin ulcers are an ideal medium for bacterial growth, and a variety of micro-organisms can be cultured from these lesions. Findings from microbiological studies suggest that 80% to 100% of leg ulcers may be colonised with bacteria (Halbert 1992; Brook 1998; Harker 2001). The most common isolates include *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Alinovi 1986; Kontiainen 1988; Halbert 1992; Brook 1998; Harker 2001; Moore 2010).

As well as the risk factors already mentioned, it has been suggested that the presence of infection can delay ulcer healing (Doughty 2007). A recent study of 66 participants showed bacterial density to be associated with the probability of non-healing in venous leg ulcers when infection was detected using swabs or tissue biopsies (Davies 2007). Findings from

earlier studies are mostly supportive of the notion of a positive correlation between bacterial load and delayed healing (Halbert 1992; Hansson 1995; Madsen 1996; Trengove 1996). It has been suggested that chronic wound healing may be influenced not only by bacterial density but also by the diversity of micro-organisms present and their interactions with one another (Trengove 1996; Bowler 2003; Davies 2007). In addition, delayed healing may be associated with the presence of certain bacterial strains such as *Pseudomonas aeruginosa, Staphylococcus aureus* and haemolytic streptococci (Madsen 1996). However, other research indicates that healing is not influenced by increasing diversity of organisms or the presence of particular species (Moore 2010).

The terms 'contamination', 'colonisation', and 'infection' are used frequently in the wound care literature. The term `contamination' describes wounds with non-replicating organisms on their surface (Dow 1999). 'Colonisation' occurs when bacteria capable of replicating on the ulcer surface inhabit non-viable tissue in the wound in the absence of host immune response (Ayton 1985; Dow 1999). The classic signs of infection include local pain, heat, redness, swelling and purulence; however, it has been suggested that these may not always manifest in patients with venous leg ulcers. In light of this, signs and symptoms of critical colonisation have been proposed as an alternative guide for assessing infection and indicating antimicrobial treatment in chronic wounds. They include: delayed healing; unexpected pain; abnormal odour; pocketing at the base of the wound; discoloured (i.e. unusually dark) granulation tissue; friable granulation tissue; and devitalised (sloughy or necrotic) tissue (Gardner 2001; Cutting 2004). Prescribing guidelines suggest that dressings impregnated with antibacterial agents should be used only to treat clinically infected wounds, not for bacterial colonisation (BNF 2013).

Description of the intervention

Compression therapy (bandages or stockings) is now considered to be the cornerstone of venous leg ulcer management (Moffatt 2007; O'Meara 2012). Primary wound contact dressings (i.e. dressings in direct contact with the wound bed) are usually applied underneath compression devices. A range of other interventions may be used concurrently with compression, including debriding agents (Davies 2005; Cardinal 2009), vasoactive drugs (Robson 2006), fibrinolytic therapy (Robson 2006), physical therapies (Flemming 1999; Cullum 2010; Aziz 2013), and topical applications (Robson 2006). When ulcer infection is suspected, antimicrobial therapy may also be considered.

Two main strategies are used to manage clinical infection in venous leg ulcers: systemic antibiotics; and topical antibiotics and antiseptics.

Antibiotics are substances that destroy or inhibit the growth of micro-organisms (Macpherson 2004). Systemic antibiotics include groups of drugs such as penicillins (e.g. amoxicillin), cephalosporins (e.g. cephalexin), aminoglycosides (e.g. gentamicin, amikacin), macrolides (e.g. erythromycin) and quinolones (e.g. ciprofloxacin). Other drugs include clindamycin, metronidazole, trimethoprim and co-trimoxazole. Most systemic antibiotics work by interfering with aspects of bacterial cell function, for example, by impeding bacterial cell wall synthesis in the case of penicillins and cephalosporins. Clindamycin is associated with antibiotic-induced colitis, a rare but serious adverse event; prescription should be withdrawn immediately in any patient who develops diarrhoea (BNF 2013).

Topical antimicrobial agents include antibiotics and antiseptics. Antiseptics are thought to prevent the growth of pathogenic micro-organisms without damaging living tissue (Macpherson 2004). Topical preparations may be divided into two categories, according to their function. One group consists of lotions with antimicrobial properties that are used to irrigate or cleanse wounds. These usually have only a brief contact time with the wound surface, unless they are used as a pack or a soak. They include products based on chlorhexidine, povidone-iodine, hydrogen peroxide and potassium permanganate (BNF 2013). Benzoyl peroxide, normally used as gels and creams to treat acne (BNF 2013), has been used in a lotion formulation to treat leg ulcers (Beitner 1985a; Beitner 1985b). Traditional preparations such as the hypochlorites (e.g. Eusol) and gentian violet are currently less favoured but may still be used in some settings (White 2001; Farid 2011).

The second group of topical agents consists of products designed to stay in contact with the wound surface for a longer period of time, ideally until the next dressing change. These include creams, ointments and impregnated dressings. Most topical antibiotics come into this category and include mupirocin and fusidic acid (both available as 2% cream and 2% ointment), and neomycin sulphate (available as 0.5% cream). If large areas of skin are treated with the latter, ototoxicity (damage to the inner ear) is a possible adverse effect. Other products in this group include those based on the peroxides, iodine, silver and honey. Hydrogen peroxide preparations are available as a 1% cream. Iodine-based applications release free iodine (an antiseptic) when in contact with wound exudate. Povidone-iodine is available in a powder spray formulation in concentrations up to 2.5%, and also as 10% ointment and impregnated dressings. Cadexomer iodine products are purported to have the additional effect of absorbing wound exudate and promoting debridement; these are available as ointment, powder, paste (all at 0.9% concentration) or microbeads, or integrated into a hydrogel dressing. Recent years have seen a resurgence of interest in silver- and honey-based preparations for management of leg ulcers. Silver-based products include silver sulphadiazine cream (1%), as well as a variety of coated or impregnated dressings (BNF 2013). These release silver ions (atoms that have an electrical charge) on contact with wound exudate; this is thought to inhibit bacterial replication. It is suggested that silver products have a broad-spectrum antimicrobial action, and that they are associated less frequently with drug resistance relative to other antibiotics (Lansdown 2002; Lo 2009; Siah 2011). Medical grade honey is thought to have antimicrobial and debriding properties. Products are available as sheet dressings or as topical applications. Topical applications are applied directly to the wound and are covered with a primary low-adherent wound dressing; an additional secondary dressing may be required for exuding wounds. Prescribing guidelines recommend that patients with diabetes should be monitored for changes in blood glucose levels during treatment with honey-based wound products (BNF 2013).

Why it is important to do this review

Whether systemic antibiotics, topical antibiotics or topical antiseptics can promote healing in venous leg ulcers remains uncertain. An earlier systematic review of antimicrobial agents used with a range of chronic wounds was not able to generate definitive conclusions about the use of systemic or topical agents in venous leg ulcers because of methodological problems in the primary literature (O'Meara 2001). Since the time of the first review, additional relevant trials have been published in relation to venous leg ulcers, and so an

updated body of evidence has become available. In addition, the scope of the review has been extended for this update to include trials of silver- and honey-based products. Although this leads to a small amount of overlap with other reviews (Vermeulen 2007; Jull 2013), it was deemed useful for clinical decision making to include within a single review all relevant evaluations of antibiotic and antiseptic preparations for management of venous leg ulcers. Pertinent questions for clinical practice include whether antibiotics and antiseptics increase healing rates compared with standard care, whether different active agents are more or less effective when compared directly, and whether any differences in outcomes have been reported in relation to the use of systemic and topical agents.

Objectives

The objective of this review was to determine the effects of systemic antibiotics and topical antibiotics and antiseptics on the healing of venous ulcers.

Methods

Criteria for considering studies for this review

Types of studies

We included prospective randomised controlled trials (RCTs), published or unpublished, evaluating systemic or topical antibiotics or topical antiseptics in the treatment of venous ulcers, irrespective of the language of the report. RCTs reported in abstract form only were eligible for inclusion, provided adequate information was presented in the abstract or was available from the trial authors. Studies using quasi-randomisation were excluded.

Types of participants

RCTs recruiting people described in the primary report as having venous leg ulcers, managed in any care setting, were eligible for inclusion. As the method of diagnosis of venous ulceration may vary, we accepted definitions as used in the RCTs. We included RCTs that recruited people with various types of wounds (e.g. arterial ulcers, diabetic foot ulcers) if the results for participants with venous ulcers were presented separately, or if most participants (at least 75%) had leg ulcers of venous aetiology (origin). Selection of trials was not restricted to those with a certain wound status at baseline (i.e. those with colonised or infected wounds); when information about these variables was given, it was recorded (see Data extraction and management).

Types of interventions

Interventions of interest included antibiotics (topical or systemic) and antiseptics (topical) as prescribed for venous leg ulceration. Systemic antibiotics could be given orally or by other routes (e.g. intravenously). Control regimens could include placebo, an alternative antibiotic or antiseptic, any other therapy, standard care or no treatment. Both intervention and control regimens could consist of antibiotics and antiseptics administered singly or in combination. Intervention schedules that included concurrent therapies (e.g. compression)

were included provided that such treatment was delivered in a standardised way across study arms. Interventions could be delivered in any setting (inpatient, outpatient, nursing home plus any others). The following were excluded: RCTs in which the presence or absence of a specific antibiotic or antiseptic intervention was not the only systematic difference between treatment groups; evaluations of antibiotics or antiseptics used as preparations for skin grafting to treat leg ulceration; and evaluations of physical therapies with purported antimicrobial effects.

Types of outcome measures

Primary outcomes

The primary outcome for the review was wound healing. Wound healing is measured and reported by trialists in many different ways, including time to complete healing, proportion of wounds healed during follow-up, change in wound size, and rate of change in wound size. For this review, we regarded RCTs that reported one or more of the following as providing the best measures of outcome in terms of relevance and rigour.

- Time to complete wound healing (correctly analysed using survival, time-to-event approaches, ideally with adjustment for relevant covariates such as baseline ulcer area and duration).
- Proportion of ulcers healing during follow-up (frequency of complete healing).
- Change (or rate of change) in wound size, with adjustment for baseline size.

The following were considered as less rigorous assessments of these outcomes: mean or median time to healing without survival analysis (i.e. treating time to healing as a continuous measure without censoring); and surrogate outcomes for complete healing such as change in wound size, or rate of change in wound size, without adjustment for baseline size. When RCTs reported a surrogate outcome of healing, in addition to complete healing or a reliable estimate of time to healing, or both, we included in the review only estimates of complete healing and time to healing, unless surrogate outcomes were adjusted for baseline values.

Secondary outcomes

When reported, the following outcomes were also recorded.

- Changes in signs and/or symptoms of clinical infection.
- Changes in bacterial flora.
- Development of bacterial resistance.
- Ulcer recurrence rates.
- All reported adverse events.
- Participant satisfaction.
- Health-related quality of life (measured using a validated, standardised, generic measure of health status such as EQ-5D, Short Form (SF)-36, SF-12 or SF-6, or a

validated disease-specific questionnaire), preferably with follow-up estimates adjusted for baseline scores.

- Costs (including cost-effectiveness estimations).

Studies were eligible for inclusion only if they reported a primary outcome.

Search methods for identification of studies

The search methods sections of previous versions of this review can be found in Appendix 1.

Electronic searches

In May 2013, for this second update, we searched the following electronic databases to identify all relevant RCTs, with no restrictions applied in relation to language, date of publication or publication status.

- The Cochrane Wounds Group Specialised Register (searched 24 May 2013).
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 4).
- Ovid MEDLINE (1948 to Week 3 May 2013).
- Ovid MEDLINE (In-Process & Other Non-indexed Citations 22 May 2013).
- Ovid EMBASE (1980 to Week 20 2013).
- EBSCO CINAHL (1982 to 17 May 2013).

The following search string was used with CENTRAL:
#1 MeSH descriptor: [Anti-Infective Agents] explode all trees 21301
#2 MeSH descriptor: [Penicillins] explode all trees 4495
#3 MeSH descriptor: [Cephalosporins] explode all trees 3644
#4 MeSH descriptor: [Aminoglycosides] explode all trees 6396
#5 MeSH descriptor: [Quinolones] explode all trees 2917
#6 MeSH descriptor: [Clindamycin] explode all trees 634
#7 MeSH descriptor: [Metronidazole] explode all trees 1621
#8 MeSH descriptor: [Trimethoprim] explode all trees 1064
#9 MeSH descriptor: [Mupirocin] explode all trees 135
#10 MeSH descriptor: [Neomycin] explode all trees 408
#11 MeSH descriptor: [Fusidic Acid] explode all trees 85
#12 MeSH descriptor: [Framycetin] explode all trees 31
#13 MeSH descriptor: [Polymyxins] explode all trees 275
#14 MeSH descriptor: [Chlortetracycline] explode all trees 15
#15 (antibiotic* or antimicrobial* or antibacterial* or penicillin* or cephalosporin* or aminoglycoside* or quinolone* or clindamycin or metronidazole or trimethoprim or mupirocin or "pseudomonic acid" or neomycin or "fusidic acid" or framycetin or polymyxin* or chlortetracycline):ti,ab,kw 23307
#16 MeSH descriptor: [Antisepsis] explode all trees 91

#17 antiseptic*:ti,ab,kw 620
#18 MeSH descriptor: [Soaps] explode all trees 165
#19 MeSH descriptor: [Iodophors] explode all trees 411
#20 MeSH descriptor: [Chlorhexidine] explode all trees 1231
#21 MeSH descriptor: [Alcohols] explode all trees 28387
#22 MeSH descriptor: [Hydrogen Peroxide] explode all trees 368
#23 MeSH descriptor: [Benzoyl Peroxide] explode all trees 127
#24 MeSH descriptor: [Gentian Violet] explode all trees 31
#25 MeSH descriptor: [Hypochlorous Acid] explode all trees 274
#26 MeSH descriptor: [Hexachlorophene] explode all trees 28
#27 MeSH descriptor: [Potassium Permanganate] explode all trees 5
#28 MeSH descriptor: [Silver] explode all trees 154
#29 MeSH descriptor: [Silver Sulfadiazine] explode all trees 133
#30 MeSH descriptor: [Honey] explode all trees 81
#31 ("soap" or "soaps" or iodophor* or povidone or iodine or chlorhexidine or betadine or "alcohol" or disinfectant* or "hydrogen peroxide" or "benzoyl peroxide" or "gentian violet" or hypochlorit* or eusol or dakin* or hexachlorophene or benzalkonium or "potassium permanganate" or "silver sulfadiazine" or "silver sulphadiazine" or honey*):ti,ab,kw 15156
#32 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 80773
#33 MeSH descriptor: [Leg Ulcer] explode all trees 1076
#34 ((varicose next ulcer*) or (venous next ulcer*) or (leg next ulcer*) or (foot next ulcer*) or (stasis next ulcer*) or (crural next ulcer*) or "ulcus cruris"):ti,ab,kw 1967
#35 #33 or #34 2136
#36 #32 and #35 262

The search strategies used for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2, Appendix 3 and Appendix 4, respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision), Ovid format (**Lefebvre 2011**). The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (**SIGN 2013**).

Searching other resources

For both the original review and all subsequent updates, we attempted to contact trialists to obtain unpublished data and information as required, and we searched the reference lists of included RCTs and relevant review articles.

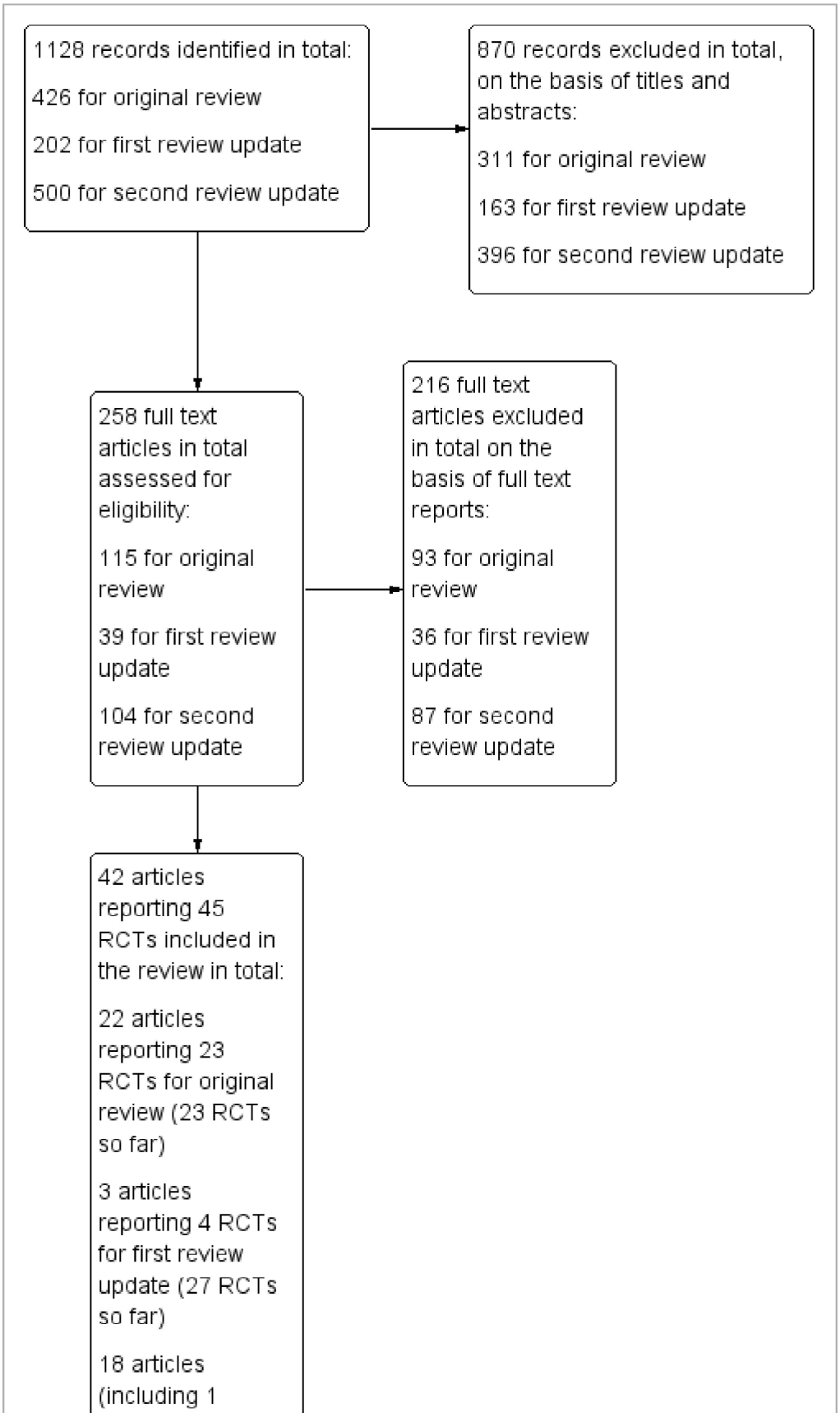
Data collection and analysis

Selection of studies

For the original review and all subsequent updates, at least two review authors independently assessed titles and abstracts for relevance. Full reports of articles were obtained if any review author considered a reference to be potentially relevant. Two review

authors then independently checked the full papers for eligibility, with disagreements resolved by discussion. All reasons for exclusion were recorded.

We have presented the study selection process as a flow diagram, according to recommendations provided in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (**Liberati 2009**) (see Figure 1 and Results of the search).



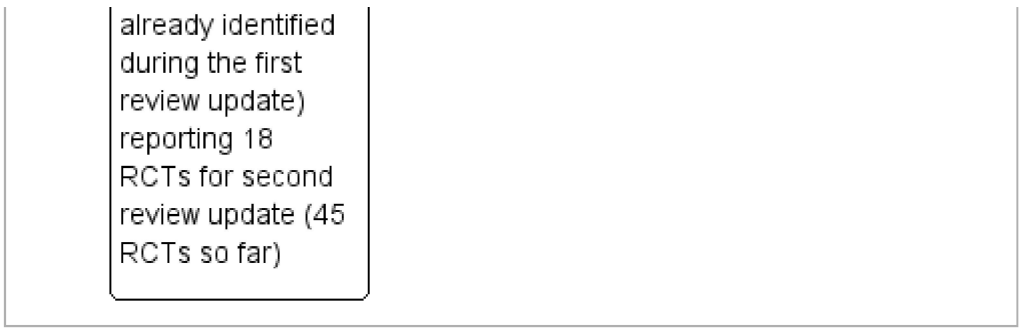


Figure 1.

Open in figure viewer

Study flow diagram.

Data extraction and management

Details of each included RCT were extracted and summarised using a standardised data extraction sheet. If data were missing from reports, trial authors were contacted and were asked to provide missing information. Data from evaluations with multiple associated publications were extracted while ensuring that all relevant data from all reports were included, whilst avoiding duplication. Data were extracted by one review author and were independently checked for accuracy by a second review author. Disagreements about data were resolved by discussion. The following data were extracted.

- Trial authors.
- Year of publication.
- Country where RCT performed.
- Setting of care.
- Trial design details (e.g. pragmatic, pilot).
- Unit of investigation (participant, limb or wound).
- Overall sample size and methods used to estimate statistical power (relates to the target number of participants to be recruited, the clinical difference to be detected and the ability of the RCT to detect this difference).
- Participant selection criteria.
- Number of participants randomly assigned to each treatment group.
- Baseline characteristics of participants per treatment group (gender, age, ulcer area, ulcer duration, prevalence of co-morbidities such as diabetes, prevalence of clinically infected or colonised wounds, identity of micro-organisms isolated).
- Details of interventions applied in each group, including specific antibiotics and antiseptics used, as well as concurrent therapies such as compression.
- Duration of treatment.

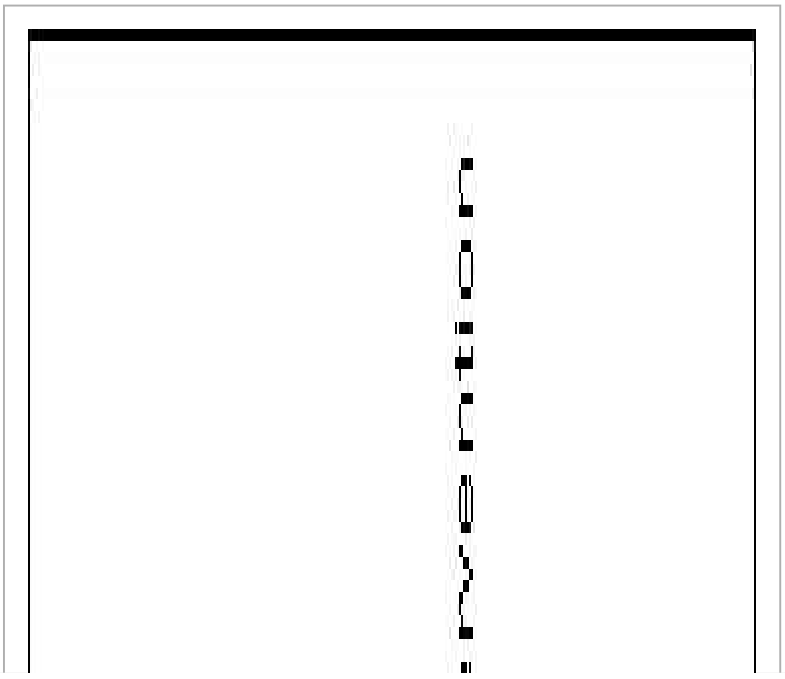
- Duration of follow-up.
- Outcomes measured, including assessment methods.
- Outcome data by treatment group.
- Withdrawals per treatment group with numbers and reasons.

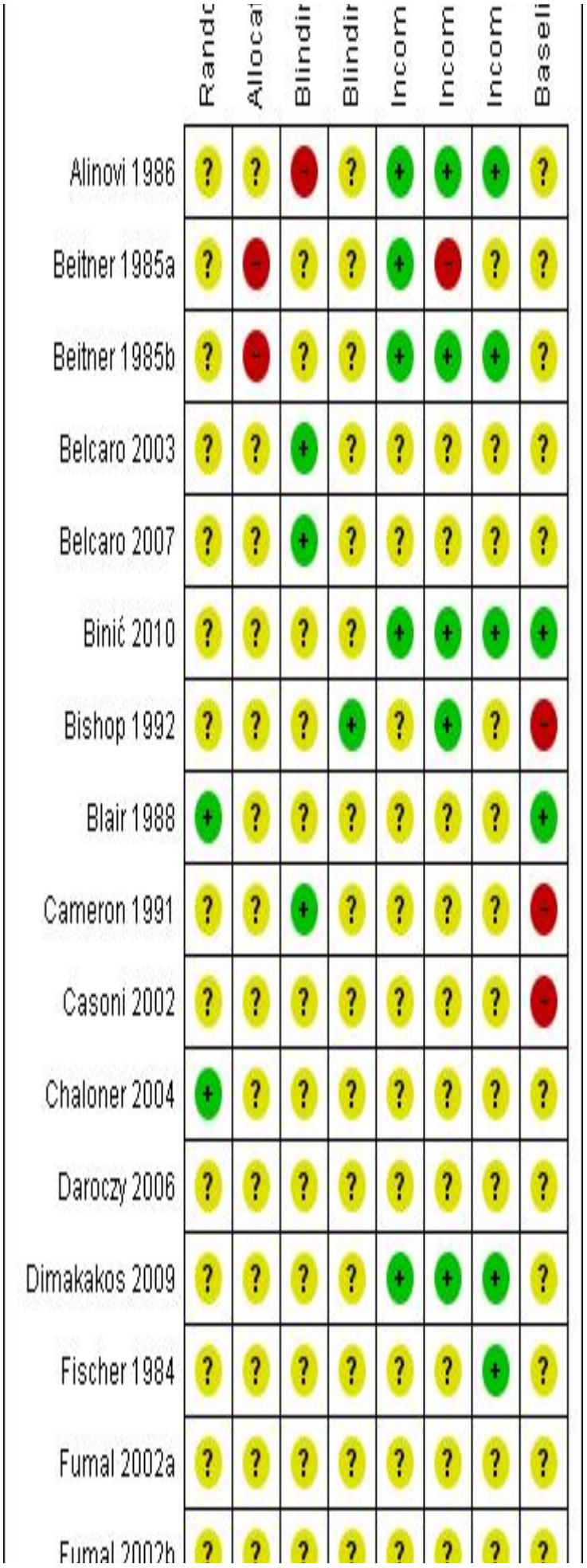
Assessment of risk of bias in included studies

We assessed each included RCT using The Cochrane Collaboration's tool for assessing risk of bias (**Higgins 2011a**). This tool includes the following domains: sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, incomplete outcome data and other sources of bias, which for this review was baseline comparability (see Appendix 5 for details of the criteria on which judgements were based). Previous versions of this review have summarised information about individual domains of risk of bias. For this update, each included RCT was additionally assigned an overall risk of bias rating using the following decision rules. RCTs were classified as being at overall high risk of bias if they were rated as having high risk in relation to at least any one of three key domains (allocation concealment, blinding of outcome assessors and completeness of outcome data - use of intention-to-treat analysis). If none of the key domains was rated as high risk, but one or more were rated as having an unclear risk of bias, the RCT was rated overall as having an unclear risk of bias. To attain an overall low risk of bias, all three key domains had to be rated as low risk individually.

Risk of bias data were extracted by one review author and were independently checked for accuracy by a second review author. Disagreements about ratings were resolved by discussion.

Details of the risk of bias assessment for each included RCT were tabulated (see Characteristics of included studies). In addition, Figure 2 shows a cross-tabulation of each individual RCT with each individual risk of bias domain, and Figure 3 shows a summary of information across all included RCTs.

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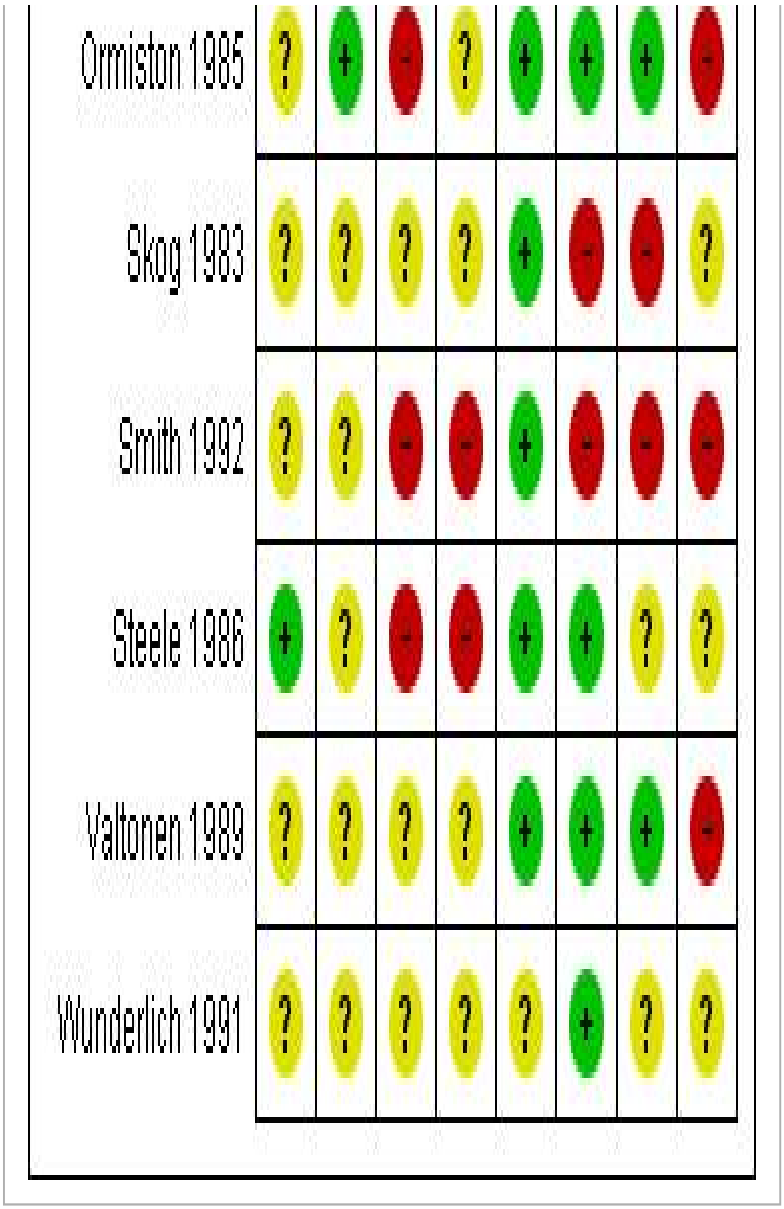

Figure 2.

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Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

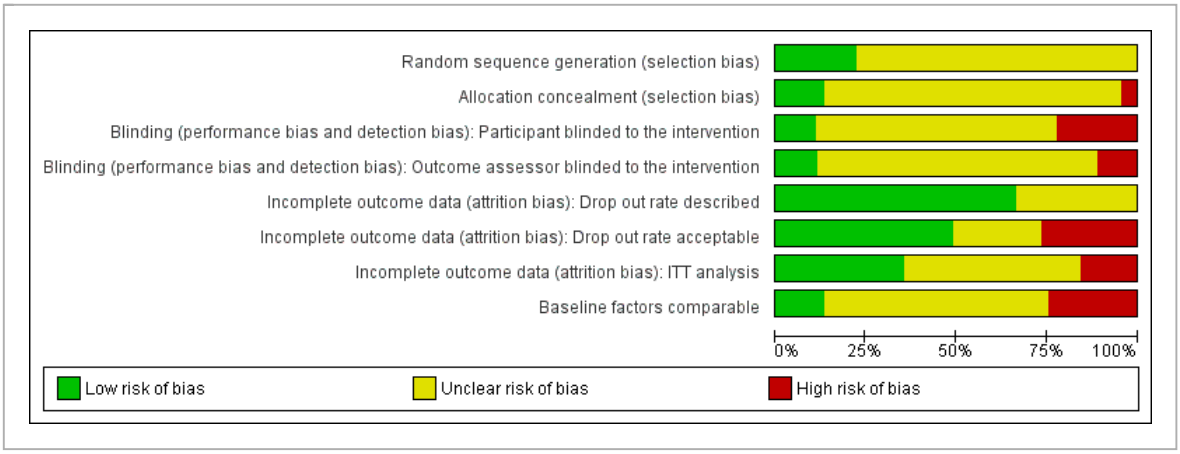

Figure 3.

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Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Measures of treatment effect

We generated estimates for dichotomous outcomes (e.g. number of ulcers healed) as risk ratios (RRs) with associated 95% confidence interval (CIs). We generated estimates for continuous data outcomes (e.g. absolute or relative change in ulcer area) as a difference in means with 95% CI. We planned to report estimates of time to healing and to plot hazard ratio (HR) estimates with 95% CI when available from trial reports. When HRs were not reported, we planned, where possible, to extrapolate HRs using other available data related to time to healing (Parmar 1998).

Unit of analysis issues

We recorded whether RCT reports specified participants, limbs or ulcers as the units of allocation and analysis. In cases where multiple limbs or ulcers of the same individual were studied, we planned to note whether the trialists' analysis was appropriate (i.e. correctly taking account of highly correlated data) or inappropriate (i.e. considering outcomes for multiple ulcers on the same participant as independent). When the number of wounds appeared to equal the number of participants, we assumed that the participant was the unit of analysis, unless otherwise stated.

Dealing with missing data

Missing data are a common problem in RCTs. Excluding randomised participants from the analysis or ignoring those participants lost to follow-up can compromise the process of randomisation and introduce bias. When RCTs reported dichotomous complete healing outcomes for only those participants who completed the RCT (i.e. participants withdrawing and lost to follow-up were excluded from the analysis), we treated the participants who were not included in the analysis as if their wound did not heal (i.e. they were included in the denominator but not in the numerator for healing outcomes). When results were reported

for participants who completed the RCT without specifying the numbers randomly assigned per group initially, we presented only complete case data. For other outcomes, we presented data for all participants randomly assigned, when reported; otherwise we based estimates on complete cases only.

Assessment of heterogeneity

We considered clinical heterogeneity (i.e. the degree to which RCTs appear similar in terms of participants, intervention type and duration and outcome type) and statistical heterogeneity. We assessed statistical heterogeneity using the Chi^2 test (P value less than 0.10 was considered to indicate statistically significant heterogeneity) in conjunction with the I^2 statistic. The I^2 statistic examines the percentage of total variation across RCTs due to heterogeneity rather than chance (Higgins 2002; Higgins 2003). We considered that I^2 values of 40% or less indicated a low level of heterogeneity and values of 75% or higher represented very high heterogeneity (Deeks 2011).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Publication bias is one of a number of possible causes of 'small-study effects' - the tendency for estimates of the intervention effect to be more beneficial in smaller trials. Funnel plots allow a visual assessment of whether small-study effects may be present in a meta-analysis. A funnel plot is a simple scatter plot of the intervention effect estimates from individual RCTs against some measure of each trial's size or precision (Sterne 2011). We planned to present funnel plots for meta-analyses comprising 10 RCTs or more using RevMan 5.2 (RevMan 2012).

Data synthesis

A narrative synthesis of all included RCTs was presented, with results grouped according to intervention characteristics. With the use of RevMan 5.2, statistical pooling was undertaken on groups of studies considered to be sufficiently similar in terms of study design and characteristics of participants, interventions and outcomes. The decision to pool data in a meta-analysis depended upon the availability of outcome data and the assessment of between-trial heterogeneity. For comparisons in which no apparent clinical heterogeneity was noted and the I^2 value was 40% or less, we applied a fixed-effect model. When no clinical heterogeneity was apparent and the I^2 value was greater than 40%, we planned to apply a random-effects model. However, we planned to refrain from pooling data when heterogeneity was very high (I^2 values of 75% or greater) (Deeks 2011).

For dichotomous outcomes, we have presented the summary estimate as an RR with 95% confidence intervals (CIs). When continuous outcomes were measured in the same way across RCTs, we have presented a difference in means with 95% CI. We planned to present a standardised mean difference (SMD) when RCTs measured the same outcome using different methods. For time-to-event data, we planned to plot (and if appropriate pool) estimates of HRs and 95% CIs as they were presented in the RCT reports using the generic inverse variance method provided in RevMan 5.2.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was investigated as described above. We planned to conduct subgroup analyses according to differences in the following variables: mean baseline ulcer area; presence of signs and/or symptoms of clinical infection at baseline; presence of wound colonisation at baseline; and, in the case of RCTs using compression, the number of components used (i.e. single component versus multiple components) and the level of compression (i.e. high versus moderate/low compression) (**O'Meara 2012**).

Results

Description of studies

Results of the search

For the original review, the search strategy generated 426 records. Of these, 115 appeared to be of possible relevance and were retrieved as full-text articles. After detailed screening with reference to the study selection criteria, 22 articles were included. One article reported two separate RCTs relevant to the review (**Beitner 1985a**; **Beitner 1985b**); therefore 23 RCTs were included.

For the first review update, the search strategy produced 202 records, of which 39 were retrieved as full-text articles. After screening, three articles were included; one article reported two separate, relevant RCTs (**Fumal 2002a**; **Fumal 2002c**), bringing the then total number of included RCTs to 27.

For the current update, 500 records were generated from the search strategy of which 104 were retrieved as full-text articles. After screening, 17 new articles were included, all reporting a single RCT. An additional new RCT was identified from a previously included paper reporting three separate trials; the trial evaluating silver became eligible for this review update in light of the expanded scope of the review (**Fumal 2002b**). Therefore, 18 new RCTs were identified during this update, bringing the current total number of included trials to 45.

In the first review update, two studies were classified as awaiting assessment: One of these has now been excluded because it is not an RCT (**Cherry 2003**), whilst the other is now listed as a secondary reference to a newly included RCT (**Miller 2010**). No studies are currently awaiting assessment, and none have been classified as ongoing.

In accordance with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (**Higgins 2011b**), some studies excluded at the full report assessment stage have been listed, together with reasons for exclusion (N = 78; see Characteristics of excluded studies). The study selection process for the original review and for both review updates is shown in Figure 1.

Included studies

Overall, 45 RCTs reporting 53 relevant comparisons and recruiting 4486 participants are included in the review. The scope of the review was expanded for this update to include trials of silver and honey products. This meant searching databases from inception to retrieve relevant trials on the new interventions, which generated a substantial review update that

included 18 new RCTs (Fischer 1984; Blair 1988; Wunderlich 1991; Bishop 1992; Fumal 2002b; Chaloner 2004; Jørgensen 2005; Meaume 2005; Münter 2006; Gethin 2008; Jull 2008; Lazareth 2008; Dimakakos 2009; Kuznetsov 2009; Michaels 2009; Binić 2010; Kerihuel 2010; Miller 2010).

Six RCTs included three study arms each, reporting 18 comparisons in total, of which 14 were relevant to the review (Fischer 1984; Bishop 1992; Huovinen 1994; Hansson 1998; Casoni 2002; Daroczy 2006). The other included evaluations reported a single RCT involving a single comparison.

The following sections further describe the RCTs and group them according to intervention characteristics. Further details of each included RCT are shown in the table of Characteristics of included studies.

Systemic antibiotics

Five RCTs recruiting 233 participants to eight relevant comparisons of oral systemic antibiotics were identified (Morias 1979; Alinovi 1986; Valtonen 1989; Huovinen 1994; Daroczy 2006). No new RCTs were identified during this review update. Two trials were conducted in Finland (Valtonen 1989; Huovinen 1994), one in Italy (Alinovi 1986), one in Hungary (Daroczy 2006) and one in Belgium (Morias 1979). None was described as multi-centre. The number of participants allocated per arm ranged between 8 and 30; Morias 1979 was the largest trial, recruiting a total of 59 participants. Morias 1979 and Valtonen 1989 recruited people with leg ulcers of different aetiologies; most were of venous origin. The duration of follow-up ranged between 20 days and 20 weeks, with 3 of the 5 trials following participants up for 12 weeks or longer (Huovinen 1994; Morias 1979; Valtonen 1989).

Cadexomer iodine topical preparations

Cadexomer iodine is a topical agent with debriding and antibacterial effects; it was evaluated in 11 RCTs that recruited 962 participants to 12 relevant comparisons (Skog 1983; Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Laudanska 1988; Holloway 1989; Hansson 1998; Miller 2010); one RCT was newly included in this update (Miller 2010). Four were multi-centre trials (Skog 1983; Lindsay 1986; Hansson 1998; Miller 2010). Five trials were based in the United Kingdom (Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Moss 1987), two in Sweden and Norway (Skog 1983; Hansson 1998), and one each in Finland (Kero 1987), Poland (Laudanska 1988), the USA (Holloway 1989), and Australia (Miller 2010). The number of people allocated to each arm of these RCTs ranged between 10 and 141; Miller 2010 was the largest study, with 281 participants recruited overall. The duration of follow-up ranged from four weeks to 24 weeks. Most studies followed up participants for a maximum of eight weeks (Skog 1983; Harcup 1986; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Laudanska 1988).

Povidone-iodine topical preparations

Six trials recruiting 639 participants to seven relevant comparisons evaluated povidone-iodine preparations (Groenewald 1981; Smith 1992; Ishibashi 1996; Casoni 2002; Fumal 2002a; Kuznetsov 2009); one RCT was newly included in this update (Kuznetsov 2009). Four were based in Europe: United Kingdom (Smith 1992); Germany (Groenewald 1981); Belgium (Fumal 2002a); and Italy (Casoni 2002). The remaining two evaluations were conducted in

Japan (Ishibashi 1996) and Russia (Kuznetsov 2009). The number of participants allocated per arm ranged between 15 and 109; the largest RCT recruited 218 participants overall (Ishibashi 1996). The duration of follow-up ranged from 21 days to four months.

Peroxide-based topical preparations

Four RCTs recruited 72 participants to four relevant comparisons that evaluated peroxide-based topical antiseptics (Beitner 1985a; Beitner 1985b; Belcaro 2003; Belcaro 2007). No new RCTs were identified during this review update. Two trials were based in Sweden (Beitner 1985a; Beitner 1985b), and two in Italy (Belcaro 2003; Belcaro 2007). The number of people in each arm ranged between seven and 18; the largest being Belcaro 2007 with 32 people. Duration of follow-up ranged between 10 and 42 days.

Honey-based topical preparations

Two multi-centre RCTs (two comparisons) recruiting 476 participants evaluated honey products; one was conducted in Ireland (Gethin 2008), and the other in New Zealand (Jull 2008). Both RCTs were added during this review update. Gethin 2008 reported that treatment duration was four weeks with 12-week follow-up. Treatment duration in the trial by Jull 2008 was 12 weeks.

Silver-based topical preparations

Twelve RCTs recruiting 1514 participants to 13 relevant comparisons evaluated silver-based topical preparations (Blair 1988; Wunderlich 1991; Bishop 1992; Fumal 2002b; Chaloner 2004; Jørgensen 2005; Meaume 2005; Münter 2006; Lazareth 2008; Dimakakos 2009; Michaels 2009; Kerihuel 2010). All were added during this review update. Three RCTs were conducted in the UK (Blair 1988; Chaloner 2004; Michaels 2009), and another three in France (Meaume 2005; Lazareth 2008; Kerihuel 2010). One was conducted in each of the following countries: Germany (Wunderlich 1991); Belgium (Fumal 2002b); Greece (Dimakakos 2009); and the USA (Bishop 1992). Two trials recruited internationally across Europe and the Americas (Jørgensen 2005; Münter 2006). Six RCTs were described as multi-centre (Bishop 1992; Jørgensen 2005; Meaume 2005; Münter 2006; Lazareth 2008; Michaels 2009). The number of participants per study arm ranged from 17 to 326; the largest was the international trial performed by Münter et al (Münter 2006), which recruited 619 participants overall. Two RCTs included participants with mixed aetiology leg ulcers (venous and arterial) (Jørgensen 2005; Münter 2006). Duration of follow-up ranged from four weeks to 12 months. An additional RCT (N = 281) compared a silver dressing with cadexomer iodine and has already been described above under 'Cadexomer iodine topical preparations' (Miller 2010).

Miscellaneous topical preparations

Five RCTs recruiting 590 participants to seven relevant comparisons were identified that did not easily fit into any of the groups described above (Fischer 1984; Cameron 1991; Binić 2010; Fumal 2002c; Geske 2005); two were newly included in this review update (Fischer 1984; Binić 2010). Three evaluated topical antibiotics (Fischer 1984; Cameron 1991; Binić 2010), and two assessed topical antiseptics (Fumal 2002c; Geske 2005). The RCTs were

conducted in the UK (Cameron 1991), Germany (Geske 2005), Belgium (Fumal 2002c) and Serbia (Binić 2010). The fifth trial was international, with study centres in Germany, Austria and Switzerland (Fischer 1984); this was the only RCT described as multi-centre. The number of participants per treatment arm ranged from 15 to 129; the largest trial recruited 258 participants overall (Fischer 1984). Inclusion of participants with mixed aetiology leg ulceration was not mentioned in any trial. Follow-up periods ranged from four to 24 weeks.

Risk of bias in included studies

Details of the risk of bias assessment for each included RCT are shown in the tables of Characteristics of included studies. A cross-tabulation of individual trial data with each risk of bias domain is shown in Figure 2. Figure 3 shows the overall information on risk of bias.

1. Adequacy of randomisation

Ten RCTs were judged as using a satisfactory method of sequence generation and were deemed to be at low risk of bias for this domain. Specific methods included random number tables (Blair 1988; Steele 1986), computerised randomisation (Chaloner 2004; Jørgensen 2005; Münter 2006; Michaels 2009; Miller 2010), and a remote, independent randomisation service (Gethin 2008; Jull 2008; Kerihuel 2010). The remaining 35 RCTs did not specify the method of randomisation and were classified as having an unclear risk of bias.

2. Adequacy of allocation concealment

Six RCTs reported the use of an adequate method of allocation concealment such as sequentially numbered, sealed, opaque envelopes (Ormiston 1985; Gethin 2008), sequentially numbered drug containers of identical appearance (Morias 1979) and a centralised, remote allocation service (Jull 2008; Michaels 2009; Kerihuel 2010); all were classified as low risk. Information from two RCTs suggested that the group allocation process could have been visible and so they were judged to be at high risk of bias (Beitner 1985a; Beitner 1985b). None of the other trials provided a clear description of allocation concealment and so were graded as 'unclear'.

3. Blinding of participants

Satisfactory methods of blinding participants to treatment allocation were described in five RCTs, leading them to be classified as having a low risk of bias for this domain (Morias 1979; Cameron 1991; Huovinen 1994; Belcaro 2003; Belcaro 2007). In all cases, the use of a placebo preparation identical to the active intervention was described; this method was used with systemic agents (Morias 1979; Huovinen 1994), and topical applications (Cameron 1991; Belcaro 2003; Belcaro 2007). Ten RCT reports provided information suggesting that participants were not blind to group allocation, with further details as follows: no attempt to use a placebo when this should have been feasible in an evaluation of systemic antibiotics (Alinovi 1986); participants involved in their own care (all cadexomer iodine trials) (Ormiston 1985; Harcup 1986; Lindsay 1986; Holloway 1989); and blinding stated as impossible because of differential characteristics between interventions and comparators (Steele 1986; Moss 1987; Smith 1992; Michaels 2009; Miller 2010). These ten RCTs were judged to be at

high risk of bias for blinding of participants. In the remaining 30 RCTs; it was not clear whether participants had been blinded to treatment allocation.

4. Blinding of outcome assessors

Five RCT reports indicated that outcome assessors had been blinded to treatment allocation, and they were accordingly awarded a low risk of bias for this domain (Bishop 1992; Jull 2008; Lazareth 2008; Michaels 2009; Kerihuel 2010). For four of these trials, a clear statement was made that the personnel evaluating outcomes had not been involved in care provision and were not aware of the treatment allocation (Bishop 1992; Lazareth 2008; Michaels 2009; Kerihuel 2010). The fifth trial did not use blinded outcome, assessment but the primary outcome (healing) was re-analysed using data from a blinded review of ulcer photographs, and this did not change the findings; we judged this to represent a low risk of bias (Jull 2008). Five RCTs were classified as having a high risk of bias for blinding of outcome assessors because of differential intervention characteristics between interventions and comparators (Steele 1986; Moss 1987; Smith 1992; Gethin 2008; Miller 2010). The remaining 35 trials did not include any information about blinding of outcome assessors, or the information provided was insufficient to allow a judgement to be made; they were therefore classified as having an unclear risk of bias.

5. Incomplete outcome data addressed (description of withdrawals)

Most trials (30/45, 67%) were deemed to be at low risk of bias for this criterion because they provided a report of numbers of participants withdrawing per treatment arm together with reasons, or a clear statement indicated that no participants withdrew (Morias 1979; Groenewald 1981; Skog 1983; Beitner 1985a; Beitner 1985b; Ormiston 1985; Alinovi 1986; Harcup 1986; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Holloway 1989; Valtonen 1989; Smith 1992; Huovinen 1994; Ishibashi 1996; Hansson 1998; Geske 2005; Jørgensen 2005; Meaume 2005; Münter 2006; Gethin 2008; Jull 2008; Lazareth 2008; Dimakakos 2009; Kuznetsov 2009; Michaels 2009; Binić 2010; Kerihuel 2010). All of the remaining 15 trials were classified as having an unclear risk of bias. Of these, one reported the number of withdrawals per group caused by ineffectiveness or allergy, but it was not clear whether other withdrawals had occurred (Fischer 1984). Another reported numbers withdrawing together with reasons, but only for the whole sample, and not per group (Laudanska 1988). A further three trials reported the numbers who withdrew per study arm but did not provide reasons (Wunderlich 1991; Bishop 1992; Miller 2010). The other ten RCTs did not mention withdrawals at all (Blair 1988; Cameron 1991; Casoni 2002; Fumal 2002a; Fumal 2002b; Fumal 2002c; Belcaro 2003; Chaloner 2004; Daroczy 2006; Belcaro 2007). No trial was considered to be at high risk of bias for this domain.

6. Incomplete outcome data addressed (withdrawal rate acceptable?)

Twenty-two RCTs were classified as being at low risk of bias for this criterion because either it was clear that no withdrawals occurred (Morias 1979; Beitner 1985b; Münter 2006; Dimakakos 2009; Kuznetsov 2009; Binić 2010), or the withdrawal rate was less than 20% in all treatment arms (Groenewald 1981; Ormiston 1985; Alinovi 1986; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Laudanska 1988; Valtonen 1989; Wunderlich 1991; Bishop 1992; Ishibashi 1996; Geske 2005; Jull 2008; Michaels 2009; Miller 2010).

Twelve RCTs were judged to be at high risk of bias because of differential withdrawal rates between treatment groups (Harcup 1986; Jørgensen 2005; Kerihuel 2010), or because the withdrawal rate exceeded 20% in at least one arm (Skog 1983; Beitner 1985a; Holloway 1989; Smith 1992; Huovinen 1994; Hansson 1998; Meaume 2005; Gethin 2008; Lazareth 2008).

Of the remaining 11 RCTs, ten did not provide any information on withdrawals (Blair 1988; Cameron 1991; Casoni 2002; Fumal 2002a; Fumal 2002b; Fumal 2002c; Belcaro 2003; Chaloner 2004; Daroczy 2006; Belcaro 2007), and one did not report full details (Fischer 1984); all of these trials were assigned an unclear risk of bias.

7. Incomplete outcome data addressed (use of intention-to-treat analysis)

Reports of 14 RCTs suggested that analysis had been conducted according to intention-to-treat, and so these RCTs were viewed as being at low risk of bias (Morias 1979; Fischer 1984; Beitner 1985b; Valtonen 1989; Meaume 2005; Münter 2006; Gethin 2008; Jull 2008; Lazareth 2008; Dimakakos 2009; Kuznetsov 2009; Michaels 2009; Binić 2010; Kerihuel 2010). A further two RCTs each excluded one participant from analysis; we considered that this would not have had an important influence on estimates of treatment effect (Alinovi 1986; Ormiston 1985). These two RCTs were rated as having low risk of bias for this domain.

Seven RCTs were classified as having high risk of bias because at least 20% of randomly assigned participants from one or more treatment groups were excluded from the analysis (Skog 1983; Holloway 1989; Hansson 1998; Jørgensen 2005), because participants were switched to an alternative treatment arm during the trial and were retained in this group for the analysis (Harcup 1986; Smith 1992), or because participants who withdrew were replaced to maintain the original numbers per group (unclear whether additional patients were randomly assigned) (Groenewald 1981).

The remaining 22 RCTs were judged as having an unclear risk of bias because it was not clear whether an intention-to-treat analysis had been conducted, or because it was clear that an intention-to-treat analysis had not been conducted, but it was difficult to judge the impact of lower rates of withdrawal (i.e. less than 20%) on estimates of treatment effect, particularly in smaller trials (Beitner 1985a; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Blair 1988; Laudanska 1988; Cameron 1991; Wunderlich 1991; Bishop 1992; Huovinen 1994; Ishibashi 1996; Casoni 2002; Fumal 2002a; Fumal 2002b; Fumal 2002c; Belcaro 2003; Chaloner 2004; Geske 2005; Daroczy 2006; Belcaro 2007; Miller 2010).

8. Comparability at baseline

Information available for six RCTs suggested that treatment groups were comparable at baseline, resulting in assignment of low risk of bias (Blair 1988; Jørgensen 2005; Gethin 2008; Jull 2008; Lazareth 2008; Binić 2010). Eleven RCTs appeared to have baseline imbalance between treatment groups for at least one predictive covariate and were graded as being at high risk of bias (Ormiston 1985; Kero 1987; Moss 1987; Holloway 1989; Valtonen 1989; Cameron 1991; Bishop 1992; Smith 1992; Huovinen 1994; Casoni 2002; Meaume 2005). The remaining 28 RCTs were classified as unclear risk of bias because information on baseline variables were lacking, or because mean rather than median values were provided for ulcer area and duration (Morias 1979; Groenewald 1981; Skog 1983;

Fischer 1984; Beitner 1985a; Beitner 1985b; Alinovi 1986; Harcup 1986; Lindsay 1986; Steele 1986; Laudanska 1988; Wunderlich 1991; Ishibashi 1996; Hansson 1998; Fumal 2002a; Fumal 2002b; Fumal 2002c; Belcaro 2003; Chaloner 2004; Geske 2005; Daroczy 2006; Münter 2006; Belcaro 2007; Dimakakos 2009; Kuznetsov 2009; Michaels 2009; Kerihuel 2010; Miller 2010).

9. Overall risk of bias

Three RCTs were classified as having a low risk of bias overall (Jull 2008; Michaels 2009; Kerihuel 2010). Thirteen RCTs were assigned a high risk of bias overall (Groenewald 1981; Skog 1983; Beitner 1985a; Beitner 1985b; Harcup 1986; Steele 1986; Moss 1987; Holloway 1989; Smith 1992; Hansson 1998; Jørgensen 2005; Gethin 2008; Miller 2010). The remaining 29 trials were judged as having an unclear risk of bias overall (Morias 1979; Fischer 1984; Ormiston 1985; Alinovi 1986; Lindsay 1986; Kero 1987; Blair 1988; Laudanska 1988; Valtonen 1989; Cameron 1991; Wunderlich 1991; Bishop 1992; Huovinen 1994; Ishibashi 1996; Casoni 2002; Fumal 2002a; Fumal 2002b; Fumal 2002c; Belcaro 2003; Chaloner 2004; Geske 2005; Meaume 2005; Daroczy 2006; Münter 2006; Belcaro 2007; Lazareth 2008; Dimakakos 2009; Kuznetsov 2009; Binić 2010).

Effects of interventions

Overall, 45 RCTs were included in this review. Results are presented according to the type of intervention, starting with systemic antibiotics. This is followed by topical preparations: cadexomer iodine, povidone-iodine, peroxides, honey, silver and miscellaneous agents (i.e. those not fitting easily into the other groups).

Systemic antibiotics

Five RCTs (eight comparisons) recruiting a total of 233 participants evaluated various types of systemic antibiotics (Morias 1979; Alinovi 1986; Valtonen 1989; Huovinen 1994; Daroczy 2006).

Systemic antibiotics given according to sensitivities compared with standard care

One RCT at unclear risk of bias overall was identified (Alinovi 1986). Alinovi 1986 compared standard care alone with a 10-day course of systemic antibiotics (co-trimoxazole, gentamicin or amikacin according to sensitivity) plus standard care. Forty-eight participants with 56 ulcers were recruited. Participants were initially treated as inpatients and were discharged the day after admission. The wounds were not infected at baseline. At 20 days, 7/26 (27%) ulcers had been healed with standard treatment alone compared with 5/30 (17%) in those additionally receiving antibiotics. The RR estimate indicated no difference between groups: RR 0.62 (95% CI 0.22 to 1.72) (Analysis 1.1). Similar proportions of participants between groups had healed when assessed at a later, unspecified, time point: RR 0.91 (95% CI 0.66 to 1.25) (Analysis 1.2). A discrepancy was noted between the unit of randomisation (participant) and the unit of analysis (ulcer), which can result in a biased estimate of treatment effect (Altman 1997). The proportion of participants with bacterial eradication was similar between groups: RR 1.60 (95% CI 0.61 to 4.19) (Analysis 1.3).

Ciprofloxacin compared with standard care/placebo

Two trials were identified, both of which had an unclear risk of bias overall (**Valtonen 1989**; **Huovinen 1994**). **Valtonen 1989** compared standard care alone with oral ciprofloxacin combined with standard care. Eligible participants had ulcers colonised by Gram-positive bacteria that were sensitive to ciprofloxacin, but it was not clear whether the wounds were clinically infected at baseline. Participants were treated in both inpatient and outpatient settings, with a treatment duration of three months. At the end of treatment, 3/18 (17%) ulcers in the ciprofloxacin-treated group had healed compared with 0/8 in the control group. The difference in the numbers of participants recruited to the treatment groups was not explained. **Huovinen 1994** conducted a three-arm trial to compare ciprofloxacin, trimethoprim and placebo. The interventions were delivered for 12 weeks in an outpatient setting. It was unclear whether the ulcers were infected at baseline. At 16 weeks, 3/11 (27%) ulcers had healed with placebo compared with 5/13 (38%) with ciprofloxacin. When these two trials were pooled, no difference was revealed between ciprofloxacin and standard care/placebo for complete healing at three to four months: RR 1.74 (95% CI 0.57 to 5.30) (Analysis 2.1). However, pooled data indicated that antibiotic-resistant strains emerged more frequently in the groups receiving ciprofloxacin: RR 8.65 (95% CI 1.76 to 42.60) (Analysis 2.2) (**Valtonen 1989**; **Huovinen 1994**). Data from one RCT suggested no difference between groups in the proportion of participants achieving bacterial eradication: RR 2.67 (95% CI 0.38 to 18.67) (Analysis 2.3) (**Valtonen 1989**).

Ciprofloxacin compared with trimethoprim

One trial at unclear risk of bias overall was identified (**Huovinen 1994**), previously described in the section above. At 16 weeks, 5/13 (38%) ulcers had healed with ciprofloxacin compared with 3/12 (25%) with trimethoprim. The RR estimate did not suggest a difference between groups: RR 1.54 (95% CI 0.46 to 5.09) (Analysis 3.1). The frequency of emergence of resistant bacterial strains was the same for both groups, occurring in 8/12 (67%) participants receiving ciprofloxacin and in 6/9 (67%) participants receiving trimethoprim: RR 1.00 (95% CI 0.54 to 1.84) (Analysis 3.2). The cost of a 12-week course of treatment with ciprofloxacin was USD 600 for ciprofloxacin and USD 120 for trimethoprim (price year not stated). The cost of concurrent topical treatment was not reported.

Trimethoprim compared with placebo

The trial described in the two preceding sections also compared trimethoprim with placebo (**Huovinen 1994**). At 16 weeks, 3/11 (27%) ulcers had healed with placebo compared with 3/12 (25%) with trimethoprim. The RR estimate did not suggest a difference between groups: RR 0.92 (95% CI 0.23 to 3.63) (Analysis 4.1). Emergence of resistant bacterial strains occurred in 6/9 (67%) participants receiving trimethoprim and in 1/10 (10%) in the placebo group. No difference between groups was detected: RR 6.67 (95% CI 0.98 to 45.29) (Analysis 4.2). Although this three-arm trial reported costs of treatment for the groups receiving ciprofloxacin and trimethoprim (see comparison above), costs were not reported for the group allocated placebo (**Huovinen 1994**).

Amoxicillin compared with topical povidone-iodine

One three-arm trial (N = 63 participants) at unclear risk of bias overall was identified for this comparison (**Daroczy 2006**). Participants were randomised to the following treatments of 12 weeks duration: topical povidone-iodine alone; povidone-iodine plus compression; and oral amoxicillin plus compression. The setting of treatment was not explained. Ulcers were described as infected in the RCT report but further details of this were not provided. Also, it is not clear whether infection was present at baseline, or whether it occurred during treatment. At 12 weeks, the number of ulcers healed was 13/21 (62%) in the group treated with povidone-iodine alone, 17/21 (81%) in the group treated with povidone -iodine plus compression and 18/21 (86%) in the amoxicillin plus compression group. The RR estimates did not suggest a difference between groups in complete healing when amoxicillin plus compression was compared with povidone-iodine alone, RR 1.38 (95% CI 0.95 to 2.02) (Analysis 5.1), nor when the former was compared with povidone-iodine plus compression, RR 1.06 (95% CI 0.81 to 1.39) (Analysis 6.1). Recurrence of ulcer infection was assessed five months after completion of the trial, comparing the group receiving amoxicillin with both povidone-iodine groups combined. The recurrence rate was lower in the group treated with povidone-iodine (11%) compared with amoxicillin (32%) (statistical significance of the between-group difference not reported by the trial authors and not evaluable by the review authors because of the limited nature of data reported in the paper).

Levamisole compared with placebo

One trial at unclear risk of bias overall was identified (**Morias 1979**). This RCT compared levamisole with placebo in an outpatient setting (N = 59 participants). Levamisole, a treatment for roundworm infection (**BNF 2013**), is postulated to have an antibacterial action in wounds (**Wilton 1978**; **Morias 1979**). Both active drug and identical placebo were given twice daily for two days a week for 20 weeks or until complete healing. It was unclear whether the ulcers were infected at baseline. At 20 weeks all ulcers in the levamisole group had healed compared with 76% in the placebo group, suggesting a benefit of levamisole: RR 1.31 (95% CI 1.06 to 1.62) (Analysis 7.1). Three participants out of 30 (10%) treated with levamisole complained of gastric adverse effects, compared with none in the placebo group. It should be noted that levamisole is unlicensed in the UK, and is only available from 'special order' suppliers for use in treating roundworm infection (**BNF 2013**). It was withdrawn from the US market in 1999 because of the risk of associated agranulocytosis (a marked decrease in granulocytes, a type of white blood cell) (**Chang 2010**).

Summary of evidence for systemic antibiotics

Five RCTs recruiting 233 participants were identified, reporting the following comparisons: co-trimoxazole, gentamicin or amikacin, prescribed according to sensitivity versus standard care (one RCT); ciprofloxacin versus standard care or placebo (two RCTs); ciprofloxacin versus trimethoprim (one RCT); trimethoprim versus placebo (one RCT); amoxicillin versus topical povidone-iodine (one RCT); and levamisole versus placebo (one RCT). More participants healed on levamisole compared to placebo. Levamisole is an oral antimicrobial product normally used to treat roundworm infection; it is not widely available. Other comparisons did not indicate between-group differences for healing. Bacterial resistance developed more

frequently with ciprofloxacin compared with standard care or placebo. Otherwise, there were few data on secondary outcomes. All the RCTs were small and had an overall unclear risk of bias. One RCT restricted patient selection to those with non-infected ulcers at baseline, and the others did not clearly report the baseline ulcer infection status. Therefore it cannot be determined from these data whether systemic antibiotics can promote healing in patients with clinically infected ulcers.

Cadexomer iodine

Eleven RCTs (12 comparisons) recruiting 962 participants in total evaluated the effects of cadexomer iodine (Skog 1983; Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Kero 1987; Moss 1987; Laudanska 1988; Holloway 1989; Hansson 1998; Miller 2010).

Cadexomer iodine compared with standard care

Seven trials compared cadexomer iodine with standard care (Skog 1983; Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Laudanska 1988; Holloway 1989). Four had a high overall risk of bias (Skog 1983; Harcup 1986; Steele 1986; Holloway 1989), and the remainder were unclear (Ormiston 1985; Lindsay 1986; Laudanska 1988). In six RCTs, participants were treated in community or outpatient settings (Skog 1983; Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Holloway 1989), whilst the seventh involved six weeks of bedrest and daily dressings in an inpatient setting (Laudanska 1988). Four RCTs mentioned using compression as a concurrent therapy for all participants, however, the information provided was limited and it was not possible to determine whether the level applied was therapeutic (Skog 1983; Ormiston 1985; Steele 1986; Holloway 1989). The other three RCTs mentioned the use of light retention or support bandages for all participants (Harcup 1986; Lindsay 1986; Laudanska 1988). Treatment duration ranged from four to 24 weeks. One RCT recruited only participants with infected ulcers (Skog 1983). The others did not specify baseline ulcer infection status explicitly, however, it appeared from the information provided that those with infected ulcers would have been allowed entry into the trials (Ormiston 1985; Harcup 1986; Lindsay 1986; Steele 1986; Laudanska 1988; Holloway 1989). Data from four RCTs were pooled for the outcome of complete healing at four to 12 weeks, indicating that 35/106 (33%) healed when given cadexomer iodine and 16/106 (15%) healed on standard care. This suggested a benefit of cadexomer iodine: RR 2.17 (95% CI 1.30 to 3.60) (Analysis 8.1; Figure 4) (Ormiston 1985; Lindsay 1986; Steele 1986; Laudanska 1988).

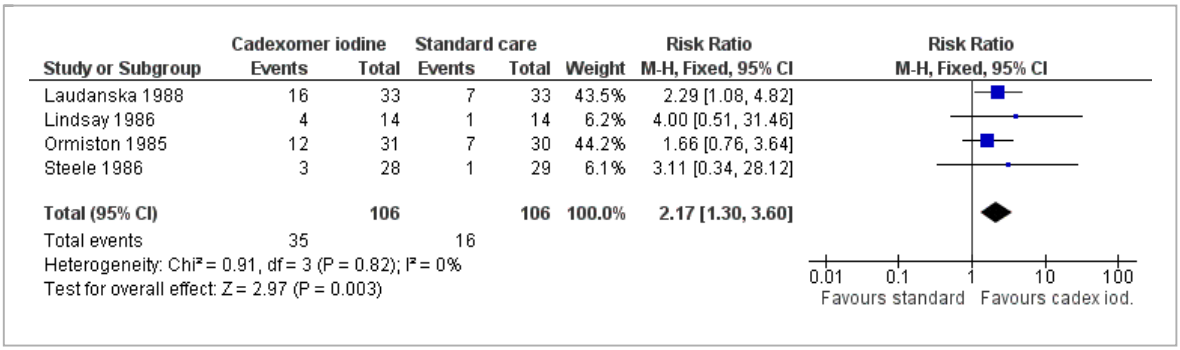

Figure 4.

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Forest plot of comparison: 8 Cadexomer iodine versus standard care, outcome: 8.1 Frequency of complete healing at 4 to 12 weeks.

Findings from the other three trials were also in favour of cadexomer iodine (Skog 1983; Harcup 1986; Holloway 1989). Two RCTs reported the mean percentage change in ulcer area, the respective values for cadexomer iodine and standard care being: reductions of 36% and 10% at four weeks (N = 72 participants, P value < 0.01) (Harcup 1986); and a reduction of 34% and an increase of 5% at six weeks (N = 74 participants, P value < 0.02) (Skog 1983). The third trial reported mean (standard error of the mean) rate of ulcer healing in cm squared per week at 24 weeks as 0.95 (0.12) for cadexomer iodine versus 0.41 (0.13) for standard care (N = 54 participants analysed, P value 0.0025). Participants were given the option to swap treatments at 12 weeks; healing data at the point of crossover were not reported (Holloway 1989). The review authors did not calculate measures of treatment effect for these trials because of the limited nature of available data (e.g. unclear group denominators). The P values shown here are for the between-group differences, as reported by the trial authors (Skog 1983; Harcup 1986; Holloway 1989).

One RCT reported statistically significant differences in favour of cadexomer iodine for the number of participants with eradication or improvement of staphylococcal infection (P value < 0.001), *Pseudomonas aeruginosa* infection (P value < 0.05), and other pathogenic organisms (listed as beta-haemolytic *Streptococcus* , *Proteus* , Enterobacteria and *Klebsiella* (P value < 0.001) (Skog 1983). The review authors did not calculate measures of effect for these outcomes, as the relevant denominators were not clearly stated (i.e. number of participants per group at baseline with the respective types of infection).

Three RCTs reported adverse effects (Skog 1983; Ormiston 1985; Holloway 1989); we pooled data from two RCTs (Skog 1983; Ormiston 1985); the denominators per group were unclear for Holloway 1989. The pooled data suggested a higher incidence of adverse events in those receiving cadexomer iodine: RR 4.59 (95% CI 1.40 to 15.05) (Analysis 8.2). Holloway 1989 reported that six participants receiving cadexomer iodine experienced adverse events compared with none allocated standard care. The types of adverse events reported by participants allocated cadexomer iodine included itching and pain (all three RCTs), as well as eczema, pruritus, rashes and difficulty in removing cadexomer iodine from the ulcer (Ormiston 1985). Those receiving standard care complained of pain (Skog 1983); and eczema, pruritus and rashes (Ormiston 1985).

Cadexomer iodine compared with hydrocolloid dressing

A three-armed RCT recruiting 153 participants compared cadexomer iodine, hydrocolloid dressing and paraffin gauze dressing; all participants received compression (a short-stretch bandage) and interventions were delivered for 12 weeks in an outpatient setting (Hansson 1998). This RCT was at high risk of bias overall. Participants with clinically infected ulcers were excluded. At 12 weeks, the number of ulcers healed was 8/56 (14%) in the cadexomer iodine group and 5/48 (10%) in the hydrocolloid group. The RR estimate did not suggest a difference between groups: RR 1.37 (95% CI 0.48 to 3.91) (Analysis 10.1). Nineteen adverse

events were reported in the cadexomer iodine group compared with 33 in the hydrocolloid group. The review authors did not calculate a measure of effect as the group denominators were unclear. This trial reported cost of treatment taking into account staff time, materials and transport. The cost presented in terms of USD per percentage ulcer area reduction was lower in the cadexomer iodine group relative to hydrocolloid (USD 8.8 compared with USD 32.5). The price year was not stated. The analysis was based on a subset of 23 participants.

Cadexomer iodine compared with paraffin gauze dressing

The RCT described in the section above also included a comparison of cadexomer iodine with paraffin gauze dressing (**Hansson 1998**). The frequency of complete healing at 12 weeks was similar for both groups, 8/56 (14%) in the cadexomer iodine group compared with 7/49 (14%) for those treated with paraffin gauze: RR 1.00 (95% CI 0.39 to 2.56) (Analysis 11.1). Nineteen adverse events were reported in the cadexomer iodine group compared with 26 in the paraffin gauze group. The cost in terms of USD/percentage of ulcer healed was USD 8.8 for cadexomer iodine and USD 12.9 for paraffin gauze (price year not stated). The analysis was based on a subset of 25 participants.

Cadexomer iodine compared with dextranomer

Two trials compared cadexomer iodine with an alternative debriding agent, dextranomer (**Kero 1987**; **Moss 1987**); both RCTs mentioned the use of compression therapy for all participants. One RCT had an overall high risk of bias (**Moss 1987**) whilst the other was at unclear risk (**Kero 1987**). Both were conducted in outpatient settings. Neither reported ulcer infection status at baseline. In one RCT, 5/13 (38%) participants healed on dextranomer and 7/14 (50%) healed on cadexomer iodine at eight weeks (**Kero 1987**). The RR estimate did not suggest a difference between groups: RR 1.30 (95% CI 0.55 to 3.09) (Analysis 9.1). The second RCT (N = 43 participants) assessed the mean percentage change in ulcer area at six weeks, reporting a reduction of 2% in the group receiving dextranomer and a reduction of 3% in those allocated cadexomer iodine (**Moss 1987**). The trial authors reported that the between-group difference was not statistically significant, but no P value was presented. Mean values were read from a graph, and available details were insufficient for the review authors to calculate a measure of treatment effect.

In terms of secondary outcomes, one RCT reported that the incidence of ulcer infection during the trial was 4/21 (19%) for those receiving cadexomer iodine and 3/21 (14%) for dextranomer **Moss 1987**. The following values were read from a graph for the same trial, for the proportions of participants eradicating organisms during six weeks of treatment with dextranomer and cadexomer iodine, respectively: beta-haemolytic *Streptococcus* 0% and 40%; *Staphylococcus aureus* 42% and 0%; *Pseudomonas* species 10% and 35%; and *Proteus* species 25% and 50% (**Moss 1987**). No P values were presented for between-group differences. No information about the baseline infection status of ulcers was available.

Cadexomer iodine compared with silver-impregnated dressing

One RCT compared cadexomer iodine with a silver-impregnated dressing, with all participants receiving compression (**Miller 2010**). This RCT was identified to be at high risk of bias overall. All participants had signs of infection or critical colonisation at baseline. The

frequency of complete healing at 12 weeks was similar between treatment groups, with 84/141 (60%) participants healing in the cadexomer iodine group compared with 85/140 (61%) in the silver-impregnated dressing group: RR 0.98 (95% CI 0.81 to 1.19) (Analysis 12.1). Bacterial growth was assessed by wound swab during the first two weeks of treatment and was categorised by the trial authors as nil/scant/low or moderate/high. In general, the distribution of participants across categories was similar between groups for the following: leucocytes; Gram-positive bacilli; Gram-negative bacilli; Gram-positive cocci; and Gram-negative cocci. *Staphylococcus aureus* was the commonly identified isolate in both groups. Eight adverse events were reported in the cadexomer iodine group compared with 13 in the silver dressings group; further details (e.g. number of participants per group affected) were not provided. No difference was noted between groups in terms of the proportions of participants expressing complete or moderate acceptability of treatment: RR 0.97 (95% CI 0.89 to 1.06) (Analysis 12.2) (**Miller 2010**).

Summary of evidence for cadexomer iodine

Eleven RCTs recruiting 962 participants evaluated the effects of cadexomer iodine. Comparators were as follows: standard care (7 RCTs); hydrocolloid dressing (one RCT); paraffin gauze dressing (one RCT); dextranomer (two RCTs); and silver-impregnated dressing (one RCT). Healing outcomes were better for cadexomer iodine when compared with standard care, however, the incidence of adverse effects was greater for those receiving cadexomer iodine. Other comparisons did not detect differences in terms of healing. The outcomes of bacterial growth and patient acceptability of treatment were similar for cadexomer iodine and silver-impregnated dressings. Otherwise, data on secondary outcomes were limited. Most the RCTs were small and had either high or unclear risk of bias. One RCT recruited only those with infected ulcers (comparator was standard care), one recruited participants with infection or critical colonisation (comparator was silver-impregnated dressing) and one excluded participants with infected ulcers (comparators were hydrocolloid and paraffin gauze dressings). The other RCTs did not provide a clear report of baseline ulcer infection status, however, it is apparent from information provided in the trial reports that participants with ulcer infection would have been permitted to enter the trials.

Povidone-iodine

Six RCTs (seven comparisons) recruiting a total of 639 participants evaluated povidone-iodine preparations (**Groenewald 1981**; **Smith 1992**; **Ishibashi 1996**; **Casoni 2002**; **Fumal 2002a**; **Kuznetsov 2009**). A seventh RCT, which included treatment groups receiving povidone-iodine, was discussed in the earlier section on systemic antibiotics (**Daroczy 2006**).

Povidone-iodine compared with dextranomer

One RCT at high risk of bias overall was identified (**Groenewald 1981**). One hundred participants were recruited. Most of the ulcers were colonised by bacteria at baseline, but it was not clear how many were clinically infected (if any). Interventions were provided in an outpatient setting. All participants received compression therapy. The trial authors reported that the mean time to healing was significantly shorter in the group receiving dextranomer: 4.4 weeks versus 5.3 weeks (P value < 0.05); however, it is unclear whether these time to event data were analysed appropriately using survival analysis. The trial authors reported

that time to eradication of *Staphylococcus aureus* colonisation was significantly shorter in the dextranomer group compared with the povidone-iodine group (14.7 days versus 18.7 days; P value < 0.01) (**Groenewald 1981**).

Povidone-iodine and sugar ointment compared with recombinant tissue growth factor

One RCT at unclear risk of bias overall was identified (**Ishibashi 1996**). This trial was conducted in Japan and recruited both inpatients and outpatients. A total of 218 participants with different wound types were recruited; 207 were analysed of which 63 had venous leg ulcers. The growth factor was applied to the ulcer daily as a spray solution (recombinant human basic fibroblast growth factor 0.01%, 0.3 mL) whilst the povidone-iodine (concentration not stated) and sugar ointment was applied once or twice daily. Use of both products was followed by application of a gauze pad with securing tape; compression therapy was not mentioned. Treatment duration was four weeks. Around two-thirds of analysed participants across all wound types had some degree of ulcer infection at baseline, but no breakdown according to wound type was provided. The number of ulcers healed at four weeks was 5/31 (16%) in the group receiving the povidone-iodine and sugar ointment and 9/32 (28%) for those allocated the growth factor. The RR estimate did not suggest a difference between treatment groups: RR 0.57 (95% CI 0.22 to 1.52) (Analysis 13.1).

Povidone-iodine compared with hydrocolloid dressing

Three RCTs were identified (**Smith 1992**; **Casoni 2002**; **Fumal 2002a**). One had a high risk of bias overall (**Smith 1992**), and the other two were unclear (**Casoni 2002**; **Fumal 2002a**). Two RCTs reported time to healing (**Smith 1992**; **Fumal 2002a**), one additionally reported complete healing (**Smith 1992**), and the third reported change in ulcer surface area (**Casoni 2002**).

Smith 1992 recruited 200 participants and did not state whether the ulcers were infected at baseline. Interventions were delivered in an outpatient setting and consisted of application of 10% povidone-iodine paint to the wound, which was then covered with paraffin gauze, compared with hydrocolloid dressing. All participants received two-layer compression or a compression stocking. Interventions were provided for four months. The trial authors reported that 10% of larger ulcers healed in less than four months in the povidone-iodine group compared with 34% in the hydrocolloid group (P value 0.02). Values for the smaller ulcers were not reported, but examination of the survival plot suggested that over 80% of participants in both groups healed within the four-month trial period. In terms of complete healing for all ulcers at four months, (50/99 (51%) healed in the hydrocolloid group compared with 47/101 (47%) in the povidone-iodine group. The RR estimate did not suggest a difference between treatment groups: RR 0.92 (95% CI 0.69 to 1.23) (Analysis 14.1). Cost estimates based on the total cost of dressings and the total cost of nursing time were reported separately for participants with an initial ulcer diameter less than 6 cm, and at least 6 cm. It was not clear why this stratification was used, as it differed from that used at randomisation and in other analyses. Overall, use of povidone-iodine was associated with lower costs. For smaller ulcers, the cost of dressings was GBP 18.55 for povidone-iodine and GBP 32.81 for hydrocolloid. The respective values for nursing time were GBP 38.95 and GBP 48.96. For larger ulcers, the cost of dressings was GBP 68.43 for povidone-iodine and GBP

441.91 for hydrocolloid. The respective estimates for nursing time were GBP 183.75 and GBP 526.63. The price year was not stated.

The second trial recruited 17 participants with two leg ulcers each, who acted as his or her own control (Fumal 2002a). Ulcers were not infected as baseline. One ulcer per participant was randomly assigned to receive 10% povidone-iodine solution plus standard treatment, and the other ulcer was treated with standard treatment alone (comprised saline cleansing, hydrocolloid dressing and a 'compressive bandage' - no further details provided). Interventions were delivered for six weeks. The trial authors reported a statistically significant shorter time to healing for the group receiving the povidone-iodine preparation. Estimation of median (range) weeks to healing derived from Kaplan-Meier survival analysis was 11 (9 to 17) versus 18 (11 to 24) (P value < 0.01; log-rank test). This finding should be treated with caution because of the small number of participants recruited.

In a three-armed, multi-factorial RCT, 74 participants were randomly assigned to receive one of three primary dressings (non-adherent paraffin gauze, hydrocolloid or hyaluronic acid/povidone-iodine) and one of three types of compression bandage (Unna's boot, multi-layer bandage or stockings plus elastic bandage) (Casoni 2002). A full report was not available; data were extracted from conference presentation slides supplied by the trial author. The trial was of three months' duration. The baseline infection status of ulcers was not reported; before the trial, participants with clinically infected wounds were treated with systemic antibiotics. For the comparison of hyaluronic acid/povidone-iodine dressing and hydrocolloid, the median percentage ulcer area reduction at three months was 100% for both groups.

Povidone-iodine compared with non-adherent paraffin gauze dressing

One trial was identified (already described in the section above), which had an unclear risk of bias overall (Casoni 2002). The trial authors reported a statistically significant difference in median percentage ulcer area reduction at three months in favour of hyaluronic acid/povidone-iodine dressing when compared with non-adherent paraffin gauze dressing (100% versus 90%, P value 0.036).

Povidone-iodine compared with moist or foam dressings

One RCT at unclear risk of bias compared a 10% povidone-iodine dressing with different dressings applied according to ulcer status (a moist wound dressing for necrotic tissue, a foam dressing for ulcers free of necrosis or a silver-impregnated foam dressing for ulcer infection) (Kuznetsov 2009). All participants received short-stretch compression bandaging. Most participants in both groups had bacteria isolated from their ulcers at baseline, but the number with clinically infected wounds was not stated. At four weeks, 2/15 (13%) participants healed in the povidone-iodine group compared with 5/15 (33%) of controls. The RR estimation suggested no difference between groups: RR 0.40 (95% CI 0.09 to 1.75) (Analysis 15.1). The mean cost of a complete course of treatment was lower for the group receiving povidone-iodine dressing: RUB 6669.84 (Roubles) versus RUB 14,360.15 (price year not stated). The mean cost of treatment per participant per day was also lower for those allocated the povidone-iodine dressing: RUB 16.47 versus RUB 36.82.

Summary of evidence for povidone-iodine

Six RCTs recruiting 639 participants evaluated the effects of povidone-iodine. Comparator interventions were: dextranomer (one RCT); growth factor (one RCT); hydrocolloid dressing (three RCTs); paraffin gauze dressing (one RCT); and moist or foam dressings given according to ulcer status (one RCT). Overall, there was no evidence from healing data to suggest a difference between treatment groups (estimates either indicated no difference, or were likely to be unreliable). Two RCTs reported that use of povidone-iodine was associated with lower costs compared with control interventions (hydrocolloid and moist or foam dressings), however, full economic evaluations were not described. Most the RCTs were small and had either high or unclear risk of bias. Participants with infected ulcers were excluded from one RCT, but ulcer infection status was unclear for the others.

Peroxides

Four RCTs (four comparisons) that recruited a total of 72 participants evaluated the effects of peroxide-based topical preparations (**Beitner 1985a**; **Beitner 1985b**; **Belcaro 2003**; **Belcaro 2007**).

Benzoyl peroxide 10% compared with saline dressing

One RCT at high risk of bias was identified (**Beitner 1985a**). Ten participants with two leg ulcers each were recruited, who acted as his or her own control. Baseline infection status of the ulcers was not described. One ulcer per participant was randomised to receive benzoyl peroxide 10% lotion and the other was treated with normal saline solution. Both study lotions were applied to ulcers by means of an sterile wound dressing sponge, cut to fit the size of the ulcer. Compression therapy was not mentioned. Interventions were delivered for six weeks in an outpatient setting. At the end of the treatment period, benzoyl peroxide lotion 10% was more effective than saline in terms of the mean percentage ulcer area remaining: difference in means -30.40% (95% CI -42.12 to -18.68 (Analysis 16.1). The trial authors reported a between-group analysis which took account of the highly correlated healing data from the two interventions groups, and also reported a statistically significant difference in favour of benzoyl peroxide 10% (P value < 0.01). Three participants reported adverse effects associated with use of benzoyl peroxide (severe irritation).

Benzoyl peroxide 20% compared with saline dressing

One RCT at high risk of bias was identified (**Beitner 1985b**), with a similar study protocol to the trial described in the section above, except that the comparison was between benzoyl peroxide 20% lotion and normal saline. Ten participants with two leg ulcers each were recruited, who acted as his or her own control. At the end of the six week treatment period, benzoyl peroxide lotion 20% was more effective than saline in terms of the mean percentage ulcer area remaining: difference in means -34.10% (95% CI -46.22 to -21.98) (Analysis 16.1). The trial authors reported a between-group analysis which took account of the highly correlated healing data from the two interventions groups, and also reported a statistically significant difference in favour of benzoyl peroxide 20% (P value < 0.05). No adverse effects were reported.

Hydrogen peroxide compared with placebo

Two RCTs with unclear risk of bias were performed by the same research group (Belcaro 2003; Belcaro 2007). Both trials provided the following treatment regimen. An initial run-in period involved administration of systemic antibiotics for 15 to 20 days to clear any underlying infection. Participants were then randomly assigned to receive hydrogen peroxide 1% cream applied to the ulcer and peri-ulcer area or a placebo cream. For all participants, the wound was covered with tissue paper, and a compression bandage applied. Study treatments were delivered in outpatient settings. Outcomes were assessed after 10 days. Insufficient data were presented to enable calculation of effect sizes, and so data could not be pooled. The earlier trial recruited 20 participants (Belcaro 2003). The trial authors reported a statistically significant difference in ulcer area reduction between groups in favour of hydrogen peroxide (median decrease 35%, range 12% to 44%) when compared with placebo (median decrease 11%, range 0% to 23.5%); P value < 0.05. Similar findings were seen for the second trial (N = 32) (Belcaro 2007). At 10 days, the reduction in ulcer area was significantly greater for the group receiving hydrogen peroxide: median decrease 44.8%, range 15% to 57% versus median decrease 32%, range 15% to 44%; P value < 0.005.

Summary of evidence for peroxide-based preparations

Four RCTs recruiting 72 participants evaluated the effects of peroxide-based topical preparations. Comparator interventions included saline dressing (two RCTs) and placebo (two RCTs). Healing estimates were based on surrogate measures (change in wound area). The data suggested that benzoyl peroxide in both 10% and 20% concentrations was more effective than saline dressing. The 10% preparation was associated with adverse effects (versus none for saline). No adverse effects were reported in either group for the comparison of 20% benzoyl peroxide versus saline. The baseline ulcer infection status was not described for either of the benzoyl peroxide RCTs. Hydrogen peroxide 1% cream resulted in greater wound area reduction when compared with a placebo cream; there were no data on secondary outcomes. For both benzoyl peroxide RCTs, it is likely that participants with infected ulcers were excluded. All of the RCTs were small and had either high or unclear risk of bias.

Honey-based preparations

Two multi-centre RCTs (two comparisons) recruiting 476 participants in total evaluated Manuka honey preparations (Gethin 2008; Jull 2008).

Honey-based preparations compared with alternative topical preparations

One RCT comparing honey topical application with hydrogel was at high risk of bias (Gethin 2008). The other, at low risk of bias, compared a honey-impregnated calcium alginate dressing with usual care (dressings applied according to clinician choice - could include iodine or silver dressings) (Jull 2008). Compression was used as a concurrent therapy in both RCTs. One RCT excluded participants who had clinically infected ulcers at baseline but reported that some participants had wounds colonised with various micro-organisms, including a small proportion (15% overall) with methicillin-resistant *Staphylococcus aureus* (MRSA) (Gethin 2008). Baseline ulcer infection status was not reported for the other trial (Jull

2008). In one RCT, the mean time to healing was reported as 63.5 days in the honey group, compared with 65.3 days in the usual care group (trial authors reported P value 0.553 for the difference in means). The unadjusted hazard ratio estimation as reported by the trial authors was 1.1 (95% CI 0.8 to 1.5; P value 0.451); the estimate adjusted for study centre and prognostic index was stated to be similar, although data were not presented. (Jull 2008). Both RCTs reported complete healing at 12 weeks, and data were pooled (Gethin 2008; Jull 2008). Overall, 128/241 (53%) participants were healed on honey, compared with 108/235 (46%) on the alternative regimens. No evidence of a difference between groups was found: RR 1.15 (95% CI 0.96 to 1.38) (Analysis 17.1; Figure 5).

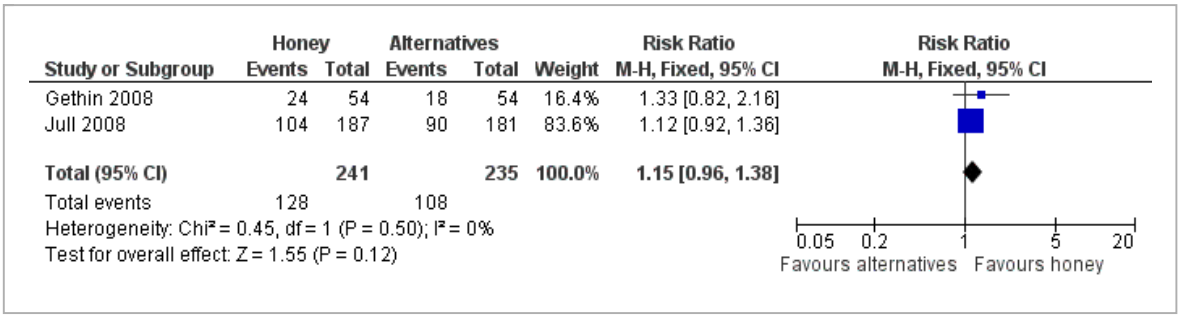

Figure 5.

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Forest plot of comparison: 18 Honey products versus alternatives, outcome: 18.1 Complete healing at 12 weeks.

In terms of secondary outcomes, pooled data suggested no between-group differences in the incidence of ulcer infection during the 12-week trial period: RR 0.71 (95% CI 0.49 to 1.04) (Analysis 17.2) (Gethin 2008; Jull 2008). One RCT additionally reported that 37 episodes of infection occurred in the group receiving honey compared with 49 in the group allocated usual care (trial authors reported P value 0.449 for the between-group difference) (Jull 2008). One RCT reported that, in both groups, fewer participants had at least one bacterial species isolated at week four relative to baseline; however, the four-week data were reported for the whole group, not just for those with isolates identified at baseline. The same finding applied to those with more than one isolate. Data from the same RCT indicated no evidence of a difference between groups for the proportions of participants with MRSA eradication at four weeks: RR 4.2 (95% CI 0.67 to 26.30) (Gethin 2008) (Analysis 17.3).

Both RCTs reported adverse events (Gethin 2008; Jull 2008), one asserting that no observed adverse events were considered to be attributable to either of the trial treatments (Gethin 2008). Data from the other RCT suggested that more adverse events were detected in the group receiving the honey dressing: RR 1.28 (95% CI 1.05 to 1.56) (Analysis 17.4) (Jull 2008). The most frequently reported local adverse event in both groups was pain; the trial authors reported that the between-group difference was statistically significant in favour of usual care (P value 0.001). Other local adverse events, reported by the trial authors as not statistically significant in incidence between groups, included bleeding, dermatitis, erythema, oedema, increased exudate, deterioration of the ulcer or peri-ulcer skin and new ulceration (Jull 2008).

One RCT reported similar outcomes between treatment groups for the SF-36 physical component summary score, the SF-36 mental component summary score, the EQ-5D and the Charing Cross Venous Ulcer Questionnaire, all of which were assessed at 12 weeks (not stated whether any of the measurements were adjusted for baseline values) (Jull 2008). The same RCT conducted a cost-effectiveness analysis in parallel with the RCT and reported that estimates from the base case analysis of mean total health service costs per participant were NZD 917.00 for the group receiving honey and NZD 972.68 for those allocated usual care (price year not stated) (Jull 2008). The incremental cost-effectiveness ratio (ICER) was NZD -9.45 (95% CI NZD -39.63 to NZD 16.07) in favour of honey when all costs were considered. Exclusion of hospitalisation costs (based on six participants receiving usual care hospitalised for a total of 40 days and three hospitalised for a total of 10 days allocated the honey dressing) reversed the ICER to NZD 11.34 (95% CI NZD -2.24 to NZD 26.25) in favour of usual care (Jull 2008).

Summary of evidence for honey-based preparations

Two RCTs recruiting 476 participants evaluated honey-based preparations. One RCT compared a honey-based topical application with hydrogel (high risk of bias) and the other compared a honey-impregnated dressing with non-honey dressings applied according to the clinician's choice (low risk of bias). Pooled data suggested no difference between groups for the outcomes of complete healing at 12 weeks and incidence of ulcer infection during the trial period. The RCT evaluating topical applications excluded participants with clinically infected wounds at baseline, but reported that some wounds were colonised with MRSA; no difference was detected between groups for eradication of MRSA at four weeks. The RCT comparing honey-impregnated dressing with non-honey dressings reported no difference between groups for time to healing and change in health-related quality of life scores. However, use of honey was associated with more adverse events. The same trial conducted a rigorous cost-effectiveness analysis in parallel with the RCT and concluded that honey was unlikely to be cost effective. This trial did not provide information about baseline ulcer infection status.

Silver-based preparations

Twelve RCTs (13 comparisons) recruiting 1514 participants evaluated the effect of silver-based preparations.

Silver sulphadiazine cream compared with non-antimicrobial dressings and topical applications

Three RCTs reporting four comparisons were identified (Blair 1988; Bishop 1992; Fumal 2002b); all had an unclear risk of bias overall. Two excluded participants with clinically infected wounds (Bishop 1992; Fumal 2002b); in the third trial, baseline ulcer infection status was not explained (Blair 1988).

One RCT recruited 17 participants, each with two leg ulcers; these participants acted as their own controls, the ulcer being the unit of randomisation (Fumal 2002b). Application of 1% silver sulphadiazine cream in addition to usual care was compared with usual care alone (hydrocolloid dressing and a 'compressive bandage'—no further details were provided). Treatment duration was six weeks. Median time to healing derived from Kaplan-Meier

survival analysis was reported as 15 weeks (range seven to 23 weeks) for the group receiving silver plus usual care, and 16 weeks (range nine to 22 weeks) for those allocated usual care alone. The trial authors described the between-group difference as not statistically significant, but the P value was not presented.

A three-armed trial (N = 93 participants) compared three different topical agents: 1% silver sulphadiazine cream; 0.4% tripeptide copper complex cream (described elsewhere as a growth factor **Maquart 1993**); and a placebo cream (**Bishop 1992**). All participants received a non-adherent dressing and compression (not described further). The respective numbers of participants healed per group at four weeks were as follows: 6/31 (19%); 0/32 (0%); and 1/30 (3%). No statistically significant difference was detected between groups for the comparisons of 1% silver sulphadiazine versus placebo: RR 5.81 (95% CI 0.74 to 45.40) (Analysis 18.1); and 1% silver sulphadiazine versus 0.4% tripeptide copper complex cream: RR 13.41 (95% CI 0.79 to 228.32) (Analysis 19.1). .

Another RCT (N = 60 ulcers) compared 1% silver sulphadiazine cream with a non-adherent dressing; all participants received four-layer compression bandaging (**Blair 1988**). At 12 weeks, 19/30 (63%) ulcers were healed on 1% silver sulphadiazine cream compared with 24/30 (80%) receiving the non-adherent dressing. The RR estimate did not suggest a difference between groups: RR 0.79 (95% CI 0.57 to 1.10) (Analysis 20.1). In the same RCT, four participants receiving 1% silver sulphadiazine cream withdrew from treatment because of erythema and pruritis; two participants in the same group developed cellulitis compared with one allocated to the non-adherent dressing (but not stated whether these participants withdrew) (**Blair 1988**). The review authors did not estimate measures of effect from these data because the denominators for participants were unclear. All ulcers were contaminated at baseline, and the most common isolate was *Staphylococcus aureus* . However, it was not stated whether wounds were clinically infected. The trial authors stated that bacterial contamination continued throughout the trial in both groups, with only three ulcers having no bacterial growth at any stage (group not stated) (**Blair 1988**). Other trials did not report secondary outcomes. Healing data were not pooled because of differences in comparators, treatment duration and follow-up periods between trials.

Silver-impregnated dressings compared with alternative silver-impregnated dressings

One RCT, with an unclear risk of bias, compared different proprietary brands of silver-impregnated dressings: a silver-impregnated polyurethane foam dressing (Avance); and a five-layer silver-impregnated dressing comprising absorbent and polyethylene net layers (Acticoat 7) (**Chaloner 2004**). All participants received a four-layer compression bandage. All participants had bacterial colonisation of ulcers at baseline, but it was not stated whether any were clinically infected. At 12 weeks, 7/20 (35%) in the Avance group had healed compared with 10/20 (50%) in the Acticoat 7 group, with no between-group difference detected: RR 1.43 (95% CI 0.68 to 3.00) (Analysis 21.1). Some secondary outcomes were mentioned but meaningful data were not provided.

Silver-impregnated dressings compared with non-antimicrobial dressings

Eight RCTs were identified (**Wunderlich 1991**; **Jørgensen 2005**; **Meaume 2005**; **Münter 2006**; **Lazareth 2008**; **Dimakakos 2009**; **Michaels 2009**; **Kerihuel 2010**). Two had low risk of

bias overall (Kerihuel 2010; Michaels 2009), one was high risk (Jørgensen 2005), and five were unclear (Wunderlich 1991; Meaume 2005; Münter 2006; Lazareth 2008; Dimakakos 2009). Ulcer infection status at baseline varied across the trials. One RCT excluded participants with infected ulcers (Kerihuel 2010), and another excluded participants taking antibiotics (Michaels 2009); we assumed that the latter meant that those with clinical infection of any type would have been excluded. Three RCTs included participants with critical colonisation of the wound but excluded those with a clinically infected ulcer (Jørgensen 2005; Meaume 2005; Lazareth 2008). Another RCT permitted those with critical colonisation or clinical infection, or both, to enter the trial (Münter 2006). One RCT included only those with infected ulcers (Dimakakos 2009), and one reported no information at all on wound infection status at baseline (Wunderlich 1991).

Four RCTs provided data on complete healing at four to 12 weeks (Wunderlich 1991; Jørgensen 2005; Dimakakos 2009; Michaels 2009). One multi-centre, pragmatic RCT (N = 213 participants) compared silver-impregnated dressings (different proprietary brands selected according to clinician judgement) with non-antimicrobial low-adherent dressings (Michaels 2009). Two RCTs compared silver-impregnated dressings with the same dressing fabric in a non-antimicrobial version (Jørgensen 2005; Dimakakos 2009), and the other compared a silver-impregnated charcoal dressing with various topical agents used according to different stages of healing (Wunderlich 1991). Three trials provided compression as concurrent treatment (Jørgensen 2005; Dimakakos 2009; Michaels 2009), but the use of compression was not mentioned in the RCT by Wunderlich 1991. Data from all four RCTs were pooled, indicating that 90/213 (42%) participants healed on silver and 76/211 (36%) healed on non-antimicrobial dressings. The RR estimate did not suggest a difference between groups: RR 1.17 (95% CI 0.95 to 1.45) (Analysis 22.1; Figure 6).

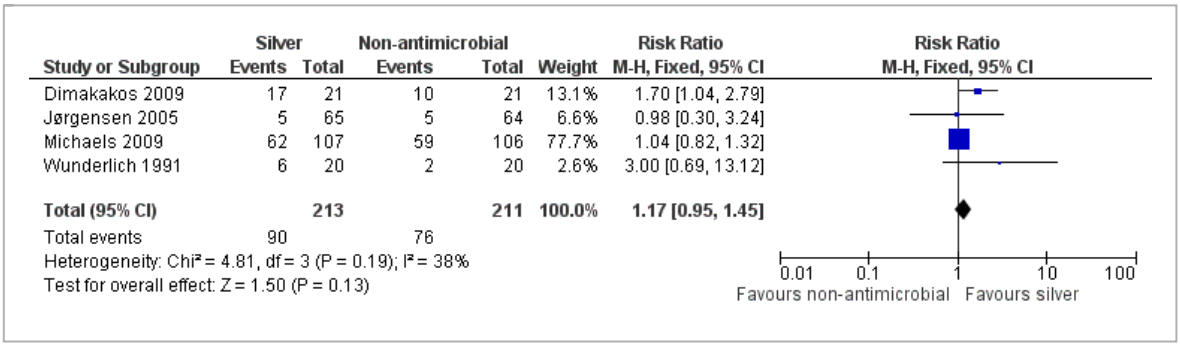

Figure 6.

Open in figure viewer

Forest plot of comparison: 23 Silver dressing versus non-antimicrobial dressing, outcome: 23.1 Complete healing at 4 to 12 weeks.

One RCT reported additional healing-related outcomes relating to longer term follow-up, time to healing and ulcer recurrence, all of which indicated no difference between treatment groups (Michaels 2009). The respective estimates for complete healing at six and 12 months were: RR 1.10 (95% CI 0.96 to 1.28) (Analysis 22.2); and RR 1.05 (95% CI 0.94 to 1.16) (Analysis 22.3). Median time to healing estimates were: 67 days (95% CI 54 to 80 days) for silver dressings, and 58 days (95% CI 43 to 73 days) for non-antimicrobial dressings (P value 0.408

reported by trial authors). The trial authors' reported hazard ratio was: 1.13 (95% CI 0.85 to 1.15), and the estimate for ulcer recurrence within the first year was: RR 0.80 (95% CI 0.38 to 1.70) (Analysis 22.4).

The other four RCTs provided outcome data on change in wound surface area (**Meaume 2005**; **Münter 2006**; **Lazareth 2008**; **Kerihuel 2010**). Three RCTs compared silver-impregnated dressings with the same dressing fabric in a non-antimicrobial version (**Meaume 2005**; **Lazareth 2008**; **Kerihuel 2010**), whilst the fourth used local best practice as the control group; this could include various types of dressings, including silver dressings as given to 17% of participants in that group (**Münter 2006**). All participants in all of these trials received compression therapy. Data from two RCTs were pooled for absolute change in ulcer surface area at four weeks, indicating a between-group difference in favour of silver: difference in means -4.7 cm squared (95% CI -8.46 to -0.94) (Analysis 22.5) (**Meaume 2005**; **Lazareth 2008**). The data for percentage change in ulcer area were not pooled because statistically significant heterogeneity was detected (Chi^2 test for heterogeneity P value 0.05 and I^2 estimation = 75%). In terms of estimates of treatment effect from the individual trials, one suggested a difference in favour of silver: difference in means -19.5% (95% CI -37.94 to -1.06) (**Lazareth 2008**), whilst the other showed no difference between groups: difference in means 7.5% (95% CI -11.68 to 26.68) (**Meaume 2005**). The pooled data on healing rate also suggested no difference between groups: pooled difference in means -0.12 cm squared per day (95% CI -0.28 to 0.03) (Analysis 22.7). The other two RCTs provided only limited data (**Münter 2006**; **Kerihuel 2010**). One reported the median (range) change in ulcer area in cm squared at four weeks as -4.5 (-30.9 to 22.5) for silver and -3.5 (-53.3 to 18.5) for non-antimicrobial dressings; the respective values for percentage change in ulcer area were -35.6 (-100.0 to 182.1) and -40.9 (-100.0 to 308.3) (P value for between-group difference not reported for either outcome) (**Kerihuel 2010**). The other reported the median percentage change in ulcer area at four weeks as -45.5 for silver and -28.8 for usual care (reported P value was 0.0001 for the between-group difference) (**Münter 2006**).

Six RCTs reported adverse events (**Jørgensen 2005**; **Münter 2006**; **Lazareth 2008**; **Dimakakos 2009**; **Michaels 2009**; **Kerihuel 2010**). Two stated that no observed adverse events were deemed related to treatment but provided no further information (**Dimakakos 2009**; **Michaels 2009**). Four presented the numbers of participants reporting various types of adverse events (**Jørgensen 2005**; **Münter 2006**; **Lazareth 2008**; **Kerihuel 2010**). Pooling of data did not suggest a difference between treatment groups: RR 0.69 (95% CI 0.36 to 1.33) (Analysis 22.8). The most commonly reported adverse events in both groups included maceration and other indications of worsening of the peri-ulcer skin. In terms of change in bacterial colonisation, one RCT (recruiting participants with critical colonisation but not clinical infection of the ulcer), reported that 39% of those receiving the silver dressing and 17% of the non-antimicrobial dressing group had no remaining signs of bacterial colonisation at four weeks (further data and P value not provided) (**Lazareth 2008**). A second RCT, which did not describe details of ulcer infection status at baseline, reported a non-significant reduction in colonisation over the whole study period for the group receiving the silver dressing, and a reduction starting only at week two in the group allocated other topical agents according to the stage of wound healing (follow-up duration was six weeks) (**Wunderlich 1991**).

Three RCTs reported change in health-related quality of life (Jørgensen 2005; Münter 2006; Michaels 2009). Findings from one trial indicated that no statistically significant between-group differences were observed at any of the follow-up times (one, three, six and 12 months) for either of the instruments used (EQ-5D and SF-6D) (estimates adjusted for baseline scores) (Michaels 2009). Available data from the other two RCTs were more limited but suggested that overall EQ-5D scores were similar between treatment groups (Jørgensen 2005; Münter 2006). One RCT reported estimates from a rigorous cost-effectiveness analysis and concluded that silver dressings were unlikely to be cost-effective (incremental cost-effectiveness ratio for silver dressings was GBP 489,250 per quality-adjusted life year gained, price year 2007) (Michaels 2009).

Summary of evidence for silver-based preparations

Twelve RCTs recruiting 1514 participants evaluated the effect of silver-based preparations. Silver sulphadiazine cream was compared with: usual care (one RCT); placebo (one RCT); growth factor (one RCT); and non-adherent dressing (one RCT). Silver-impregnated dressings were compared with alternative silver dressings (one RCT) and non-antimicrobial dressings (eight RCTs). There was no difference between treatment groups for most healing outcomes; some short-term surrogate measures of healing suggested benefit of silver dressing compared with non-antimicrobial dressings, whilst others suggested no between-group difference. Data on secondary outcomes suggested no difference between silver-impregnated dressing and non-antimicrobial dressings for adverse effects and changes in health-related quality of life scores. A rigorous cost-effectiveness analysis conducted alongside one RCT concluded that silver-impregnated dressings were unlikely to be cost-effective when compared with non-antimicrobial dressings. Two RCTs were large; one had low risk of bias and the other was unclear. The remainder were small with mostly unclear risk of bias. The ulcer infection status at baseline varied across trials.

Miscellaneous topical preparations

Five RCTs (seven comparisons) recruiting 590 participants overall were identified that did not easily fit into any of the groups described above (Fischer 1984; Cameron 1991; Fumal 2002c; Geske 2005; Binić 2010). Three RCTs evaluated topical antibiotics (Fischer 1984; Cameron 1991; Binić 2010), and the other two assessed the effects of topical antiseptics (Fumal 2002c; Geske 2005).

Chloramphenicol-containing ointment versus enzymatic wound cleansing preparation

One multi-centre RCT recruited 258 participants and comprised three study arms (Fischer 1984). Trial interventions were: an ointment containing an antibiotic (chloramphenicol) combined with an enzyme (clostridiopeptidase); an ointment containing an alternative antibiotic (framycetin sulphate) combined with the enzyme trypsin; and an enzymatic wound cleansing preparation (proprietary name Fibrolan) without added antibiotics. This generated three comparisons, all of which were relevant to the review. All participants received compression bandaging, according to usual care in each study centre. The overall risk of bias was unclear. There was no information about baseline ulcer infection status. The data suggested that more participants were healed at four weeks when receiving the non-

antibiotic enzymatic cleanser compared with the chloramphenicol-containing ointment: RR 0.13 (95% CI 0.02 to 0.99) (Analysis 23.1). Adverse events were reported as the number of participants who withdrew from treatment because of ineffectiveness (not defined further) or allergy. The data indicated no difference between groups: RR 2.02 (95% CI 0.52 to 7.84) (Analysis 23.2).

Framycetin sulphate–containing ointment versus enzymatic wound cleansing preparation

Data from the RCT described in the comparison above suggested no difference between groups in healing at four weeks: RR 0.69 (95% CI 0.23 to 2.01) (Analysis 24.1) (**Fischer 1984**). Adverse events were assessed as described in the comparison above. No evidence was found of a between-group difference: RR 2.93 (95% CI 0.80 to 10.67) (Analysis 24.2).

Chloramphenicol-containing ointment versus framycetin sulphate–containing ointment

Data from the RCT described in the two comparisons above suggested no difference between groups in healing at four weeks: RR 0.18 (95% CI 0.02 to 1.54) (Analysis 25.1) (**Fischer 1984**). Adverse events were assessed as for the two comparisons above. No evidence was found of a between-group difference: RR 0.69 (95% CI 0.25 to 1.90) (Analysis 25.2).

Mupirocin compared with vehicle

One RCT with overall unclear risk of bias was identified which compared the application of 2% mupirocin in a white soft paraffin tulle gras, with vehicle (N = 30 participants) (**Cameron 1991**). Both study groups received compression therapy. The setting of treatment was not stated. At 12 weeks, 8/15 (53%) participants healed on mupirocin and 7/15 (47%) healed on vehicle, with the RR estimate suggesting no difference between groups: RR 1.14 (95% CI 0.56 to 2.35) (Analysis 26.1). Baseline wound infection was not reported, but five participants in each group had colonisation of the ulcer with Gram-positive bacteria. Eradication of Gram-positive bacteria from ulcers was observed in all participants receiving mupirocin compared with none allocated the vehicle preparation. The numbers analysed were very small and did not suggest a difference between groups: RR 11.00 (95% CI 0.77 to 158.01) (Analysis 26.2).

Topical antibiotics versus herbal ointment

One RCT (N = 32 participants) at overall unclear risk of bias compared topical antibiotics with an herbal ointment (**Binić 2010**). The topical antibiotics were given according to cultures and sensitivities and included gentamicin, chloramphenicol 5%, enbecin, povidone-iodine 2%, metronidazole and fusidic acid. The herbal ointment (Plantoderm) was described as having antimicrobial properties. All participants received ulcer cleansing, debridement, dressings and bandages (but not compression therapy); dressings were changed twice daily. All ulcers showed signs of contamination or colonisation at baseline, with no signs of ulcer infection or systemic infection. The frequency of complete healing at week seven was 2/17 (12%) in the herbal ointment group compared with none in the topical antibiotics group: RR 4.44 (95% CI 0.23 to 85.83) (Analysis 27.1). The data suggested no differences between groups in terms of

eradication of bacteria from ulcers at seven weeks: RR 8.00 (95% CI 0.47 to 137.35) (Analysis 27.2).

Chlorhexidine plus usual care versus usual care alone

One RCT was identified, which recruited 17 participants, each with two leg ulcers, who acted as his or her own controls; the ulcer was the unit of randomisation (**Fumal 2002c**). Application of 5% chlorhexidine digluconate solution in addition to usual care was compared with usual care alone (defined as hydrocolloid dressing and a 'compressive bandage'—no further details were provided). Treatment duration was six weeks. Ulcers were not clinically infected at baseline. The overall risk of bias was unclear. Median time to healing as derived from Kaplan-Meier survival analysis was reported as 14 weeks (range 7 to 17 weeks) for the group receiving chlorhexidine plus usual care, and 15 weeks (range 7 to 19 weeks) for those allocated usual care alone. The trial authors described the between-group difference as not statistically significant, but the P value was not presented.

Ethacridine lactate ointment compared with placebo ointment

One multi-centre RCT (N = 253 participants) with unclear risk of bias was identified (**Geske 2005**). Participants were assigned to ethacridine lactate ointment 0.1% or placebo ointment, both applied twice daily for 28 days (**Geske 2005**). All participants received compression therapy. Treatment was provided in an outpatient setting. Baseline ulcer infection status was not reported. The number of responsive ulcers (defined as > 20% reduction in ulcer surface area) was greater in the group treated with ethacridine compared with the placebo group (RR 1.45, 95% CI 1.21 to 1.73; estimate based on all randomised participants) (Analysis 28.1). In addition, the trial authors reported that the mean reduction in ulcer surface area was 34.1% for the group receiving ethacridine lactate ointment and 24.7% for those allocated the placebo ointment (no further data or P value for the between-group difference was provided).

The proportion of participants reporting at least one adverse event was similar between groups: RR 1.06 (95% CI 0.50 to 2.22; estimate based on those who completed the trial) (Analysis 28.2) (**Geske 2005**). In terms of the types of adverse events observed, these were mainly headaches, migraines and pruritis in the group receiving ethacridine, and aches, back pain and nausea in those allocated placebo. The trial authors considered that all adverse events were unlikely to be related to trial treatments. When asked about their satisfaction with the intervention, a significantly larger proportion of participants rated their experience as 'excellent' in the ethacridine group when compared with placebo: 50% versus 17.9% (RR 2.83, 95% CI 1.85 to 4.34; estimate based on those completing the trial) (Analysis 28.3) (**Geske 2005**). The trial authors assessed quality of life using the Freiburg Quality of Life Questionnaire at baseline and at endpoint. The group receiving ethacridine achieved a median reduction in score of 0.75 points (reduction indicating improvement), whilst those treated with placebo had a median reduction of 0.3 points (statistical significance of difference not reported by trial authors and not evaluable by review authors) (**Geske 2005**).

Summary of evidence for miscellaneous topical preparations

Five RCTs recruiting 590 participants evaluated the effect of topical applications: topical antibiotics (three RCTs) and topical antiseptics (two RCTs). All had unclear risk of bias.

The comparisons involving topical antibiotics were: chloramphenicol-containing ointment versus enzymatic wound cleanser (one RCT); framycetin sulphate-containing ointment versus enzymatic wound cleanser (one RCT); chloramphenicol-containing ointment versus framycetin sulphate–containing ointment (one RCT); mupirocin versus vehicle (one RCT); and topical antibiotics according to cultures and sensitivities versus herbal ointment (one RCT). More participants healed at four weeks using an enzymatic wound cleanser when compared with a chloramphenicol-containing ointment. No other between-group differences were found in terms of healing, or for secondary outcomes (adverse effects and bacterial eradication). Two RCTs were small. One trial excluded participants with baseline ulcer infection, but in the other two there was no information about baseline ulcer infection status.

No difference was found in terms of time to healing for chlorhexidine added to usual care versus usual care alone (one small RCT); participants with infected ulcers were excluded. Another trial reported that the number of responsive ulcers (defined as > 20% reduction in ulcer surface area) was greater, and also that participant-reported satisfaction was greater, with ethacridine lactate treatment when compared with placebo. For the same trial, adverse effects were reported as similar between groups. There was no information about baseline ulcer infection.

Discussion

Summary of main results

Summary of main results for systemic antibiotics

Five RCTs reported eight comparisons involving various systemic antibiotics (Morias 1979; Alinovi 1986; Valtonen 1989; Huovinen 1994; Daroczy 2006). The only comparison in which a statistically significant between-group difference was detected in terms of healing was that in favour of levamisole (a product normally used to treat roundworm infection) when compared with placebo. This trial, in common with the other evaluations of systemic antibiotics, was small, and so the observed effect could have occurred by chance (Morias 1979). In terms of secondary outcomes, data from two RCTs revealed no difference between antibiotics and usual care for rates of bacterial eradication; those with clinically infected ulcers were excluded at baseline in one RCT (Alinovi 1986), whilst in the other, this variable was not reported (Valtonen 1989). A separate analysis suggested that those receiving placebo were less likely to develop antibiotic-resistant strains of bacteria compared with those given ciprofloxacin (Valtonen 1989; Huovinen 1994). Otherwise, few data were reported for secondary outcomes. The overall risk of bias for all RCTs in this comparison was unclear (Morias 1979; Alinovi 1986; Valtonen 1989; Huovinen 1994; Daroczy 2006). One RCT restricted participant selection to those with non-infected ulcers at baseline (Alinovi 1986), whilst the others did not clearly report the baseline ulcer infection status. Therefore it

cannot be determined from current evidence whether systemic antibiotics can promote healing in patients with clinically infected ulcers.

Summary of main results for topical antibiotics and antiseptics

The evidence for the effects of a variety of topical preparations was reviewed; this update extended the range of eligible comparisons to include evaluations of silver- and honey-based products.

Data from four RCTs pooled suggests that more participants healed at four to 12 weeks on cadexomer iodine compared with standard care: RR 2.17 (95% CI 1.30 to 3.60) (Analysis 8.1; Figure 4) (**Ormiston 1985**; **Lindsay 1986**; **Steele 1986**; **Laudanska 1988**). No between-group differences in complete healing were detected when cadexomer iodine was compared with the following: hydrocolloid dressing; paraffin gauze dressing; dextranomer; and silver-impregnated dressings. Cadexomer iodine may be associated with decreased bacterial load compared with usual care in participants with infected ulcers at baseline (**Skog 1983**). The available data suggest that more participants reported adverse events for cadexomer iodine relative to standard care (**Ormiston 1985**; **Holloway 1989**).

No between-group differences were detected in terms of complete healing when povidone-iodine was compared with paraffin gauze, moist or foam dressings given according to wound status, or growth factor (**Smith 1992**; **Ishibashi 1996**; **Casoni 2002**; **Kuznetsov 2009**). Other estimates of healing were of unknown validity (**Groenewald 1981**; **Fumal 2002a**). Few data on secondary outcomes were provided.

Four RCTs presented findings in favour of peroxide-based preparations when compared with usual care for surrogate healing outcomes (change in ulcer area) (**Beitner 1985a**; **Beitner 1985b**; **Belcaro 2003**; **Belcaro 2007**). No report described complete healing or time to healing. In two RCTs, all cases of clinical infection were resolved before randomisation (**Belcaro 2003**; **Belcaro 2007**); the other two RCTs did not report ulcer infection status at baseline (**Beitner 1985a**; **Beitner 1985b**). All four RCTs were very small, and so findings should be viewed with caution.

Pooled data from two RCTs suggested no difference between honey-based products and usual care for complete healing at 12 weeks (**Gethin 2008**; **Jull 2008**). One RCT was at low risk of bias overall and reported additional outcomes suggesting no difference in groups in terms of time to healing or health-related quality of life, however, more frequent adverse effects associated with honey. In addition, a cost-effectiveness analysis was conducted in parallel with the clinical trial and found that whilst the incremental cost-effectiveness ratio favoured honey when all costs were considered, the finding was reversed when a small number of hospitalised participants across both groups were excluded (**Jull 2008**). In terms of other secondary outcomes, no differences between groups were detected for incidence of ulcer infection (**Gethin 2008**; **Jull 2008**) or eradication of MRSA (**Gethin 2008**).

In terms of silver-based preparations, no between-group differences in complete healing were detected when 1% silver sulphadiazine ointment was compared with standard care/placebo and tripeptide copper complex; or when different brands of silver-impregnated dressings were compared; or when silver-impregnated dressings were compared with non-antimicrobial dressings. When estimates of time to healing were available, these also did not indicate a difference between groups (**Fumal 2002b**; **Michaels 2009**). However, some

shorter-term reports of surrogate healing outcomes (change in ulcer area at four weeks) favoured silver-impregnated dressings. The overall evidence suggested no difference between silver-impregnated dressings and non-antimicrobial dressings for incidence of adverse events, ulcer recurrence and changes in health-related quality of life. One RCT, at overall low risk of bias, included a rigorously conducted cost-effectiveness analysis and concluded that silver-impregnated dressings were unlikely to be cost-effective (**Michaels 2009**).

In terms of other topical antibiotics, data from one RCT suggested that more participants healed at four weeks when treated with a non-antibiotic enzymatic cleanser compared with a chloramphenicol-containing ointment (additional active ingredients were included in the ointment): RR 0.13 (95% CI 0.02 to 0.99) (Analysis 23.1) (**Fischer 1984**). No between-group differences were detected in complete healing for the following comparisons: framycetin sulphate–containing ointment versus enzymatic cleanser; chloramphenicol-containing ointment versus framycetin sulphate–containing ointment; mupirocin ointment versus vehicle; and topical antibiotics given according to antibiogram versus an herbal ointment. In terms of secondary outcomes, no between-group differences were detected for adverse events (chloramphenicol versus framycetin versus enzymatic cleanser - three-arm RCT); bacterial eradication (mupirocin versus vehicle); or changes in bacterial flora (various topical antibiotics versus herbal ointment).

Two RCTs evaluated topical antiseptics (**Fumal 2002c**; **Geske 2005**). A large German study (N = 253) found that ethacridine lotion was better than placebo in achieving greater than 20% ulcer area reduction at 28 days. Although the sample size is larger than many of the other included trials, the period of follow-up is too short for exploration of clinically meaningful outcomes (i.e. frequency of complete healing or time to complete healing), and the validity of this intermediate variable is unknown. Secondary outcomes reported for the same trial indicated that whilst no difference was noted between groups for adverse events, patient satisfaction with treatment was better for ethacridine (**Geske 2005**). No between-group difference was detected between chlorhexidine solution and usual care in terms of time to healing (**Fumal 2002c**).

Overall completeness and applicability of evidence

The role of systemic and topical antibiotics and topical antiseptics in managing venous leg ulcers remains poorly understood. Evidence suggests that these agents are widely used to manage chronic wounds, regardless of whether ulcers are clinically infected at the outset of treatment (**Lorimer 2003b**; **Howell-Jones 2005**; **Öien 2013**). Clinical and prescribing guidelines state that antimicrobial therapy should only used in cases of confirmed clinical infection (**AAWC 2010**; **SIGN 2010**; **BNF 2013**). There was considerable variation across included RCTs in reporting of baseline ulcer infection status. Of 45 RCTs included, only three provided clear statements that all included participants had clinically infected ulcers at the start of treatment (**Skog 1983**; **Daroczy 2006**; **Dimakakos 2009**). Information provided in another eight trials suggested that participants with ulcer infection would have been eligible for inclusion, but in each case the proportion with clinical infection was not described (**Ormiston 1985**; **Harcup 1986**; **Lindsay 1986**; **Steele 1986**; **Laudanska 1988**; **Holloway 1989**; **Ishibashi 1996**; **Münter 2006**). A further four RCTs (all evaluating silver-impregnated dressings) stipulated that participants had to present with signs of critical colonisation in

order to be included (Jørgensen 2005; Meaume 2005; Lazareth 2008; Miller 2010). Signs and symptoms of critical colonisation have been proposed as an alternative to the classic signs and symptoms of wound infection for assessing infection in chronic wounds (Gardner 2001; Cutting 2004). Only two RCTs mentioned assessing resolution of relevant signs and symptoms as an outcome variable, and neither provided full details (Ormiston 1985; Lazareth 2008).

A further 13 included RCTs either excluded participants with clinically infected ulcers or treated existing infections prior to randomisation (Alinovi 1986; Hansson 1998; Smith 1992; Casoni 2002; Fumal 2002a; Fumal 2002b; Fumal 2002c; Belcaro 2003; Belcaro 2007; Gethin 2008; Michaels 2009; Binić 2010; Kerihuel 2010). The remaining RCTs provided either no details, or unclear information about participants' baseline ulcer infection status (Morias 1979; Groenewald 1981; Fischer 1984; Beitner 1985a; Beitner 1985b; Kero 1987; Moss 1987; Blair 1988; Valtonen 1989; Cameron 1991; Wunderlich 1991 ;Bishop 1992; Huovinen 1994; Chaloner 2004; Geske 2005; Jull 2008; Kuznetsov 2009).

There is widespread global concern with regard to the development of antibiotic resistance, and the misuse of both systemic and topical agents (Bisht 2009; Boucher 2009; Lazarus 2011). Prescribing guidelines in the UK state that such agents should not be used with chronic wounds, such as leg ulcers, except in cases of demonstrable clinical infection, and that their prescription for bacterial colonisation is inappropriate (BNF 2013). In this review, data from two trials suggested that the emergence of antibiotic-resistant strains of bacteria occurred more often in groups receiving systemic antibiotics (ciprofloxacin) when compared with standard care or placebo (Valtonen 1989; Huovinen 1994) (Analysis 2.2). However, no difference was noted when trimethoprim was compared with placebo, or when ciprofloxacin was compared with trimethoprim, in a small, single RCT (Huovinen 1994).

The relationship between ulcer infection and wound healing is unclear. Two RCTs of systemic antibiotics included subgroup analyses to assess the impact of wound infection or bacterial colonisation on healing (Alinovi 1986; Huovinen 1994). For bacterial colonisation, one study showed a statistically significant association between positive post-treatment wound cultures and lower healing rates (Alinovi 1986), whilst the other suggested that bacterial contamination of ulcers with *Staphylococcus aureus* did not appear to delay healing (Huovinen 1994). In addition, three RCTs assessing cadexomer iodine provided an assessment of the association between bacterial colonisation and healing (Skog 1983; Moss 1987; Miller 2010). One RCT reported no difference in healing rates between silver-impregnated dressing and cadexomer iodine when bacterial growth during the first two weeks of the trial (assessed by wound swab) was classified as moderate or heavy. However, when bacterial growth was classified as nil, scant or low, those receiving silver had a significantly faster healing rate compared with those allocated cadexomer iodine in relation to leucocytes (P value < 0.01), Gram-positive bacilli (P value < 0.05), Gram-positive cocci (P value < 0.01) and Gram-negative cocci (P value < 0.05) (Miller 2010). Moss 1987 reported that eradication of *Pseudomonas* species was significantly associated with a greater reduction in mean ulcer size in both treatment groups (cadexomer iodine and dextranomer) (P value < 0.05); and Skog 1983 reported a statistically significant association between eradication of *Staphylococcus aureus* and a faster healing rate (P value < 0.002). It should be noted that the numbers used for analysis in most of these cases were small, and therefore these findings should be interpreted with caution.

In summary, the sparse evidence from RCTs recruiting participants with infected wounds, the variation in outcome assessment and the lack of clarity concerning the prognostic ability of wound infection in relation to healing, means that it is difficult to interpret the effects of antibiotics and antiseptics on both healing and infection.

Quality of the evidence

The methods of this review have now been updated to assign each included RCT an overall rating of risk of bias. Three RCTs had a low risk of bias overall (Jull 2008; Michaels 2009; Kerihuel 2010). Of the remainder, 12 were at high risk of bias, and 27 were unclear. All five RCTs evaluating systemic antibiotics had an unclear risk of bias (Morias 1979; Alinovi 1986; Valtonen 1989; Huovinen 1994; Daroczy 2006). Many RCTS were small and there were not many opportunities for pooling data because of clinical heterogeneity across trials. Whislt most RCTs reported complete healing during the trial period, the most meaningful outcome, time to healing (with appropriate methods of estimation) was conducted in few trials and we were unable to plot, or consider pooling, hazard ratio estimates. We were also unable to carry out our planned sub-group analyses and so were unable to explore differential treatment effect in: participants with, on average, larger or smaller ulcers at baseline; those with and without ulcer infection or colonisation at baseline; and those using different levels of compression as a concurrent therapy. These factors, together with short follow-up periods (mainly four to 12 weeks), hinder interpretation of much of the available evidence.

Potential biases in the review process

We were not able to generate funnel plots as planned because of the small number of RCTs in each meta-analysis. Although the search strategy was comprehensive, the effect of publication bias cannot be discounted. However, given the poor quality of most of the published evidence and the absence of treatment effects in the majority of published studies, it may be the case that inclusion of unpublished data would not add further useful information to this body of evidence.

Agreements and disagreements with other studies or reviews

Several systematic reviews evaluating antimicrobial interventions used in patients with venous leg ulcers have been published during the last 10 years (Chambers 2007; Vermeulen 2007; Lo 2009; Carter 2010; Jull 2013). Four of these reviews focused on silver-based products (Chambers 2007; Vermeulen 2007; Lo 2009; Carter 2010). One concluded that the evidence was too limited to derive firm conclusions (Chambers 2007). Another noted similar findings to our review, namely that although there was some evidence in favour of silver when shorter-term, surrogate measures of healing were considered, benefits were not maintained in terms of complete healing in the longer term (Carter 2010). A third review reported benefit of silver in relation to several outcomes (healing, reduced odour, pain, reduced exudate and dressing wear time), however, trials recruiting participants with a range of wound aetiologies were pooled, and so findings should be regarded with caution (Lo 2009). The fourth review only included RCTs of topical silver used with contaminated or infected acute or chronic wounds (including leg ulcers) and concluded that benefit of silver was not demonstrated (Vermeulen 2007). These findings are broadly in agreement with our

review. UK-based clinical guidelines for venous leg ulcers do not recommend the use of silver (SIGN 2010), however, this is contrary to US guidelines, where use of silver is endorsed (AAWC 2010). One systematic review of honey was identified (Jull 2013), which included the same two RCTs included in this review (Gethin 2008; Jull 2008), and reached similar conclusions to us (i.e. that current evidence does not show a beneficial effect of honey-based products for venous leg ulcers). We were not able to identify recent systematic reviews focusing on participants with venous leg ulcers that evaluated systemic antibiotics, topical antibiotics, or antiseptics such as iodine- or peroxide-based products.

Authors' conclusions

Implications for practice

At present, the evidence does not support the routine use of systemic antibiotics to promote healing in venous leg ulcers. However, the lack of reliable evidence means that it is not possible to recommend the discontinuation of any of the agents reviewed. There was some evidence to suggest that systemic antibiotics were associated with emergence of antibiotic-resistant micro-organisms compared with non-antibiotic treatment. Few data were available on adverse effects. Levamisole (an oral antimicrobial product normally used to treat roundworm infection) was the only systemic agent where data showed a benefit in terms of healing. Levamisole is unlicensed in the UK, and is only available from 'special order' suppliers for use in treating roundworm infection (BNF 2013). It was withdrawn from the US market in 1999. In terms of topical preparations, some evidence supports the use of cadexomer iodine. However, cadexomer iodine is associated with more frequent adverse effects than standard care. Current evidence does not support the routine use of honey- and silver-based preparations. Further good quality research is required before definitive conclusions can be made about the effectiveness of systemic antibiotics and topical preparations such as povidone-iodine, peroxide-based preparations, chloramphenicol, framycetin sulphate, mupirocin, topical antibiotics given according to antibiogram, ethacridine lactate and chlorhexidine in healing venous leg ulceration. Honey-based products and silver-impregnated dressings may not be cost-effective; otherwise, there were few reliable data on cost-effectiveness. In light of the increasing problem of bacterial resistance to antibiotics, current prescribing guidelines recommend that antibacterial preparations should be used only in cases of clinical infection, not for bacterial colonisation (BNF 2013).

Implications for research

Most of the trials were small, and most of the evidence was of high or unclear risk of bias. Much of the research requires replication in larger, well-designed studies. Future research should pay attention to the following: clearly defined participant selection criteria, particularly with reference to baseline infection and colonisation of wounds, sample size with sufficient power to detect true treatment effects, use of true randomisation with allocation concealment, measures to help ensure comparability of treatment arms at baseline (e.g. stratification for ulcer size and ulcer duration), blinded outcome assessment, use of objective outcome measurement and appropriate methods for data analysis (e.g. complete healing rates and survival analysis using appropriate methods of estimation) and use of the intention-to-treat protocol.

Further research is required to clarify the relationship between healing and infection, colonisation, and critical colonisation of ulcers and to clarify these definitions in terms of chronic wounds. Attention should also be paid to the potential development of resistance to antimicrobial agents, and follow-up should include an assessment of this. The cost-effectiveness of both systemic and topical antimicrobials needs to be established, taking into account the patterns of healing and recurrence that can occur with chronic wounds.

Future studies should make inclusion and exclusion criteria clear with reference to infection and colonisation of wounds. In trials in which the presence of infection does not exclude patients, numbers of participants with and without the clinical signs of infection should be reported at baseline, and groups should be comparable for infection rates and types.

Acknowledgements

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Data and analyses

Download statistical data

Comparison 1. Systemic antibiotic given according to sensitivities versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 3 weeks	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.22, 1.72]
2 Complete healing—eventual, assessment point not stated	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.66, 1.25]
3 Bacterial eradication	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.6 [0.61, 4.19]

Comparison 2. Ciprofloxacin versus standard care/placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	2	50	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.57, 5.30]
2 Emergence of antibiotic-resistant strains	2	48	Risk Ratio (M-H, Fixed, 95% CI)	8.65 [1.76, 42.60]
3 Bacterial eradication	1	26	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.38, 18.67]

Comparison 3. Ciprofloxacin versus trimethoprim

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.46, 5.09]
2 Emergence of antibiotic-resistant strains	1	21	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.54, 1.84]

Comparison 4. Trimethoprim versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.23, 3.63]
2 Emergence of antibiotic-resistant strains	1	19	Risk Ratio (M-H, Fixed, 95% CI)	6.67 [0.98, 45.29]

Comparison 5. Amoxicillin plus compression verus povidone-iodine alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.95, 2.02]

Comparison 6. Amoxicillin plus compression verus povidone-iodine plus compression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.39]

Comparison 7. Levamisole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	59	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.06, 1.62]

Comparison 8. Cadexomer iodine versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing at 4 to 12 weeks	4	212	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.30, 3.60]
2 Adverse events	2	134	Risk Ratio (M-H, Fixed, 95% CI)	4.59 [1.40, 15.05]

Comparison 9. Cadexomer iodine versus dextranomer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.3 [0.55, 3.09]

Comparison 10. Cadexomer iodine versus hydrocolloid dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	104	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.48, 3.91]

Comparison 11. Cadexomer iodine versus paraffin gauze

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	105	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.39, 2.56]

Comparison 12. Cadexomer iodine dressing versus silver dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	281	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.19]
2 Participant satisfaction	1	207	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.89, 1.06]

Comparison 13. Povidone-iodine plus sugar versus growth factor

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing at 4 weeks	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.22, 1.52]

Comparison 14. Povidone-iodine plus compression versus hydrocolloid plus compression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.23]

Comparison 15. Povidone-iodine plus compression versus moist or foam dressings plus compression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 weeks	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.75]

Comparison 16. Peroxide-based topical preparation versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage ulcer area remaining	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 10% benzoyl peroxide dressing vs normal saline dressing	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 20% benzoyl peroxide dressing vs normal saline dressing	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 17. Honey products versus alternatives

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 12 weeks	2	476	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.96, 1.38]
2 Incidence of ulcer infection during the 12-week trial period	2	476	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.49, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Participants with MRSA eradication at 4 weeks	1	16	Risk Ratio (M-H, Fixed, 95% CI)	4.2 [0.67, 26.30]
4 Participants reporting at least 1 adverse event	1	368	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.05, 1.56]

Comparison 18. 1% silver sulphadiazine cream versus placebo cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 weeks	1	61	Risk Ratio (M-H, Fixed, 95% CI)	5.81 [0.74, 45.40]

Comparison 19. 1% silver sulphadiazine cream versus 0.4% tripeptide copper complex cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 weeks	1	63	Risk Ratio (M-H, Fixed, 95% CI)	13.41 [0.79, 228.32]

Comparison 20. 1% silver sulphadiazine cream versus non-adherent dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 12 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]

Comparison 21. Silver dressing (Avance) versus silver dressing (Acticoat 7)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 12 weeks	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.68, 3.00]

Comparison 22. Silver dressing versus non-antimicrobial dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 to 12 weeks	4	424	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.95, 1.45]
2 Complete healing at 6 months	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.96, 1.28]
3 Complete healing at 12 months	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.94, 1.16]
4 Ulcer recurrence within first year	1	185	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.70]
5 Change in ulcer surface area (cm squared) at 4 weeks	2	170	Mean Difference (IV, Fixed, 95% CI)	-4.70 [-8.46, -0.94]
6 Change in ulcer surface area (%) at 4 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Healing rate (cm squared per day)	2	170	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.28, 0.03]
8 Proportion of participants reporting any type of adverse event	4	706	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.36, 1.33]

Comparison 23. Chloramphenicol-containing ointment versus enzymatic cleanser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 weeks	1	177	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.99]
2 Participants discontinuing treatment because of ineffectiveness or allergy	1	177	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.52, 7.84]

Comparison 24. Framycetin sulphate-containing ointment versus enzymatic cleanser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 weeks	1	170		

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
			Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.23, 2.01]
2 Participants discontinuing treatment because of ineffectiveness or allergy	1	170	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.80, 10.67]

Comparison 25. Chloramphenicol-containing ointment versus framycetin sulphate-containing ointment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 4 weeks	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.02, 1.54]
2 Participants discontinuing treatment because of ineffectiveness or allergy	1	169	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.25, 1.90]

Comparison 26. Mupirocin versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of complete healing	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.56, 2.35]
2 Eradication of gram-positive bacteria	1	10	Risk Ratio (M-H, Fixed, 95% CI)	11.0 [0.77, 158.01]

Comparison 27. Topical antibiotics versus herbal ointment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete healing at 7 weeks	1	32	Risk Ratio (M-H, Fixed, 95% CI)	4.44 [0.23, 85.83]
2 Participants with bacterial eradication at 7 weeks	1	32	Risk Ratio (M-H, Fixed, 95% CI)	8.0 [0.47, 137.35]

Comparison 28. Ethacridine lactate versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of responsive ulcers	1	253	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.21, 1.73]
2 Participants reporting at least 1 adverse event	1	241	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.50, 2.22]
3 Participant satisfaction (treatment rated as excellent)	1	241	Risk Ratio (M-H, Fixed, 95% CI)	2.83 [1.85, 4.34]

Appendices

Appendix 1. Search methods used in the first update of this review 2009

Electronic searches

For this update the following electronic databases were searched for all relevant studies, regardless of language, date of publication or publication status:

Cochrane Wounds Group Specialised Register (searched 24/09/09)
The Cochrane Central Register of Controlled Trials (CENTRAL) - *The Cochrane Library* Issue 3 2009
Ovid MEDLINE - 1950 to September Week 3 2009
Ovid EMBASE - 1980 to 2009 Week 38
EBSCO CINAHL - 1982 to September Week 3 2009

The following shows the search strategy used with CENTRAL:

#1 MeSH descriptor Anti-Infective Agents explode all trees
#2 MeSH descriptor Penicillins explode all trees
#3 MeSH descriptor Cephalosporins explode all trees
#4 MeSH descriptor Aminoglycosides explode all trees
#5 MeSH descriptor Quinolones explode all trees
#6 MeSH descriptor Clindamycin explode all trees
#7 MeSH descriptor Metronidazole explode all trees
#8 MeSH descriptor Trimethoprim explode all trees
#9 MeSH descriptor Mupirocin explode all trees
#10 MeSH descriptor Neomycin explode all trees
#11 MeSH descriptor Fusidic Acid explode all trees
#12 MeSH descriptor Framycetin explode all trees
#13 MeSH descriptor Polymyxins explode all trees
#14 MeSH descriptor Chlortetracycline explode all trees
#15 (antibiotic* or antimicrobial* or antibacterial* or penicillin* or cephalosporin* or aminoglycoside* or quinolone* or clindamycin or metronidazole or trimethoprim or

mupirocin or "pseudomonic acid" or neomycin or "fusidic acid" or framycetin or polymyxin* or chlortetracycline):ti,ab,kw
#16 MeSH descriptor Antisepsis explode all trees
#17 antiseptic*:ti,ab,kw
#18 MeSH descriptor Soaps explode all trees
#19 MeSH descriptor Iodophors explode all trees
#20 MeSH descriptor Chlorhexidine explode all trees
#21 MeSH descriptor Alcohols explode all trees
#22 MeSH descriptor Hydrogen Peroxide explode all trees
#23 MeSH descriptor Benzoyl Peroxide explode all trees
#24 MeSH descriptor Gentian Violet explode all trees
#25 MeSH descriptor Hypochlorous Acid explode all trees
#26 MeSH descriptor Hexachlorophene explode all trees
#27 MeSH descriptor Potassium Permanganate explode all trees
#28 MeSH descriptor Silver explode all trees
#29 MeSH descriptor Silver Sulfadiazine explode all trees
#30 (“soap” or “soaps” or iodophor* or povidone or iodine or chlorhexidine or betadine or “alcohol” or disinfectant* or "hydrogen peroxide" or "benzoyl peroxide" or "gentian violet" or hypochlorit* or eusol or dakin* or hexachlorophene or benzalkonium or "potassium permanganate" or "silver sulfadiazine" or "silver sulphadiazine"):ti,ab,kw
#31 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
#32 MeSH descriptor Leg Ulcer explode all trees
#33 (varicose NEXT ulcer*) or (venous NEXT ulcer*) or (leg NEXT ulcer*) or (foot NEXT ulcer*) or (stasis NEXT ulcer*) or ((lower NEXT extremit*) NEAR/2 ulcer*) or (crural NEXT ulcer*):ti,ab,kw
#34 (#32 OR #33)
#35 (#31 AND #34)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL can be found in Appendix 2, Appendix 3 and Appendix 4 respectively. The Ovid MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. The EMBASE and CINAHL searches were combined with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).

Searching other resources

The reference lists of included studies and review articles were examined to identify additional references for both the original review and the update.

Appendix 2. Ovid MEDLINE search strategy

1 exp Anti-Infective Agents/ (614173)
2 exp Penicillins/ (16923)
3 exp Cephalosporins/ (12724)

4 exp Aminoglycosides/ (48702)
5 exp Quinolones/ (22074)
6 exp Clindamycin/ (2024)
7 exp Metronidazole/ (4816)
8 exp Trimethoprim/ (3822)
9 exp Mupirocin/ (640)
10 exp Neomycin/ (1890)
11 exp Fusidic Acid/ (473)
12 exp Framycetin/ (166)
13 exp Polymyxins/ (2141)
14 exp Chlortetracycline/ (351)
15 (antibiotic$ or antimicrobial$ or antibacterial$ or penicillin$ or cephalosporin$ or aminoglycoside$ or quinolone$ or clindamycin or metronidazole or trimethoprim or mupirocin or pseudomonic acid or neomycin or fusidic acid or framycetin or polymyxin$ or chlortetracycline).ti,ab. (191275)
16 exp Antisepsis/ (710)
17 antiseptic$.ti,ab. (2623)
18 exp Soaps/ (697)
19 exp Iodophors/ (1188)
20 exp Chlorhexidine/ (3330)
21 exp Alcohols/ (210358)
22 exp Hydrogen Peroxide/ (28460)
23 exp Benzoyl Peroxide/ (498)
24 exp Gentian Violet/ (991)
25 exp Hypochlorous Acid/ (3254)
26 exp Hexachlorophene/ (30)
27 exp Potassium Permanganate/ (526)
28 exp Silver/ (7101)
29 exp Silver Sulfadiazine/ (434)
30 exp Honey/ (1518)
31 (soap$1 or iodophor$ or povidone or iodine or chlorhexidine or betadine or alcohol$1 or disinfectant$ or hydrogen peroxide or benzoyl peroxide or gentian violet or hypochlorit$ or eusol or dakin$ or hexachlorophene or benzalkonium or potassium permanganate or silver sulfadiazine or silver sulphadiazine or honey$).ti,ab. (159344)
32 or/1-31 (982110)
33 exp Leg Ulcer/ (10032)
34 (varicose ulcer$ or venous ulcer$ or leg ulcer$ or stasis ulcer$ or (lower extremit$ adj ulcer$) or crural ulcer$ or ulcus cruris).ti,ab. (3777)
35 or/33-34 (10770)
36 32 and 35 (1383)
37 randomized controlled trial.pt. (248241)
38 controlled clinical trial.pt. (40205)
39 randomized.ab. (202576)
40 placebo.ab. (93758)
41 clinical trials as topic.sh. (81126)
42 randomly.ab. (139357)

43 trial.ti. (75545)
44 or/37-43 (560427)
45 (animals not (humans and animals)).sh. (1653788)
46 44 not 45 (509737)
47 36 and 46 (165)

Appendix 3. Ovid EMBASE search strategy

1 exp Antiinfective Agent/ (1364874)
2 exp Penicillin G/ (33954)
3 exp Cephalosporin/ (10924)
4 exp Aminoglycoside/ (7100)
5 exp Quinolone/ (2425)
6 exp Clindamycin/ (23558)
7 exp Metronidazole/ (31416)
8 exp Trimethoprim/ (8460)
9 exp Pseudomonic Acid/ (3886)
10 exp Neomycin/ (7156)
11 exp Fusidic Acid/ (3695)
12 exp Framycetin/ (597)
13 exp Polymyxin/ (1362)
14 exp Chlortetracycline/ (1375)
15 (antibiotic$ or antimicrobial$ or antibacterial$ or penicillin$ or cephalosporin$ or aminoglycoside$ or quinolone$ or clindamycin or metronidazole or trimethoprim or mupirocin or neomycin or fusidic acid or framycetin or polymyxin$ or chlortetracycline).ti,ab. (285818)
16 exp antisepsis/ (1455)
17 antiseptic$.ti,ab. (4015)
18 exp Soap/ (2050)
19 exp Iodophor/ (205)
20 exp Chlorhexidine/ (7046)
21 exp Alcohol/ (106780)
22 exp Hydrogen Peroxide/ (47414)
23 exp Benzoyl Peroxide/ (2117)
24 exp Gentian Violet/ (2153)
25 exp Hypochlorous Acid/ (1376)
26 exp Hexachlorophene/ (470)
27 exp Potassium Permanganate/ (1499)
28 exp Silver/ (17835)
29 exp Silver Sulfadiazine/ (1903)
30 exp Honey/ (2797)
31 (soap$1 or iodophor$ or povidone or iodine or chlorhexidine or betadine or alcohol$1 or disinfectant$ or hydrogen peroxide or benzoyl peroxide or gentian violet or hypochlorit$ or eusol or dakin$ or hexachlorophene or benzalkonium or potassium permanganate or silver sulfadiazine or silver sulphadiazine or honey$).ti,ab. (242236)
32 or/1-31 (1667271)

33 exp Leg Ulcer/ (6146)
34 (varicose ulcer$ or venous ulcer$ or leg ulcer$ or stasis ulcer$ or (lower extremit$ adj ulcer$) or crural ulcer$ or ulcus cruris).ti,ab. (5715)
35 or/33-34 (8168)
36 32 and 35 (1624)
37 exp Clinical trial/ (803713)
38 Randomized controlled trial/ (291695)
39 Randomization/ (51287)
40 Single blind procedure/ (15938)
41 Double blind procedure/ (87430)
42 Crossover procedure/ (32553)
43 Placebo/ (170444)
44 Randomi?ed controlled trial$.tw. (83428)
45 RCT.tw. (11057)
46 Random allocation.tw. (935)
47 Randomly allocated.tw. (14665)
48 Allocated randomly.tw. (1229)
49 (allocated adj2 random).tw. (266)
50 Single blind$.tw. (9924)
51 Double blind$.tw. (92426)
52 ((treble or triple) adj blind$).tw. (248)
53 Placebo$.tw. (140784)
54 Prospective study/ (208229)
55 or/37-54 (1111238)
56 Case study/ (17028)
57 Case report.tw. (171644)
58 Abstract report/ or letter/ (521196)
59 or/56-58 (705463)
60 55 not 59 (1082630)
61 animal/ (732590)
62 human/ (8857186)
63 61 not 62 (490450)
64 60 not 63 (1059985)
65 36 and 64 (317)

Appendix 4. EBSCO CINAHL search strategy

S30 S26 and S29
S29 S27 or S28
S28 TI (varicose ulcer* or venous ulcer* or leg ulcer or stasis ulcer* or crural ulcer* or cruris) or AB (varicose ulcer* or venous ulcer* or leg ulcer* or stasis ulcer* or crural ulcer* or cruris)
S27 (MH "Leg Ulcer+")
S26 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25
S25 TI (soap* or iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol*

or disinfectant* or hydrogen peroxide or benzoyl peroxide or gentian violet or hypochlorit* or eusol or dakin* or hexachlorophene or benzalkonium or potassium permanganate or silver sulfadiazine or silver sulphadiazine or honey*) or AB (soap* or iodophor* or povidone or iodine or chlorhexidine or betadine or alcohol* or disinfectant* or hydrogen peroxide or benzoyl peroxide or gentian violet or hypochlorit* or eusol or dakin* or hexachlorophene or benzalkonium or potassium permanganate or silver sulfadiazine or silver sulphadiazine or honey*)
S24 (MH "Honey")
S23 (MH "Silver Sulfadiazine")
S22 (MH "Silver")
S21 (MH "Hexachlorophene")
S20 (MH "Gentian Violet")
S19 (MH "Hydrogen Peroxide")
S18 (MH "Alcohols+")
S17 (MH "Chlorhexidine")
S16 (MH "Povidone-Iodine")
S15 (MH "Iodine")
S14 (MH "Soaps")
S13 TI antiseptic*
S12 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11
S11 TI (antibiotic* or antimicrobial* or antibacterial* or penicillin* or cephalosporin* or aminoglycoside* or quinolone* or clindamycin or metronidazole or trimethoprim or mupirocin or pseudomonic acid or neomycin or fusidic acid or framycetin or polymyxin* or chlortetracycline) or AB (antibiotic* or antimicrobial* or antibacterial* or penicillin* or cephalosporin* or aminoglycoside* or quinolone* or clindamycin or metronidazole or trimethoprim or mupirocin or pseudomonic acid or neomycin or fusidic acid or framycetin or polymyxin* or chlortetracycline)
S10 (MH "Polymyxins+")
S9 (MH "Neomycin")
S8 (MH "Mupirocin")
S7 (MH "Trimethoprim+")
S6 (MH "Metronidazole")
S5 (MH "Clindamycin")
S4 (MH "Aminoglycosides+")
S3 (MH "Cephalosporins+")
S2 (MH "Penicillins+")
S1 (MH "Antiinfective Agents+")

Appendix 5. Risk of bias criteria

The following descriptions of risk of bias criteria are paraphrased from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

1. Adequacy of the sequence generation (randomisation)

Low risk: adequate sequence generation was reported using methods such as random number tables, computerised random number generator, dice throwing, coin tossing or dealing previously shuffled cards.

High risk: a system involving alternation, date of birth, date of presentation or case record number was used for the allocation of participants. Such studies were considered as quasi-randomised and were excluded from the review.

Unclear risk: study authors did not describe one of the adequate methods but mentioned randomisation.

2. Adequacy of allocation concealment

Low risk: a group allocation method was described that would not allow an investigator or a participant to know or influence allocation to an intervention group up to and including the point of randomisation. Adequate methods include central randomisation by a third party and serially numbered, opaque, sealed envelopes that have been opened sequentially, once the envelope has been irreversibly assigned to the participant.

High risk: group allocation methods such as alternation, date of birth, date of presentation or case record number cannot be adequately concealed. A classification of high risk may also be given if reference is made to the use of unsealed envelopes, or if information in the trial report indicates that investigators or participants could have known or influenced group allocation.

Unclear risk: the trial report mentioned randomisation or allocation concealment, but no information on the methods used was provided.

3. Blinding of participants

Low risk: explicit statement that participants were blind or inclusion of any information in the trial report suggests that participants were not aware of treatment allocation.

High risk: explicit statement indicates that participants were not blind to treatment allocation.

Unclear risk: terms such as 'open' or 'double-blind' are used with no further explanation or with no reference at all to blinding of participants.

4. Blinding of outcome assessors

Low risk: explicit statement that outcome assessors were blind or inclusion of any information in the trial report suggests that outcome assessors were not aware of treatment allocation.

High risk: explicit statement indicates that outcome assessors were not blind to treatment allocation.

Unclear risk: terms such as 'open' or 'double-blind' are used with no further explanation or with no reference at all to blinding of outcome assessors.

5. Incomplete outcome data addressed (description of withdrawals)

Low risk: numbers of withdrawals per group are provided, together with reasons; or it is clear from the report that no withdrawals occurred.

High risk: some withdrawal is evident or mentioned, but numbers per group, or reasons, or both, are not provided.

Unclear risk: trial report is unclear about whether any withdrawals occurred.

6. Incomplete outcome data addressed (withdrawal rate acceptable)

Low risk: RCT report states that withdrawal rate did not exceed 20% per treatment group; or outcome data are missing in all treatment groups, but reasons are reported and balanced across groups (and therefore are unlikely to be related to treatment); or it is clear that no withdrawals occurred.

High risk: RCT report states that withdrawal rate exceeded 20% in at least one treatment group; or differential proportions of incomplete outcome data across groups are likely to be related to treatment outcome; or, even if incomplete outcome data are balanced in numbers across groups, reasons for missing outcomes differ.

Unclear risk: withdrawal rates are not reported.

7. Incomplete outcome data addressed (use of intention-to-treat (ITT) analysis)

We defined ITT analysis as analysis conducted when all trial participants were analysed in the group to which they were randomly assigned, regardless of which (or how much of) treatment they actually received, and regardless of other protocol irregularities, such as ineligibility.

Low risk: RCT report stated that ITT was undertaken, and this was confirmed on study assessment, or it was not stated but it was evident from study assessment that ITT was undertaken.

High risk: ITT was not confirmed on study assessment (participants who were randomly assigned were not included in the analysis because they did not receive the study intervention, they withdrew from the study or they were not included because of protocol violation), regardless of whether the analysis was described as ITT. Analyses described as 'as treated' or 'per protocol' or similar, unless the numbers of switches or missing data are too small to reveal any important difference in the estimated treatment effect.

Unclear risk: analysis is described as ITT, but this cannot be confirmed on study assessment, or it is not reported and cannot be confirmed by study assessment. ITT is not done, but a small number of participants are excluded from the analysis, and it is difficult to judge the impact of this on estimates of treatment effect, particularly in smaller trials.

8. Comparability at baseline

Findings from prognostic studies have suggested that the two most important predictors of delayed healing in participants with venous leg ulceration are baseline ulcer duration and wound surface area; participants with larger and more chronic wounds are more likely to experience longer times to healing (Margolis 2000; Margolis 2004). In addition, the presence

of infection may impede healing (Doughty 2007). Data on ulcer area and duration are likely to be positively skewed, with large proportions of people having smaller ulcers and wounds of relatively short duration at the start of treatment. Therefore it is much easier to make a meaningful assessment of baseline data if median values with interquartile ranges are provided for these variables. When mean values are reported, it is difficult to interpret the data and to decide whether any observed between-group differences are clinically important. When imbalances occur, primary investigators should attempt to adjust for the pertinent variables in their analyses. Responses to this assessment criterion were as follows:

Low risk: groups appeared to be similar at baseline for ulcer infection status, ulcer duration and surface area (with median values and interquartile ranges reported for duration and area); or differences were observed but were adjusted for in the analysis.

High risk: group imbalance was observed at baseline for ulcer infection status, ulcer duration or surface area, and no adjustment was made.

Unclear risk: information on one or more predictive variables was not provided, or the information was difficult to interpret (e.g. only mean values provided for ulcer area/duration).

What's new

Date	Event	Description
9 January 2014	Amended	minor text amendment
10 September 2013	New citation required and conclusions have changed	Conclusions updated, additional review authors joined the team.
10 September 2013	New search has been performed	Second update, new search; 18 trials added (Fischer 1984; Blair 1988; Wunderlich 1991; Bishop 1992; Fumal 2002b; Chaloner 2004; Jørgensen 2005; Meaume 2005; Münter 2006; Gethin 2008; Jull 2008; Lazareth 2008; Dimakakos 2009; Kuznetsov 2009; Michaels 2009; Binić 2010; Kerihuel 2010; Miller 2010).

History

Protocol first published: Issue 2, 2002
Review first published: Issue 1, 2008

Date	Event	Description
11 August 2010	Amended	Declaration of interest and sources of support amended

Date	Event	Description
4 November 2009	New search has been performed	New search, 3 additional studies included, 14 studies added to the Table of excluded studies, 2 studies awaiting assessment. No change to conclusions. Risk of bias table added.
4 November 2009	New citation required but conclusions have not changed	Additional author joined the review team
11 November 2008	Amended	Contact details updated
18 June 2008	Amended	Converted to new review format.
12 November 2007	New citation required and conclusions have changed	Substantive amendment

Contributions of authors

Susan O'Meara: drafted the protocol, initial review and both updates; screened studies for inclusion (initial review and both updates); checked data extraction and risk of bias assessment for all studies included in the initial review and both updates; analysed and interpreted data (initial review and both updates).
Deyaa Al-Kurdi: screened studies for inclusion; extracted data; undertook risk of bias assessment and analyses; drafted the review (all in relation to the initial review).
Yemisi Ologun: screened studies for inclusion and extracted data for included studies; undertook risk of bias assessment for all studies and contributed to the draft update (all in relation to the first update).
Liza G Ovington: commented on the protocol and review; screened studies for inclusion (all in relation to the initial review).
Marrissa Martyn-St James: screened studies for inclusion; extracted data; undertook assessment of risk of bias; analysed data; contributed to drafting the review (all in relation to the second update).
Rachel Richardson: screened studies for inclusion in the second update, commented on the text of this update and reviewed the peer referee feedback.
Susan O'Meara is the guarantor for the review.

Contribution of editorial base

Nicky Cullum: advised, edited and approved the original review and the first update and approved them for submission.
Andrea Nelson, Editor: approved the second update for submission.
Sally Bell-Syer: coordinated the editorial process, advised, commented and edited all versions of the review.
Ruth Foxlee: designed and ran the searches for the review and the updates.

Declarations of interest

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Liza G Ovington is an employee of Ethicon, USA. This company does not have any commercial products that are considered in this review.

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- NIHR Programme Grants for Applied Research, UK.
- NIHR/Department of Health (England), Cochrane Wounds Group, UK.

Characteristics of studies

Characteristics of included studies [ordered by study ID]

Alinovi 1986

Methods	Randomised controlled trial conducted in Italy. Some details of sample size estimation described but unclear whether this was a priori
Participants	48 people with 56 venous leg ulcers randomly assigned: Group 1: 24 people/26 legs Group 2: 24 people/30 legs Mean ± SD baseline ulcer size, cm^2: Group 1 completers (24 people/26 legs): 12.5 ± 14.4 Group 2 completers (23 people/29 legs): 14.1 ± 15.9 Mean ± SD baseline ulcer duration (months): Group 1 completers: 11.7 ± 12.6

	Group 2 completers: 10.4 ± 8.9 Patients with clinically infected ulcers were excluded from the trial, but all included patients had wounds with positive bacterial cultures
Interventions	1. Bed rest, and standard treatment of merbromin 2% solution applied to ulcer surface. Betamethasone dipropionate 0.05% cream applied to rest of leg, zinc oxide and ichthammol–impregnated gauze bandage wrapped around the leg and elastic support bandage applied from toes to knee. The bandage remained in place for 20 days 2. Bed rest with standard treatment and a 10-day course of systemic antibiotics (co-trimoxazole, gentamicin or amikacin according to sensitivity)
Outcomes	After 20 days: Complete healing: 1. 7/26 (27%) 2. 5/30 (17%) Following the 20-day treatment period, participants whose ulcers had not healed were treated with bandages alone (further details of bandages not provided). Eventual rates of complete healing reported as follows (assessment point not stated): 1. 20/26 (77%) 2. 21/30 (70%) Mean percentage decrease in ulcer area: 1. 57.2 ± 29.3 2. 61.6 ± 25.8 The trial authors reported the between-group difference as not statistically significant (P value 0.56) Secondary outcomes: Bacterial eradication 1. 5/24 2. 8/24 Relationship between ulcer healing and bacteriological results in people with positive pretreatment culture, excluding healed ulcers: mean percentage decrease in ulcer area (persistent bacterial colonisation) 1. 44.8 ± 31.8 (n = 19) 2. 42.1 ± 11.9 (n = 24) Mean percentage decrease in ulcer area (eradicated bacterial colonisation) 1. 70.8 ± 19.4 (n = 19) 2. 76.6 ± 13.6 (n = 24) The trial authors reported that within-group differences for change in ulcer area between those with persistent bacterial colonisation and eradication were statistically significant (P value 0.04 for Group 1; and P value 0.00003 for Group 2)
Notes	Bacterial culture: *Staphylococcus aureus:* 25.4%; *Pseudomonas aeruginosa:* 18.2%; B-haemolytic strep: 14.5% Withdrawals: Group 1: 0 Group 2: intolerant of compression bandage (1) Total = 1 Unit of analysis:

	Some participants had multiple leg ulcers studied, but this did not appear to have been accounted for in the trialists' analyses

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Reported that "patients were.....randomly allocated." It was not reported how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	"randomisation was by sealed envelope", but it was not reported whether the envelopes were opaque or sequentially numbered
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	Not reported that those allocated to standard treatment only were given placebo
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No details about who performed the outcome assessment or how it was performed
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	One withdrawal from Group 2 because could not tolerate compression bandage
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	No withdrawals from Group 1; 1/24 (4%) withdrew from Group 2
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Participant withdrew from intervention Group 2 because could not tolerate bandage and was "excluded from analysis". It is unlikely that exclusion of one participant from the analysis had an important impact on estimates of treatment effect
Baseline factors comparable	Unclear risk	Mean values reported for ulcer size and ulcer duration (these variables are often skewed), and so difficult to judge comparability

Beitner 1985a

Methods

	Randomised controlled trial conducted in Sweden. Each participant had 2 leg ulcers each and acted as his or her own control. Ulcers were the unit of randomisation
Participants	10 participants (20 ulcers) were recruited. There were no details of baseline characteristics, including ulcer infection status
Interventions	Interventions were applied to 10 participants with 2 leg ulcers each, acting as his or her own control. For each participant, one ulcer was treated with 10% benzoyl peroxide lotion and the other with normal saline solution. For both ulcers, treatment was applied by moistening a sterile sponge compress, cut to the exact shape of the ulcer, with the respective solution. The sponge dressings were then covered with a thick pad and kept in place with a gauze stocking. The ulcer margins were protected with zinc ointment, and a supporting elastic bandage was applied. Dressings were changed 3 times a week for 42 days
Outcomes	Mean ± SD percentage ulcer area remaining at 42 days: Normal saline solution 94.7% ± 12.7% 10% benzoyl peroxide lotion 64.3% ± 14.0% Adverse effects: 3 participants reported severe irritation from use of 10% benzoyl peroxide lotion. No information about adverse effects for ulcers treated with the normal saline solution
Notes	3 participants withdrew; it was not stated whether withdrawal was related to adverse effects (severe irritation from use of 10% benzoyl peroxide lotion). This trial report described 3 separate RCTs recruiting 31 participants in total. All participants had 2 leg ulcers each and acted as his or her own control. One other RCT was included (Beitner 1985b) and the other was excluded (Beitner 1985c).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The ulcer chosen for BPO treatment was randomised according to left or right leg and most distal or proximal location. When ulcers were situated at the same level, medial or lateral localization was randomised" Comment: the sequence generation method was not stated
Allocation concealment (selection bias)	High risk	Quote: "the randomisation and treatment was given in the day care unit by personnel not involved in the evaluation of results" Comment: the information provided suggests that group allocation was likely to be unconcealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: no information provided

Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "the randomisation and treatment was given in the day care unit by personnel not involved in the evaluation of results" Comment: no statement that outcome assessors were blind to treatment allocation
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: clearly stated that 3 participants withdrew, and reasons provided
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Comment: 3/10 (30%) participants withdrew
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Comment: no information provided
Baseline factors comparable	Unclear risk	Comment: no information provided on baseline characteristics of participants/ulcers in each group

Beitner 1985b

Methods	Randomised controlled trial conducted in Sweden. Each participant had 2 leg ulcers each and acted as his or her own control. Ulcers were the unit of randomisation
Participants	10 participants (20 ulcers) were recruited. There were no details of baseline characteristics, including ulcer infection status
Interventions	Interventions were applied to 10 participants with 2 leg ulcers each, acting as his or her own control. For each participant, one ulcer was treated with 20% benzoyl peroxide lotion and the other with normal saline solution. For both ulcers, treatment was applied by moistening a sterile sponge compress, cut to the exact shape of the ulcer, with the respective solution. The sponge dressings were then covered with a thick pad and kept in place with a gauze stocking. The ulcer margins were protected with zinc ointment, and a supporting elastic bandage was applied. Dressings were changed 3 times a week for 42 days
Outcomes	Mean ± SD percentage ulcer area remaining at 42 days: Normal saline solution 93.7% ± 15.2% 20% benzoyl peroxide lotion 59.6% ± 12.3% Adverse effects: No information provided for either treatment

Notes	There were no withdrawals. This trial report described 3 separate RCTs recruiting 31 participants in total. All participants had 2 leg ulcers each and acted as his or her own control. One other RCT was included (Beitner 1985a) and the other was excluded (Beitner 1985c).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The ulcer chosen for BPO treatment was randomised according to left or right leg and most distal or proximal location. When ulcers were situated at the same level, medial or lateral localization was randomised" Comment: the sequence generation method was not stated
Allocation concealment (selection bias)	High risk	Quote: "the randomisation and treatment was given in the day care unit by personnel not involved in the evaluation of results" Comment: the information provided suggests that group allocation was likely to be unconcealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "the randomisation and treatment was given in the day care unit by personnel not involved in the evaluation of results" Comment: Comment: no statement that outcome assessors were blind to treatment allocation
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: it was clear that there were no withdrawals
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Comment: it was clear that there were no withdrawals
Incomplete outcome data	Low risk	

(attrition bias) ITT analysis		Comment: it was clear that there were no withdrawals, and the review authors assume that all randomised participants were included in the analysis
Baseline factors comparable	Unclear risk	Comment: no information provided on baseline characteristics of participants/ulcers in each group

Belcaro 2003

Methods	Randomised controlled trial conducted in Italy	
Participants	20 people with venous ulceration with minimum and maximum ulcer diameters > 2 cm and < 5 cm Group 1: 10 Group 2: 10 Mean ± SD baseline ulcer area (cm^2): Group 1: 3.98 ± 0.4; Group 2: 3.76 ± 0.4 Mean ± SD baseline ulcer duration (months): Group 1: 2.9 ± 2.0; Group 2: 2.5 ± 1.0 All participants were treated with systemic antibiotics for 15 to 20 days before the start of trial treatment to resolve clinical infection	
Interventions	1. The lower limb and the area of ulceration were cleaned with water and neutral soap; skin was dried with tissue paper; 2 g of placebo cream was applied to the ulcerated area and surrounding skin, and compression below-knee stockings were applied 2. 2 g hydrogen peroxide cream 1% was used instead of placebo	
Outcomes	After 10 days, median decrease in ulcerated area: 1. 11% 2. 35% (P value < 0.05) Mean percentage ulcer area remaining: 1. 89% 2. 65% (P value < 0.05) Improvement in microcirculatory parameters was significant in Group 2 No adverse effects reported	
Notes	No information given about withdrawals	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"the effects of a new compound (Crystacide) were assessed in a randomised controlled study"; it was not stated how the sequence was generated
	Unclear risk	No information given

Allocation concealment (selection bias)		
Blinding (performance bias and detection bias) Participant blinded to the intervention	Low risk	The trial authors stated that participants in Group 1 received the same treatment and that: "A placebo cream, comparable in aspect and density to Crystacide, was used. The creams were given to patients in containers without labels"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information given
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	No mention of dropouts or withdrawals
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	No information given
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	No exclusions described
Baseline factors comparable	Unclear risk	Mean values appear to have been reported for ulcer size and ulcer duration, and so difficult to judge comparability

Belcaro 2007

Methods	Randomised controlled trial conducted in Italy
Participants	32 people with venous ulceration with ulcer diameter > 2 cm and < 4 cm Group 1: 14 Group 2: 18 Mean ± SD baseline ulcer area (cm^2): Group 1: 3.5 ± 0.8; Group 2: 3.3 ± 0.6 Mean ± SD baseline ulcer duration (months): Group 1: 1.2 ± 0.3; Group 2: 1.1 ± 0.2 All participants were treated with systemic antibiotics for 2 weeks before the start of trial treatment to resolve clinical infection
Interventions	1. The lower limb and the area of ulceration were cleaned with water and neutral soap; skin was dried with tissue paper; 2 g of placebo cream was applied to the ulcerated area and surrounding skin and compression below-knee stockings were applied 2. 2 g hydrogen peroxide cream 1% was used instead of placebo

Outcomes	After 10 days, median decrease in ulcerated area: 1.32% 2. 44.8% P value < 0.005 Improvements in microcirculatory parameters were significant in Group 2
Notes	No information given about withdrawals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information from author suggested randomised sequence
Allocation concealment (selection bias)	Unclear risk	No information given about how assignment to treatment groups was concealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	Low risk	A placebo cream comparable in aspect and density with crystacide was used. The creams were given to participants in containers without labels
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information given about blinding the outcome assessor to intervention
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	No mention of withdrawals
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	No information given
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	No information given
Baseline factors comparable	Unclear risk	Mean values appear to have been reported for ulcer size and ulcer duration, and so difficult to judge comparability

Binić 2010

Methods	Randomised controlled trial (pilot study) conducted in Serbia
Participants	32 people with venous leg ulcers ≤ 10 cm^2 of not longer than 2 months' duration Group 1: 15 people Group 2: 17 people Information given by the trial authors suggested that some people had more than one ulcer, but full details not provided Mean ± SD baseline ulcer size (cm^2): Group 1: 6.7 ± 1.09; Group 2: 7.04 ± 1.37 Mean ± SD (range) baseline ulcer duration (weeks): Group 1: 5.80 ± 2.66 (2.3 to 8); Group 2: 5.53 ± 1.95 (1.8 to 8) Those with ulcers with signs of clinical infection at baseline were excluded. All ulcers of included patients showed signs of contamination or colonisation from swab, without signs of ulcer infection or systemic infection. All participants had at least one micro-organism identified at baseline, the most frequent isolates being *Staphylococcus aureus* and *Pseudomonas aeruginosa*
Interventions	1. Topical antibiotics applied to ulcers, selected according to antibiogram results and including gentamicin, chloramphenicol 5%, enbecin, povidone-iodine 2%, metronidazole and fusidic acid. Antiexudative, anti-inflammatory and disinfectant wet dressing bandages applied (further details of these interventions not provided) 2. Plantoderm ointment applied to ulcers and Fitoven gel applied to skin on lower leg and peri-ulcer area Plantoderm ointment contains extracts of *Calendula officinalis* (marigold), *Symphytum officinale* (comfrey), *Achillea millefolium* (yarrow) and *Salvia officinalis* (sage), and is described by the trial authors as having antimicrobial properties. Fitoven gel contains extracts of *Aesculus hippocastanum* (horse chestnut), *Melilotus officinalis* (yellow sweet clover), *Rosmarinus* (rosemary) and *Lavandula* (lavender) All participants received the following: ulcer cleansing with sterile saline solution or sterile boric acid 3%; debridement using scissors and tweezers; routine dressings (not specified further, but excluding hydrocolloid, foam, alginate and hydrogel dressings); and routine bandages (no further details provided). Compression was not used in any participant (confirmed through correspondence with trial authors). All participants were treated twice daily, with dressings removed and reapplied each time to reapply the study treatments. The treatment duration was 7 weeks Some information about intervention regimens was confirmed through contact with the trial authors
Outcomes	At 7 weeks: Number of participants with healed ulcers (data confirmed by trial authors): 1. 0/15 (0%) 2. 2/17 (12%) Mean % change in ulcer surface area: 1. -35.65% 2. -42.68% Secondary outcomes at 7 weeks: Number of participants with bacterial eradication of ulcer:

	1. 0/15 (0%) 2. 4/17 (24%) Number of participants with at least one bacterial isolate: 1. 15/15 (100%) 2. 13/17 (76%) Number of participants with more than 1 bacterial isolate: Group 1: 6/15 (40%) Group 2: 3/17 (18%) Most of the isolates in both groups were *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* Adverse effects: 1. 1/15 (7%) (small increment of the ulcerated area). 2. 0/17 (0%) No details were provided defining what adverse effects were monitored, nor methods of monitoring used
Notes	No information about withdrawals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The study was opened, randomised and controlled". Report contains no statement regarding generation of random number sequence
Allocation concealment (selection bias)	Unclear risk	"The study was opened, randomised and controlled". Report contains no statement regarding allocation process
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Report describes study as "open" with no further details
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Report describes study as "open" with no further details
Incomplete outcome data	Low risk	Although no statement, it appears from the report that all randomly assigned participants completed the trial

(attrition bias) Drop out rate described		
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Although no statement, it appears from the report that all randomly assigned participants completed the trial
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Although no statement, it appears from the report that all randomly assigned participants completed the trial
Baseline factors comparable	Low risk	Patients with non-infected venous leg ulcers with surface area ≤ 10 cm^2 and ulcer duration not longer than 2 months were recruited. Ulcer area and duration appear comparable between groups

Bishop 1992

Methods	Randomised controlled trial (2 centres) conducted in the USA
Participants	93 participants randomly assigned, with venous stasis ulcers 3 cm^2 to 50 cm^2 in size, of at least 3 months' duration Group 1: 30 participants Group 2: 31 participants Group 3: 32 participants Mean baseline ulcer size of completers, cm^2 ± SD (median): Group 1: 9.6 ± 8.1 (6.2) Group 2: 11.9 ± 11.2 (6.9) Group 3: 9.9 ± 8.5 (6.5) Mean baseline ulcer duration of completers, months ± SD (median): Group 1: n = 29, 38.0 ± 88.7 (12.0) Group 2: n = 28, 44.1 ± 58.0 (19.0) Group 3: n = 29, 57.1 ± 94.9 (11.0) Patients with > 10^5 bacteria/gram ulcer tissue (confirmed by tissue biopsy) were excluded, as were those with systemic sepsis or bone infection
Interventions	Group 1: Placebo (topical preparation comprising petroleum-based cream, vehicle of preparation used for Group 3) Group 2: Topical preparation comprising 1% silver sulphadiazine cream Group 3: Topical preparation comprising 0.4% tripeptide copper complex cream All participants received ulcer cleansing with normal saline and compression; and were instructed to apply treatment daily followed by nonadherent dressing and elastic wrap, and to keep the affected limb elevated when sitting. The treatment duration was 4 weeks

Outcomes	Numbers (%) of participants with ulcers healed at week 4: Group 1: 1/30 (3) Group 2: 6/31 (19) Group 3: 0/32 (0) Numbers (%) of participants whose ulcers remained healed after 1 year, having received no further topical treatment, just elastic support: Group 1: 1/1 (100) Group 2: 5/6 (83) Group 3: 0/0 (0) Mean percentage change in ulcer size % ± SE at week 4: Group 1: -22.5 ± 10.2 Group 2: -44.0 ± 8.21 Group 3; -18.7 ± 9.07 Secondary outcomes: No microbiological outcomes reported Adverse events: The trial authors reported no statistically significant between-group differences for burning, itching, pain or oedema observed (numbers of participants and P values not provided). Only placebo group complained of pain, itching or burning after 15 days. On a scale of 0 to 3+, all mean scores were less than 1+ (direction and administration of scale not explained)
Notes	Withdrawals Group 1: 1/30 (3%) Group 2: 3/31 (10%) (2 were immediate withdrawals) Group 3: 3/32 (9%) (1 was an immediate withdrawal) Apart from the information about immediate withdrawals, other information, including reasons for withdrawal, was not provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients...were stratified by lesion size and randomly assigned to one of three treatment groups". No information regarding sequence generation reported
Allocation concealment (selection bias)	Unclear risk	"Patients meeting the inclusion criteria and completing an informed consent form were stratified by lesion size and randomly assigned to one of three treatment groups". No information regarding allocation concealment reported
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information regarding blinding of participants reported

Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Low risk	"Before evaluation, all medication was removed and the ulcer cleaned to keep the evaluator blinded"
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Numbers of withdrawals reported per treatment arm but reasons not provided
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Withdrawals: Group 1: 1/30 (3%) Group 2: 3/31 (10%) Group 1: 3/32 (9%) Overall withdrawal rate 8%; 86/93 (92%) completed the study
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Per protocol, "eighty-six were evaluable for efficacy". It is unclear how these withdrawals might have impacted estimates of treatment effect (this is a small RCT)
Baseline factors comparable	High risk	On the basis of median values, Group 2 (1% silver sulphadiazine) included participants with longer ulcer duration, on average, than the other groups. Treatment groups appear comparable in terms of ulcer area

Blair 1988

Methods	Randomised, controlled trial conducted in the UK. 2 separate trials are reported in the paper; only 1 is relevant to this review
Participants	60 ulcers, with surface area up to 10 cm^2 were randomly assigned: Group 1: 30 ulcers Group 2: 30 ulcers Initial mean ulcer surface area cm^2 ± SEM: Group 1: 3.8 ± 0.6; Group 2: 3.4 ± 0.5 Ulcer duration (described as time since ulcer last healed), mean months ± SEM: Group 1: 27.8 ± 3.4; Group 2: 33.4 ± 4.1 All ulcers were initially contaminated, with 80% of wounds growing more than one organism. Most common organisms were *Staphylococcus aureus* (73% of ulcers) and beta-haemolytic *Streptococcus* (35% of ulcers). Data not presented by group
Interventions	Group 1: non-adherent dressing Group 2: silver sulphadiazine cream (Flamazine, Smith & Nephew) All participants received ulcer cleansing with saline; four-layer compression bandaging designed to provide 42 mmHg initial ankle pressure; weekly change of

	dressings and bandages at outpatient venous leg ulcer clinic. The treatment duration was 12 weeks
Outcomes	Numbers (%) of ulcers healed at 12 weeks: Group 1: 24/30 (80) Group 2: 19/30 (63) Mean % healing rate per week first 6 weeks: Group 1: -12.8% Group 2: -11.0% Mean % healing rate per week last 6 weeks: Group 1: -2.5% Group 2: -1.7% Secondary outcomes: Adverse effects: Group 1: 1 participant developed cellulitis (not stated whether treatment was stopped) Group 2: 4 participants—treatment stopped because of erythema and pruritis. 2 participants developed cellulitis (not stated whether treatment stopped) In participants with cellulitis from both groups, the predominant organism was beta-haemolytic *Streptococcus* , Lancefield group G Microbial outcomes: In both groups, bacterial contaminants were continued throughout the study (monitored by fortnightly swabs), with only 3 ulcers having no bacterial growth at any stage during the trial (group not stated)
Notes	The units of randomisation and analysis are not clear (whether ulcers or participants) Apart from the 4 participants in Group 2 who stopped treatment because of adverse effects, no information was presented about withdrawals; it is not clear whether these participants were included in all analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Ulcers were cleaned with saline and the dressing applied according to randomization using a sequential system of sealed envelopes with treatment allocation by random number table"
Allocation concealment (selection bias)	Unclear risk	"Ulcers were cleaned with saline and the dressing applied according to randomization using a sequential system of sealed envelopes with treatment allocation by random number table" No statement whether envelopes were opaque or not
Blinding (performance bias and detection bias)	Unclear risk	No information on blinding of participants reported

Participant blinded to the intervention		
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information on blinding of outcome assessors reported
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	No information on withdrawals reported
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	No information on withdrawals reported
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	No information on withdrawals reported. Apart from the 4 participants in Group 2 who stopped treatment because of adverse effects, no information was presented about withdrawals; it is not clear whether these participants were included in all analyses
Baseline factors comparable	Low risk	Ulcer size and duration at baseline appear comparable between groups (inclusion criteria for ulcer size < 10 cm^2—this will have restricted variation in size)

Cameron 1991

Methods	Randomised controlled trial conducted in the UK
Participants	30 people with venous leg ulcers: Group 1: 15 Group 2: 15 Mean baseline ulcer area (cm^2—variability data not reported): Group 1: 17.3. Group 2: 16.3 Mean (range) baseline ulcer duration: Group 1: 6 years (1 month to 36 years); Group 2: 2.7 years (6 months to 9 years) 5 participants in each group had Gram-positive bacteria present in their wounds at baseline. There was no report of signs and symptoms of clinical infection.
Interventions	1. White soft paraffin tulle gras and compression therapy 2. Mupirocin-impregnated tulle gras and compression therapy
Outcomes	After 12 weeks complete healing: 1. 46% 2. 53%

	Mean percentage change in ulcer area: 1. 68% 2. 50% Eradication of Gram-positive bacteria 1. 0/5 2. 5/5	
Notes	No withdrawals reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomised into 2 treatment groups" Comment: It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomised into 2 treatment groups" Comment: allocation concealment was not mentioned
Blinding (performance bias and detection bias) Participant blinded to the intervention	Low risk	Quote: "The study was a randomised double-blind placebo controlled pilot study"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "The study was a randomised double blind placebo controlled pilot study" Comment: It was not stated that outcome assessors were blinded
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	30 patients were recruited; no withdrawals were reported
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	Withdrawal rate was not described
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Method of analysis not described
Baseline factors comparable	High risk	The ulcers in Group 1 had longer mean duration than those in Group 2 (2.7 years versus 6 years)

Casoni 2002

Methods	Randomised controlled trial conducted in Italy
Participants	74 participants with vascular leg ulcers (information from author: ABPI had to be at least 0.6 for patient to be included; some patients had leg ulcers of mixed arterial/venous aetiology): Group 1: 22 participants Group 2: 26 participants Group 3: 26 participants Mean ± SD [range] baseline ulcer area (mm^2): Group 1: 162 ± 167 [40 to 810]; Group 2: 202 ± 140 [40 to 650]; Group 3: 180 ± 117 [60 to 560] Median (interquartile range) baseline ulcer area (mm^2—read from box plot): Group 1: 125 (90, 170); Group 2: 170 (90, 300); Group 3: 150 (125, 220) Median (interquartile range) baseline ulcer duration (months—read from box plot): Group 1: 10.5 (6, 24); Group 2: 7 (4, 12.5); Group 3: 7 (3, 8) Participants in all groups received systemic antibiotics as necessary before trial treatment
Interventions	All participants received the following interventions 2 weeks before trial treatment: compression, local antiseptics and systemic antibiotics in cases of proven infection Trial treatments: Group 1: non-adherent, paraffin gauze (Vaseline) dressing plus compression Group 2: hyaluronic acid and povidone-iodine dressing plus compression Group 3: hydrocolloid dressing plus compression Trial dressings and bandages were changed weekly. Compression could be in the form of Unna's boot; multilayer bandages; or stockings plus elastic bandage (removed at night)
Outcomes	At 3 months—median percentage area reduction/25th percentile (read from box plot): Group 1: 90%/65% Group 2: 100%/90% Group 3: 100%/80%
Notes	In terms of the median percentage area reduction—no data are available on those whose ulcers enlarged during the trial, the box plot shows only those with area reduction; full interquartile ranges are not shown No information given about withdrawals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: Patients were "randomised in three groups" Comment: no information about methods for generating sequence
	Unclear risk	Quote: Patients were "randomised in three groups"

Allocation concealment (selection bias)		Comment: no mention of allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information provided
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	No information provided
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	No information provided
Baseline factors comparable	High risk	Ulcers in Group 2 were larger than those in the other groups. Ulcer in Group 1 were of longer during than those in the other groups.

Chaloner 2004

Methods	Randomised controlled trial conducted in the UK
Participants	40 patients with chronic venous leg ulcers recruited from 3 centres within primary care setting: Group 1: 20 participants Group 2: 20 participants Median ulcer duration, weeks (range): 52 (6 weeks to 20 years), breakdown per group not provided Median ulcer area, cm^2 (range): 4.9 (0.9 to 196.1), breakdown per group not provided The available information suggests that all participants had bacterial colonisation of ulcers at baseline, but not stated whether any were clinically infected
Interventions	Group 1: silver-impregnated polyurethane foam dressing (Avance)

	Group 2: 5-layer silver impregnated dressing comprising two layers of an absorbent inner core sandwiched between three layers of silver-coated, low-adherent polyethylene net (Acticoat 7) All participants received four-layer compression bandage (Profore), providing 40 mmHg at the ankle Duration of treatment was 12 weeks unless the ulcer healed before this time
Outcomes	Number (%) of ulcers healed at 12 weeks: Group 1: 7/20 (35) Group 2: 10/20 (50) Median percentage (%) change in ulcer area at 12 weeks: Group 1: -80.4% Group 2: -95.1% The trial authors reported that the between-group difference was not statistically significant but did not provide the P value Seondary outcomes: The trial authors reported that there was a greater reduction in the total number of bacteria (colony forming units per cm^2) in Group 2 compared with Group 1, but the between-group difference was not statistically significant (data and P value not provided) The trial authors reported that more pathogenic bacterial groups were eliminated in Group 2 compared with Group 1, including *Staphylococcus aureus,* beta-haemolytic streptococci, anaerobes and coliforms. No further data or P values were provided Adverse events at 12 weeks: The trial authors reported that a higher proportion of participants in Group 2 reported no pain from the study ulcer and a healthy condition of the peri-ulcer skin compared with Group 1
Notes	Data were extracted from a conference poster and abstract, and further details were confirmed through correspondence with the study author. A full report was not available Microbiological analysis (bacterial counts and bacterial identification) was by wound swabs taken at 0, 2, 4, 8 and 12 weeks. No details of techniques used were provided The median baseline value in ulcer duration as recorded above was taken from the conference abstract (52 weeks); the conference poster reported a different value (34.7 weeks) In the conference abstract, the trial authors reported: "the rate of healing was on average 16.8% faster" in Group 2 compared with Group 1, but did not explain how this statistic was estimated; also, contradictory information was given in the poster, which suggested that participants in Group 1 healed faster, on average Withdrawals (available from a brief interim report only): Group 1: 2 participants withdrew because of adverse events (further details not provided) Group 2: no information provided
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation achieved using computer-generated programme (confirmed through email communication with trial author)
Allocation concealment (selection bias)	Unclear risk	"A prospective, multi-centre, randomised, comparative study to compare the effects of Acticoat 7 antimicrobial barrier dressing to Avance silver impregnated foam film dressing in the treatment of chronic venous leg ulcers" Comment: no details of allocation concealment reported
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information on participant blinding reported
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information on outcome assessor blinding reported
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	"In the Avance group.....2 patients had been withdrawn due to adverse reactions" Comment: The above information was taken from a brief, interim report. No information on withdrawals was provided in relation to the Acticoat 7 group, and no information was available for either group at the final analysis
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	"In the Avance group.....2 patients had been withdrawn due to adverse reactions" Comment: The above information was taken from a brief, interim report. No information on withdrawals was provided in relation to the Acticoat 7 group, and no information was available for either group at the final analysis
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	From conference abstract: "Results from 40 patients have demonstrated" From conference poster: "The primary analysis could only be conducted on 18 (45%) patients who had a baseline bacteria count and at least one post baseline bacteria count" Comment: no statement as to whether analysis conducted per protocol or according to intention-to-treat
Baseline factors comparable	Unclear risk	Baseline participant characteristics were not presented per group

Daroczy 2006

Methods	Randomised controlled trial conducted in Hungary
Participants	63 people with ulcerated stasis dermatitis due to deep venous reflux, of < 5 cm 'size' Group 1: 21 Group 2: 21 Group 3: 21 No information provided on baseline characteristics such as ulcer area and ulcer duration. Ulcers were described as infected, but no further details provided, and not clear if this referred to baseline status or incidence during the trial treatment.
Interventions	1. Povidone-iodine with compression 2. Amoxicillin (dose, route and frequency of administration not stated) with compression 3. Povidone-iodine without compression The treatment duration was 12 weeks
Outcomes	After 12 weeks complete healing: 1. 82% 2. 85% 3. 62% 5 months after conclusion of trial: relapse of superficial bacterial infection: 1. 11% 2. 32% 3. 11%
Notes	No withdrawals mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"A total of 63 patients were enrolled in this prospective randomised controlled study." It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No mention of this in the paper
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information given
	Unclear risk	No information given

Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention		
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	No withdrawals or dropouts reported
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	No withdrawals or dropouts reported
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	No information given about mode of analysis
Baseline factors comparable	Unclear risk	Not sufficient information in tables to illustrate baseline characteristics

Dimakakos 2009

Methods	Randomised controlled trial conducted in Greece
Participants	42 participants with venous leg ulcers that were classified as exclusively infected: Group 1: 21 participants Group 2: 21 participants Initial ulcer diameter: Group 1: < 1 cm, n = 3; 1 to 2 cm, n = 4; 2 to 3 cm, n = 5; 3 to 4 cm, n = 5; > 4 cm, n = 4 Group 2: < 1 cm, n = 2; 1 to 2 cm, n = 5; 2 to 3 cm, n = 4; 3 to 4 cm, n = 7; > 4 cm, n = 3 Initial ulcer depth: Group 1: < 0.5 cm, n = 16; > 0.5 cm, n = 5 Group 2: < 0.5 cm, n = 14; > 0.5 cm, n = 7 Number of (%) participants with ulcer duration > 1 month: Group 1: 14/21 (67) Group 2: 12/21 (57) Number of participants with initial ulcer pain (assessed with VAS where 0 = no pain, < 4 = mild pain, 4 to 7 = moderate pain, > 7 = severe pain, and 10 = worst imaginable pain): Group 1: severe, n = 5; moderate, n = 8; none/mild, n = 8 Group 2: severe, n = 5; moderate, n = 11; none/mild, n = 5 Number of participants with *Staphylococcus aureus* identified from swab: Group 1: 4/21

	Group 2: 9/21 Number of participants with *Pseudomonas aeruginosa* identified from swab: Group 1: 5/21 Group 2: 7/21 *Escherichia coli, Staphylococcus capitis, Enterococcus* species and other bacteria were also present in some participants in both groups Number of participants with >1 wound isolate: Group 1: 13/21 Group 2: 11/21 All ulcers were infected and had clinical signs of inflammation
Interventions	Group 1: non-adhesive foam (Biatain) Group 2: non-adhesive silver-releasing foam (Contreet Ag) All participants received wound cleansing using sterile water and a 10% povidone-iodine solution; short stretch bandage as compression therapy; twice-weekly dressing changes; and antibiotics if wound cultures were positive Treatment duration was 9 weeks
Outcomes	Numbers (%) of ulcers healed at 9 weeks: Group 1: 10/21 (48) Group 2: 17/21 (81) Number of ulcers healed at 3/4/5/6/7/8/9 weeks: Group 1: 2/1/1/1/0/2/3 Group 2: 2/3/3/2/1/2/4 Secondary outcomes: Adverse events: The trial authors reported that none of the participants experienced systemic or local side effects that could be attributed to the treatments, but no further details were provided Pain: Group 1: 1/5 participants with severe pain and 3/8 participants with moderate pain were pain-free at 4 weeks. Moderate pain persisted in 4 participants until the end of the nine weeks. 13/21 participants were pain-free by the end of the study Group 2: 2/5 participants with severe pain and 8/11 participants with moderate pain were pain-free at 3 weeks. 21/21 participants were pain-free by week 8. No microbiological outcomes were reported
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Forty-two patients were included in the study and were randomised into two groups"

		Comment: No information was reported on the method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	"Forty-two patients were included in the study and were randomised into two groups" Comment: No information was reported on the method of allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information reported on participant blinding
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information reported on assessor blinding
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: It appears that all randomly assigned participants completed the study
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Comment: It appears that all randomly assigned participants completed the study
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Comment: It appears that all randomly assigned participants completed the study
Baseline factors comparable	Unclear risk	Comment: Categorical data were provided for baseline ulcer diameter and depth, and groups appeared comparable. The only information regarding baseline ulcer duration was the number of participants in each group with ulcers > 1 month duration

Fischer 1984

Methods	Randomised controlled trial (multi-centre, involving 6 hospitals in Germany, 1 hospital in Austria and 1 phlebology practice in Switzerland)
Participants	258 participants randomly assigned, with venous leg ulcers 3 cm to 10 cm in diameter Group 1: 89 participants Group 2: 88 participants Group 3: 81 participants

Interventions	Group 1: non-antibiotic enzymatic cleanser - topical preparation comprising 1 unit bovine fibrinolysin to 666 units desoxyribonuclease in a water-free basic ointment (Fribolan) Group 2: enzymatic cleanser with added antibiotic - topical preparation comprising 0.6 units clostridiopeptidase A to 10 mg chloramphenicol in a lipophilic water-free basic ointment (no proprietary name provided) Group 3: enzymatic cleanser with added antibiotic - topical preparation comprising 20 units trypsin to 20 mg framycetin sulphate in water-soluble basic ointment (no proprietary name provided) All participants received compression bandages, according to the standard practice of each hospital. Wound cleansing was standardised across study groups (but not specified). No information regarding the frequency of dressing changes was reported Treatment was discontinued in the following instances: after complete ulcer healing; if there were complications or allergies ('complications' not defined); or if no improvement was noted after 7 days ('no improvement' not defined) Although not specifically reported, treatment duration appears to be 28 days
Outcomes	Numbers (%) of participants healed (translated as treatment discontinued because of rapid healing; assessment point not clear but could be 28 days): Group 1: 8/89 (9) Group 2: 1/88 (1) Group 3: 5/81 (6) Secondary outcomes: Adverse events: Numbers (%) of participants who discontinued treatment because of ineffectiveness (not defined) or allergy: Group 1: 3/89 (3) Group 2: 6/88 (7) Group 3: 8/81 (10)
Notes	Paper translated from German Clinical examinations were undertaken at baseline and at days 4, 7, 14 and 28

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The allocation of preparations was carried out with a random criteria" (translated from German) Comment: no statement on methods used to generate the randomisation sequence
Allocation concealment (selection bias)	Unclear risk	"The allocation of preparations was carried out with a random criteria" (translated from German) Comment: no statement regarding the group allocation process

Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Described as "open trial" (translated from German) Comment: no further information provided about blinding participants
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Described as "open trial" (translated from German) Comment: no further information provided about blinding outcome assessors
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Comment: The study reports treatment discontinuation because of ineffectiveness or allergy per group. Unclear if other withdrawals occurred
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	Comment: The study reports treatment discontinuation because of ineffectiveness or allergy per group. No reporting on other withdrawals
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Comment: no information reported on whether the analyses were conducted on a per-protocol or intention-to-treat basis; however, it appears that all randomly assigned participants were included in the analyses
Baseline factors comparable	Unclear risk	Comment: Although the study reported specific inclusion criteria for ulcer size (leg ulcers 3 cm to 10 cm diameter), no data per group are reported for baseline ulcer size or duration

Fumal 2002a

Methods	Randomised controlled trial conducted in Belgium. Each participant had 2 leg ulcers each and acted as his or her own control. Ulcers were the unit of randomisation
Participants	17 participants (34 ulcers) were recruited. The minimum ulcer size was 16 cm^2. Other information about baseline ulcer area and ulcer duration was not presented. Wounds were not clinically infected at baseline
Interventions	Interventions were applied to 17 participants with 2 leg ulcers each, acting as his or her own control. One ulcer was managed with usual treatment consisting of hydrocolloid dressing and compression (described as a 'compressive bandage' - no further details provided). The other ulcer was treated with 10% povidone-iodine solution applied underneath usual treatment. All dressings and bandages were changed three times per week.
Outcomes	Median (range) time to healing in weeks, estimated from Kaplan-Meier survival curves: Usual treatment alone 18 (11 to 24) 10% povidone-iodine and usual treatment 11 (9 to 17)

	The trial authors reported P value < 0.01 (log rank test) for the difference between treatments Median (range) healing rate at 6 weeks (assessed using a healing index, see notes below for method of calculation - higher value means better outcome): Usual treatment alone 6.8 (3.9 to 13.2) 10% povidone-iodine and usual treatment 10.2 (4.4 to 16.0) The trial authors reported P value < 0.01 for the difference between treatments
Notes	There was no information about withdrawals. Healing index = $DA[P(t0)]^{-1}$ where: A = Area; P = Perimeter; DA = Differential Area = equal to baseline area minus follow-up area; t0 = baseline. This trial report described 3 separate RCTs recruiting 51 participants in total. All participants had 2 leg ulcers each and acted as his or her own control. The other 2 RCTs are included in the review and described under Fumal 2002b and Fumal 2002c.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At entry in the study the two target ulcers in each patient were randomly assigned to receive one of the two treatment modalities" Comment: It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Comment: No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Quote: "51 patients were enrolled in this open study" Comment: The 51 patients refers to all 3 RCTs reported in this paper, of which 17 were included in this RCT. There was no clear statement about participants being blind to intervention
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "51 patients were enrolled in this open study" Comment: The 51 patients refers to all 3 RCTs reported in this paper, of which 17 were included in this RCT. There was no clear statement about outcome assessors being blind to intervention
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Comment: No information provided

Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	Comment: No information provided
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Comment: No information provided
Baseline factors comparable	Unclear risk	No clear description of baseline characteristics of participants in each group

Fumal 2002b

Methods	Randomised controlled trial conducted in Belgium. Each participant had two leg ulcers and acted as his or her own control. Ulcers were the unit of randomisation
Participants	17 participants (34 ulcers) were recruited. The minimum ulcer size was 16 cm^2. Other information about baseline ulcer area and ulcer duration was not presented. Wounds were not clinically infected at baseline
Interventions	Interventions were applied to 17 participants with 2 leg ulcers each, acting as his or her own control. One ulcer was managed with usual treatment consisting of hydrocolloid dressing and compression (described as a 'compressive bandage' - no further details provided). The other ulcer was treated with 1% silver sulphadiazine cream applied underneath usual treatment. All dressings and bandages were changed three times per week.
Outcomes	Median (range) time to healing in weeks, estimated from Kaplan-Meier survival curves: Usual treatment alone 16 (9 to 22) 1% silver sulphadiazine and usual treatment 15 (7 to 23) The trial authors reported that the difference between treatments was not statistically significant, but no P value was presented Median (range) healing rate at 6 weeks (assessed using a healing index, see notes below for method of calculation - higher value means better outcome): Usual treatment alone 7.2 (3.4 to 13.6) 1% silver sulphadiazine &and usual treatment 7.5 (3.6 to 14.3) The trial authors reported that the difference between treatments was not statistically significant, but no P value was presented
Notes	There was no information about withdrawals. Healing index = $DA[P(t0)]^{-1}$ where: A = Area; P = Perimeter; DA = Differential Area = equal to baseline area minus follow-up area; t0 = baseline. This trial report described 3 separate RCTs recruiting 51 participants in total. All participants had 2 leg ulcers each and acted as his or her own control. The other 2 RCTs are included in the review and described under Fumal 2002a and Fumal 2002c.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At entry in the study the two target ulcers in each patient were randomly assigned to receive one of the two treatment modalities" Comment: It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Comment: No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Quote: "51 patients were enrolled in this open study" Comment: The 51 patients refers to all 3 RCTs reported in this paper, of which 17 were included in this RCT. There was no clear statement about participants being blind to intervention
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "51 patients were enrolled in this open study" Comment: The 51 patients refers to all 3 RCTs reported in this paper, of which 17 were included in this RCT. There was no clear statement about outcome assessors being blind to intervention
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Comment: No information provided
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	Comment: No information provided
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Comment: No information provided
Baseline factors comparable	Unclear risk	No clear description of baseline characteristics of participants in each group

Fumal 2002c

Methods	Randomised controlled trial conducted in Belgium. Each participant had two leg ulcers and acted as his or her own control. Ulcers were the unit of randomisation
Participants	17 participants (34 ulcers) were recruited. The minimum ulcer size was 16 cm^2. Other information about baseline ulcer area and ulcer duration was not presented. Wounds were not clinically infected at baseline
Interventions	Interventions were applied to 17 participants with 2 leg ulcers each, acting as his or her own control. One ulcer was managed with usual treatment consisting of hydrocolloid dressing and compression (described as a 'compressive bandage' - no further details provided). The other ulcer was treated with 5% chlorhexidine digluconate solution applied underneath usual treatment. All dressings and bandages were changed three times per week.
Outcomes	Median (range) time to healing in weeks, estimated from Kaplan-Meier survival curves: Usual treatment alone 15 (7 to 19) 5% chlorhexidine digluconate solution and usual treatment 14 (7 to 17) The trial authors reported that the difference between treatments was not statistically significant, but no P value was presented Median (range) healing rate at 6 weeks (assessed using a healing index, see notes below for method of calculation - higher value means better outcome): Usual treatment alone 7.3 (4.0 to 11.9) 5% chlorhexidine digluconate solution and usual treatment 7.6 (4.1 to 12.4) The trial authors reported that the difference between treatments was not statistically significant, but no P value was presented
Notes	There was no information about withdrawals. Healing index = $DA[P(t0)]^{-1}$ where: A = Area; P = Perimeter; DA = Differential Area = equal to baseline area minus follow-up area; t0 = baseline. This trial report described 3 separate RCTs recruiting 51 participants in total. All participants had 2 leg ulcers each and acted as his or her own control. The other 2 RCTs are included in the review and described under Fumal 2002a and Fumal 2002b.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At entry in the study the two target ulcers in each patient were randomly assigned to receive one of the two treatment modalities" Comment: It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Comment: No information provided
	Unclear risk	Quote: "51 patients were enrolled in this open study"

Blinding (performance bias and detection bias) Participant blinded to the intervention		Comment: The 51 patients refers to all 3 RCTs reported in this paper, of which 17 were included in this RCT. There was no clear statement about participants being blind to intervention
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "51 patients were enrolled in this open study" Comment: The 51 patients refers to all 3 RCTs reported in this paper, of which 17 were included in this RCT. There was no clear statement about outcome assessors being blind to intervention
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Comment: No information provided
Incomplete outcome data (attrition bias) Drop out rate acceptable	Unclear risk	Comment: No information provided
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Comment: No information provided
Baseline factors comparable	Unclear risk	No clear description of baseline characteristics of participants in each group

Geske 2005

Methods	Randomised controlled trial conducted in Germany
Participants	253 people with venous leg ulcers were randomly assigned (241 completed the trial and were analysed per protocol) 1. 124 randomly assigned, 119 completed 2. 129 randomly assigned, 122 completed Median baseline ulcer area (cm^2): Group 1: 7.28; Group 2: 9.3 (ranges not reported) Median baseline ulcer duration (months): Group 1: 6.12; Group 2: 6.73 (ranges not reported) Patients with ulcers infected with MRSA were excluded from the trial, but otherwise it was unclear whether wounds were clinically infected at baseline
Interventions	

	1. Ulcer treated with placebo preparation in the same fashion, plus compression therapy 2. Ulcer treated with 0.1% ethacridine lactate ointment for 30 minutes twice daily for 28 days, plus compression therapy
Outcomes	After 28 days—response indicated by > 20% decrease in ulcer surface area Number of responders 1. 69/124 (56%) 2. 104/129 (81%) Median decrease in ulcer surface area 1. 7.2 ± 18.17 points 2. 12.7 ± 17.43 points NB: It is unclear what the 'points' refer to; also unclear whether the variance data refer to standard deviation or a different statistic Mean decrease in ulcer surface area 1. 24.7% 2. 34.1% Subjective outcomes: Effectiveness of treatment rated as 'excellent' by physician 1. 13.6% 2. 55.7% Effectiveness of treatment rated as 'excellent' by participant 1. 17.9% 2. 50% Secondary outcomes: Quality of life according to the Freiburg Quality of Life Questionnaire Mean points reduced (reduction = improved quality) 1. 0.3 points 2. 0.75 points Numbers (%) of participants experiencing at least one adverse event (total number of adverse events and description): 1. 12/119 (10.1%) (12 participants reported a total of 16 adverse events, mostly aches/back pain and nausea) 2. 13/122 (10.7%) (13 participants reported a total of 21 adverse events, classed as mild to moderate—headaches/migraines and pruritis) The trial authors reported that all adverse events were unlikely to be related to treatment. Two cases of serious adverse events were noted (hip operation and erysipelas), both considered unrelated to treatment (unclear which treatment group these related to)
Notes	Withdrawals: 1. 5/124 (4%) 2. 7/129 (5%) Reasons for withdrawal (unclear which group these relate to): discontinued therapy (5); beyond inclusion criteria (6); serious adverse event (unrelated to treatment) (1) Total = 12 Paper was published in German; data were extracted by a translator
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"We carried out a randomised placebo controlled clinical study"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information provided
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	253 participants were randomly assigned, of whom 12 were classed as withdrawals (5 discontinued therapy before trial end, 6 were ineligible, 1 suffered serious adverse event)
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	In Group 1: 5/124 (4%) withdrew; and in Group 2: 7/129 (5%) withdrew
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	241 of 253 randomly assigned participants were analysed per protocol. No mention of ITT analysis. It is unclear how these withdrawals might have impacted estimates of treatment effect
Baseline factors comparable	Unclear risk	Limited data presented on baseline characteristics

Gethin 2008

Methods	Randomised controlled trial conducted in Ireland (pragmatic, multicentre involving 10 study centres). A priori sample size estimation determined that 156 participants were required to show a 20% difference between treatments for the primary outcomes (healing and desloughing) at a 5% two-sided significance level, but only 108 participants were recruited because of slower than expected recruitment rates
Participants	108 participants with venous leg ulcers < 100 cm^2 with ≥ 50% wound area covered in slough Group 1: 54 participants

	Group 2: 54 participants Mean wound duration weeks ± SD: Group 1: 29.93 ± 35.20 Group 2: 39.46 ± 40.50 Mean wound area cm^2 ± SD (median): Group 1: 9.87 ± 12.90 (4.2) Group 2: 10.52 ± 12.30 (5.4) Patients with clinical diagnosis of wound infection or taking antibiotics for any reason were excluded. None of the ulcers or surrounding skin showed signs of inflammation at baseline Coliforms, *Staphylococcus aureus* and *Proteus* species were the most common isolates at baseline and were found in 25%, 23% and 19% of all wounds, respectively (assessed with wound swab) Numbers (%) of participants with at least one isolate: Group 1: 44/54 (81) Group 2: 51/54 (94) Numbers (%) of participants with > 1 isolate: Group 1: 22/54 (41) Group 2: 29/54 (54) Numbers (%) of participants with methicillin-resistant *Staphylococcus aureus* (MRSA): Group 1: 6/54 (11) Group 2: 10/54 (19) Mean pain scores ± SD (assessed using 5-point visual analogue scale, where 0 = no pain and 5 = worst pain ever): Group 1: 1.39 ± 1.15 Group 2: 1.41 ± 1.05
Interventions	Group 1: Hydrogel therapy (IntraSite Gel, Smith & Nephew, Hull, UK) 3 g/20 cm^2 applied weekly Group 2: Manuka honey (topical agent) (Woundcare 18+, Comvita, Te Puke, New Zealand) 5 g/20 cm^2 applied weekly All participants received wound cleansing with warm tap water; secondary foam dressings (Allevyn); and compression therapy, usually four-layer bandage. Treatment period was four weeks. After four weeks, all participants received follow-up treatment based on clinicians' judgement; this varied between participants. The final follow-up assessment was conducted at week 12. Participants requiring antibiotics or immunosuppressants during the trial were withdrawn
Outcomes	Percentage change in wound size at week 12 (unclear whether mean or median): Group 1: -13% Group 2: -34% Trial authors report P value < 0.001 for between-group difference Numbers (%) of ulcers healed at week 12: Group 1: 18/54 (33) Group 2: 24/54 (44) Secondary outcomes:

	Adverse events: The trial authors reported no adverse events directly attributable to either wound agent (see information below on withdrawals for further details) Bacterial changes during 4 weeks of treatment (detected by wound swab): Numbers (%) of participants with at least one isolate at week 4: Group 1: 29/54 (54) Group 2: 35/54 (65) Numbers (%) of participants with > 1 isolate at week 4: Group 1: 15/54 (28) Group 2: 22/54 (41) Numbers of participants (%) with MRSA eradication at week 4: Group 1: 1/6 (16) Group 2: 7/10 (70) Coliforms, coagulase-negative *Staphylococcus* and *Staphylococcus aureus* were the most common isolates at four weeks and were found in 16%, 15% and 13% of all wounds, respectively The authors reported no statistically significant differences between groups in pain outcome as assessed by visual analogue scale score at any follow-up point
Notes	Unit of analysis was the participant. For participants with multiple ulcers, the uppermost or largest ulcer was selected for study Procedure for taking wound swabs at baseline, 1 week and 4 weeks: 2 swabs taken after wound cleansed with warm tap water to safeguard against loss/damage; cotton-tipped swab rotated 360 degrees in the wound bed; then swabs placed in transport media and transported immediately to the laboratory for routine qualitative culture Numbers (%) of participant withdrawals (reasons—wound infection diagnosed on clinical presentation): Group 1: 17/54 (31%) (infection in reference wound 12; infection elsewhere 1; participant request 3; did not attend follow-up 1) Group 2: 9/54 (17%) (infection in reference wound 6; infection elsewhere 1; non-compliance with treatment 1; did not attend follow-up 1) The trial authors reported that the between-group difference for time to withdrawal because of infection was not statistically significant (P value < 0.07, log rank test) Note: A discrepancy is evident between text and table for numbers of participants with MRSA eradication; data have been extracted from the main text (relates to secondary reference of Gethin 2008) The main primary outcome for the RCT was reduction in slough; the trial authors reported no statistically significant differences between groups in percentage reduction of slough at four weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence	Low risk	"Following screening, and when consent was provided, patients were randomised via remote phone allocation to either treatment group"

generation (selection bias)		Comment: This was judged to be a satisfactory method of random sequence generation
Allocation concealment (selection bias)	Low risk	"The allocation sequence was generated using serially numbered, sealed, opaque envelopes, prior to the study by two persons independent of the study" Comment: This was judged to be a satisfactory method of allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Described as "open label" with no further information about blinding of participants
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	High risk	Quote in relation to healing outcomes: "Blinded outcome assessment was not possible because of obvious differences in the colour and presentation of the products, specifically orange staining of the peri-wound skin when MH was used" Quote in relation to microbiological outcomes: "The laboratory was blinded to treatment allocation" Comment: judged as high risk of bias because healing is the primary outcome in the review
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Withdrawal rate and reasons for withdrawal were reported per group
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Group 1: 31% of patients withdrew Group 2: 17% of patients withdrew Comment: the withdrawal rate in Group 1 was greater than 20%
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Quote: "All patients were included in the final analysis" Comment: it is clearly shown in the paper that all patients received their allocated treatment and were followed up
Baseline factors comparable	Low risk	Both wound size and wound duration appear comparable at baseline

Groenewald 1981

Methods	Randomised controlled trial conducted in South Africa
Participants	

	100 people with varicose stasis ulcers Group 1: 50 Group 2: 50 Scant data on baseline characteristics such as ulcer area and ulcer duration. Unclear whether wounds clinically infected at baseline
Interventions	1. Existing dressing removed, ulcer and surrounding area washed with a soft brush in povidone-iodine solution; appropriate treatment for frequently occurring fungal infections then applied; povidone-iodine swabbed on the ulcer surface; 2.5 cm thick foam rubber pad placed directly on ulcer; whole foot and lower leg covered with zinc oxide–impregnated gauze bandage and covered by an elastic bandage 2. Treated similarly in all respects, except that dextranomer beadlets applied to the ulcer surface to form a 2 to 3 mm layer instead of the final application of povidone-iodine
Outcomes	Objective outcome: Average healing time (no information about methods of estimation): 1. 5.3 weeks 2. 4.4 weeks (significant at 95% CI) Secondary outcome: Average eradication time: for *Staph aureus* : 1. 18.7 days 2. 14.7 days (significant at 99.5% CI) Mean cleansing time: 1. 15.4 ± 6.4 days 2. 5.9 ± 2.8 days (P value < 0.001) People with painful ulcers: 1. 35 2. 30 Immediate improvement of pain 1. 7 /35 (20%) 2. 20/30 (66.6%) Worsened pain: 1. 4/35 (11.4%) 2. 0/30
Notes	Withdrawal total = 5 People withdrawn from the trial were replaced to keep population size N = 100

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...a single-blind study of 100 patients randomised into two equal groups..." It was not stated how the sequence was generated

Allocation concealment (selection bias)	Unclear risk	No information given about how knowledge of assignment to treatment groups was concealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	"patients were incorporated into in a single blind randomised trial"; no other information given
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"at each visit the ulcers were evaluated by 2 independent investigators"; no other information given
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	"a total of 100 patients were evaluated with 50 in each group, five dropped out"
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	5/50 (10%) withdrawals - withdrawal rate is acceptable
Incomplete outcome data (attrition bias) ITT analysis	High risk	"five dropped out and were replaced to keep the final number at 50/group"; no further information given
Baseline factors comparable	Unclear risk	Insufficient information on baseline characteristics provided to allow a judgement to be made

Hansson 1998

Methods	Randomised controlled trial conducted in Sweden
Participants	153 people with non-infected venous leg ulcers randomly assigned, only withdrawals judged to be unrelated to treatment efficacy were excluded from the analysis Group 1: 49 Group 2: 56 Group 3: 48 Mean ± SD baseline ulcer area (cm^2): Group 1: 7.1 ± 7.1; Group 2: 8.8 ± 11.9; Group 3: 10.7 ± 20.6

	Data on baseline ulcer duration not reported. Patients with clinically infected ulcers excluded
Interventions	1. Paraffin gauze dressing, which was changed when saturated or leaking 2. Cadexomer iodine paste, which was changed when moisture saturated, indicated by a colour change 3. Hydrocolloid dressing, which was changed when saturated or leaking All participants received a short-stretch compression bandage (Comprilan). Treatment duration was 12 weeks.
Outcomes	At 12 weeks: Ulcers completely healed: 1. 7/49 2. 8/56 5. 5/48 Mean percentage reduction in ulcer area: 1. 23.9 ± 97.4% 2. 61.6 ± 36.9% 3. 40.7 ± 56.5% Mean ulcer area reduction per week (%/wk) 1. 3 ± 14 2. 8 ± 10 3. 9 ± 8 Secondary outcomes: No statistically significant difference in the time to cease exudation between groups of the study Adverse effects: Total number of adverse events per group (group denominators unclear): 1. 26 2. 19 3. 33 Erosions around ulcer: 1. 15 2. 0 3. 10 Pain 1. 1 2. 8 3. 2 Allergy 1. 1 2. 2 3. 6 Cost of treatment in 38 people (staff time, materials, and transport) USD/ percentage ulcer area reduction 1. 12.9 2. 8.8 3. 32.5

Notes	Withdrawals (NB 1 to 2 reasons per participant) Group 1: Allergy (1); increased size (8); pain (1); infection (4); adverse effects (2); not related A/Es (6); refused to continue (2) Total = 24 Group 2: Pain (6); infection (1); not related A/Es (4); poor compliance (1); protocol violation (1) Total = 13 Group 3: Allergy (5); increased size (3); infection (5); use of systemic Abx (2); not related A/Es (1); refused to continue (1) Total = 17

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomised to receive one of three treatments"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information about how assignment to treatment groups concealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	"A 12-week, randomised, open, controlled, multicentre multinational trial...."
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"A 12-week, randomised, open, controlled, multicentre multinational trial...."
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	153 participants were randomly assigned, of whom 48 withdrew
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Dropout rate > 20% in all treatment groups
Incomplete outcome data (attrition bias) ITT analysis	High risk	"28 patients (12 in cadexomer iodine, 7 in hydrocolloid, 9 in paraffin gauze group) were withdrawn from the study for reason unrelated to efficacy and were excluded from the analysis"

Baseline factors comparable	Unclear risk	Mean values were presented for baseline ulcer area, making comparability difficult to judge. No data on baseline ulcer duration were presented

Harcup 1986

Methods	Randomised controlled trial conducted in the UK
Participants	72 people over 30 years of age with venous leg ulcers 1. 31 2. 41 Statistics for baseline ulcer area in cm^2 (presume mean ± SD, but not stated): Group 1: 7.74 ± 1.04; Group 2: 9.08 ± 1.37 Mean (range) baseline ulcer duration for all participants was 16.9 (1 to 256) months (breakdown per group not provided) Unclear whether wounds were clinically infected at baseline (but it appeared that those with infected ulcers might have been allowed into the trial).
Interventions	1. Support bandaging or stocking with a dry dressing. Multiple treatment modalities used 2. Ulcer was cleaned with sterile saline swabs; cadexomer iodine applied to the surface; sterile dressing used and secured in place with bandaging or stocking. Cadexomer iodine removed daily All patients were treated by general practitioners, in a community setting.
Outcomes	At 4 weeks: Ulcers completely healed: 1. 1/31 (3.2%) 2. 13/41 (31.7%) Percentage reduction in ulcer size at 4 weeks (72 participants analysed) 1. 10% 2. 36% P value < 0.01 Secondary outcome: Significantly improved pain, erythema, exudation, oedema, pus/debris and granulation in the group treated with cadexomer iodine
Notes	Withdrawals: Group 1: 2 participants withdrew at 6 weeks because of insufficient effect of treatment and failure to attend Group 2: 3 participants withdrew at 2 weeks because of diarrhoea, erythema, oedema, ulcer irritation and unhappiness with treatment 3 participants withdrew at 4 weeks because of burning sensation (1) and insufficient effect (2) 2 participants withdrew at 6 weeks because of development of multiple ulcers, dry skin, itching and pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomised to receive either standard dressing or Cadexomer iodine"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	"the patient, or whoever was to manage the patient, was instructed on how to treat the ulcer"; those in the cadexomer iodine group had to apply CI to the wound before the dressing, while those with standard treatment did not
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information mentioned regarding this
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Describes number of people withdrawn at 2, 4, 6 weeks from both groups
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Withdrawal rates differed between groups: Group 1 6.5%; Group 2 19.5%
Incomplete outcome data (attrition bias) ITT analysis	High risk	"two patients were randomised to standard therapy, but were treated with CI during the trial. The analysis was carried out assigning these patients to the CI group"
Baseline factors comparable	Unclear risk	Not clear about all baseline characteristics in each group

Holloway 1989

Methods	Randomised controlled trial conducted in the USA
Participants	75 people with venous leg ulcers were recruited: Group 1: 37 Group 2: 38 Median (range) baseline ulcer area in cm^2: Group 1: 9.8 (3.0 to 37.0); Group 2: 10.7 (0.6 to 136.0)

	Median (range) baseline ulcer duration in months: Group 1: 4.5 (3 to 130); Group 2: 7.5 (3 to 240) Unclear whether ulcers were infected at baseline (but it appeared that those with infected ulcers might have been allowed into the trial).
Interventions	1. Wet-to-dry dressings with saline-soaked gauze pads changed by the participant daily plus toe-to-knee elastic compression bandage 2. Ulcer irrigated with saline, cadexomer iodine sprinkled onto the surface, then covered with a dry gauze dressing; done daily plus toe-to-knee elastic compression bandage Information provided suggests that all participants were treated in a community setting.
Outcomes	Outcomes were assessed at 24 weeks, with analyses based on 54 participants overall (breakdown of completers per group not stated) Mean (standard error of the mean) rate of ulcer healing (cm^2/wk): 1. 0.41 (0.13) 2. 0.95 (0.12) The trial authors reported a statistically significant between-group difference (P value 0.0025) Mean (standard error of the mean) rate of ulcer healing versus baseline circumference (cm^2/wk/cm) 1. 0.03 (0.01) 2. 0.04 (0.01) The trial authors reported that the between-group difference was not statistically significant (P value 0.072) Secondary outcomes: Bacterial eradication The trial authors reported: "Neither treatment was superior in causing a reduction in bacterial numbers on a semiquantitative (categorized as profuse, moderate or sparse) basis." No further information or data were provided Adverse effects: burning, itching or pain 1. 0 2. 6
Notes	Withdrawals from both groups (breakdown per group not provided): Death (2); dropped out or failed to return (9); failed to respond to trial treatment (4) Excluded from statistical analysis: do not satisfy inclusion criteria (2); lost to follow-up (4)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomly assigned to either the standard or cadexomer iodine group"; it was not stated how the sequence was generated

Allocation concealment (selection bias)	Unclear risk	No information given about whether/how assignment to treatment groups was concealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	Wound care: "treatment was repeated on a daily basis by the patient"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"each ulcer was evaluated serially by the same person as each medical centre"; no further information given
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	"Of the 75 patients starting the trial,15 did not complete the study for reasons other than healing of the ulcer. Four failed to respond to one or both treatments and required more aggressive treatment. Two died during the study of causes unrelated to the ulcers, & 9 dropped out or failed to return. An additional 6 patients were excluded from statistical analysis"
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	dropout rate > 20%; breakdown per group not provided
Incomplete outcome data (attrition bias) ITT analysis	High risk	"6 patients were excluded from statistical analysis" "A total of 12 patients switched treatments during the trial: all 12 crossed over from the control treatment to using cadexomer iodine because of a failure of healing..." It is not clear whether these participants were retained in their original groups for the purposes of data analysis
Baseline factors comparable	High risk	Ulcers were larger and of longer duration in Group 2

Huovinen 1994

Methods	Randomised controlled trial conducted in Finland
Participants	36 people initially recruited, 5 people withdrawn and excluded from analysis Group 1: 11 randomly assigned, 10 completed Group 2: 13 randomly assigned and 12 completed Group 3: 12 randomly assigned, 9 completed Average—unclear if this is the mean value (range) baseline ulcer area (cm^2): Group 1: 27 (1 to 154); Group 2: 53 (1 to 475); Group 3: 31 (1 to 145)

	Average (range) baseline ulcer duration (months): Group 1: 29 (3 to 96); Group 2: 72 (3 to 126); Group 3: 67 (4 to 252) The trial authors stated that 26/31 (84%) ulcers had *Staphylococcus aureus* at baseline, but it was not clear whether wounds were colonised or clinically infected
Interventions	1. Placebo tablet twice daily plus local treatment with 0.2 g zinc in 1 g petroleum-paraffin ointment and Comprilan elastic bandage 2. Ciprofloxacin 750 mg twice daily plus the above local treatment 3. Trimethoprim 160 mg twice daily plus the above local treatment Treatment duration was 12 weeks in all groups
Outcomes	At 16 weeks: Complete healing: 1. 3/11 (27%) 2. 5/13 (38%) 3. 3/12 (25%) Average (range) change in ulcer size, calculated as % of original size (estimated from graph): 1. Excluding outlier -70% (+35 to -100), including outlier -20% (+200 to -100) 2. -75% (+15 to -100) 3. -35% (+70 to -100) The trial authors did not report P values for between-group differences for change in ulcer size Secondary outcomes: Emergence of antibiotic-resistant flora during treatment period (30 participants included in analysis overall): 1. 1/10 2. 8/12 3. 6/9 The trial authors reported that the difference between Group 1 and the other groups was statistically significant (P value 0.02, appears to apply to Group 1 vs Group 2, and also to Group 1 vs Group 3) Proportion of bacterial species isolated from ulcers resistant to ciprofloxacin/trimethoprim at the end of the study (16 weeks): 1. 4%/8% 2. 94%/63% 3. 12%/65% The trial authors reported P value < 0.0001 in relation to the difference between groups for ciprofloxacin resistance; it was not stated which comparison(s) this applied to. For trimethoprim resistance, the trial authors reported the following between-group differences: P value 0.004 for Group 1 versus Group 2; and P value 0.0003 for Group 1 versus Group 3 Persistence of presence of *Staph. aureus* in open ulcers at 16 weeks (denominators as reported by trial authors): 1. 7/7 2. 1/7 3. 5/6 Cost of treatment in Finland, in USD: 1. not reported

	2. 600 3. 120	
Notes	Withdrawals: Group 1: osteitis (1) Group 2: personal reasons (1) Group 3: adverse effects (3—rash, mild vertigo and nausea, chest pain)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients randomly assigned to groups"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Low risk	"The patients were.....treated in a double-blind manner...
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No mention of who the outcome assessor was and the adequacy of blinding
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Describes 5 patients excluded and states reasons for exclusion
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	The dropout rate differed between groups: Group 1: 9%; Group 2: 8%; Group 3: 25%
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	"five were eventually excluded"; no other information provided about analysis
Baseline factors comparable	High risk	Ulcer area and duration varied considerably across groups

Ishibashi 1996

Methods	Randomised controlled trial conducted in Japan
Participants	Setting: Japan (inpatients and outpatients) Inclusion criteria: ulcer size 2 cm to 12 cm (unclear whether this is diameter or surface area); ulcer aetiology decubitus, burn injury or chronic venous insufficiency; participant aged 16 years or over 218 participants recruited in total (109 participants allocated per group) Numbers of participants according to ulcer aetiology of 207 participants analysed (decubitus, burn injury, venous insufficiency): Group 1: 31, 41, 32; Group 2: 32, 40, 31 Numbers of participants with baseline ulcer area (in mm^2 < 250, 250 to < 500, 500 to < 1000, 1000 to < 2500, ≥ 2500): Group 1: 4, 27, 24, 29, 20; Group 2: 8, 24, 29, 22, 20 Mean ± SE baseline ulcer area (mm^2): Group 1: 1716.4 ± 217.8; Group 2: 1440.4 ± 153.5 Numbers of participants with baseline ulcer duration (in months, < 1, 1 to < 3, 3 to < 6, 6 to < 12, ≥ 12, unknown): Group 1: 18, 45, 15, 10, 16, 0; Group 2: 21, 42, 16, 10, 13, 1 Mean ± SD baseline ulcer duration (days): Group 1: 270.4 ± 63.4; Group 2: 300.9 ± 87.4 Numbers of participants with infected ulcer at baseline (category assessed by clinical examination—much, moderate, slight, none): Group 1: 4, 8, 32, 60; Group 2: 1, 9, 26, 67
Interventions	Group 1: spray solution containing recombinant human basic fibroblast growth factor (KCB-1 0.01% solution 0.3 mL) to ulcer once a day after the ulcer was cleansed with antiseptic solution (unspecified). Three minutes after spraying, gauze pad was applied and secured with tape Group 2: sugar and povidone-iodine ointment applied to ulcer once or twice daily after cleansing with antiseptic solution (unspecified), then gauze pad applied and secured with tape No details of co-interventions such as compression
Outcomes	Analysis based on 207 participants in total: Group 1: 104 participants; Group 2: 103 participants Numbers (%) of venous leg ulcer participants with complete healing at 4 weeks: Group 1: 9/32 (28%); Group 2: 5/31 (16%)
Notes	If participants had multiple ulcers, one was selected for study (method of selection not stated) Withdrawals due to protocol violation (excluded from analysis): Group 1: 5/109 (4.6%) (1 took disallowed medication before trial, 1 had traumatic ulcer, 2 previously used sugar and povidone-iodine ointment, 1 nutritionally depleted) Group 2: 6/109 (5.5%) (1 had hypothyroidism and did not use study medication, 1 had previously used sugar and povidone-iodine ointment and did not use study medication, 1 had positive patch test for povidone-iodine and did not use study

	medication, 1 general condition deteriorated because of sepsis and participant did not use study medication, 1 had traumatic ulcer, 1 had ulcer smaller than 2 cm) Further withdrawals during the trial (included in analysis): Group 1: 4 withdrawals (1 worsening condition, 1 concomitant disease, 2 other reasons); Group 2: 9 withdrawals (3 adverse events, 1 worsening condition, 2 no effect of trial treatment, 1 discharged, 1 died, 1 other reason) Withdrawal data were not broken down by wound aetiology Sponsor of study not stated; KCB-1 provided by Kaken Pharmaceutical Company Ltd, and sugar and povidone-iodine ointment provided by Kowa Company Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as "randomised controlled trial", but no further information provided as to how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Information from the translator suggested that central randomisation was used. From English language abstract: "The study was performed by the telephone or fax registration method." Exact methods not clear
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information provided
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Dropout rate of each group described: Group 1: 109 participants randomly assigned, 5 excluded for protocol violation; Group 2: 109 participants randomly assigned, 6 excluded (5 for protocol violation, 1 for worsening clinical condition)
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Dropout rate about 5% in both groups
	Unclear risk	

Incomplete outcome data (attrition bias) ITT analysis		Patients excluded from analysis: Group 1: 109 - 5 = 104 patients analysed; Group 2: 109 - 6= 103 patients analysed—these values relate to the whole trial population, which consisted of people with various wound types. It is unclear how these withdrawals might have impacted estimates of treatment effect for those with venous leg ulceration
Baseline factors comparable	Unclear risk	Ulcer area, duration and infection appear similar across all participants, but data were not provided per wound type

Jull 2008

Methods	Randomised controlled trial (multi-centre, involving 4 community-based district nursing services in New Zealand). A sample size of 400 people was estimated as required to detect a 30% between-group difference in the proportion of healed ulcers at 12 weeks, with 90% power and 5% significance level, and allowing for 10% loss to follow-up. Recruitment achieved 92% of planned target; this was deemed to retain 90% power, as the anticipated loss to follow-up did not occur
Participants	368 participants with venous ulceration (ABPI > 0.8) or mixed venous and arterial ulceration (ABPI > 0.7), able to tolerate compression, were randomly assigned: Group 1: 181 participants Group 2: 187 participants Ulcer duration at baseline, weeks, median (range) [mean ± SD]: Group 1: 16 (2 to 999) [47.9 ± 118.1] Group 2: 20 (3 to 688) [38.7 ± 76.3] Baseline ulcer area, cm^2, median (range) [mean ± SD]: Group 1: 2.6 (0.2 to 81.0) [6.4 ± 9.8] Group 2: 2.7 (0.1 to 193.0) [7.4 ± 18.2] Numbers (%) of participants with mixed venous and arterial ulceration (ABPI > 0.7 but < 0.8): Group 1: 5/181 (2.8) Group 2: 2/187 (1.1) Baseline SF-36 physical component summary score, mean ± SD: Group 1: 34.0 (9.8) Group 2: 36.7 (10.1) Baseline SF-36 mental component summary score, mean ± SD: Group 1: 50.5 (12.4) Group 2: 48.7 (11.6) The number of participants with signs and symptoms of infected ulcers at baseline is not reported
Interventions	Group 1: usual care, with dressings applied according to district nurse choice (alginate, hydrofibre, hydrocolloid, foam, hydrogel, non-adherent, iodine or silver dressings) Group 2: calcium alginate dressing impregnated with Manuka honey (ApiNate, Comvita, Te Puke, New Zealand) .

	All participants received compression bandaging in accordance with usual practice in the study centres and dressing changes when compression bandaging was changed, with frequency determined by district nurses Numbers (%) of participants with baseline compression system: Group 1: short stretch 5 (3); long stretch 5 (3); three layer 65 (36); four layer 106 (59) Group 2: short stretch 2 (1); long stretch 5 (3); three layer 74 (40); four layer 106 (57) Treatment duration was 12 weeks
Outcomes	Primary outcomes: Numbers (%) of participants with ulcers completely healed at 12 weeks: Group 1: 90/181 (50) Group 2: 104/187 (56) The trial authors reported a 5.9% (95% CI -4.3% to 15.7%) absolute increase in healing in Group 2, P value 0.258, and stated that findings were similar with adjustment for study centre and prognostic index (statistics not provided) Mean time to healing, days at 12 weeks: Group 1: 65.3 Group 2: 63.5 The trial authors reported a difference in means of -1.8 days (95% CI -7.7 days to 4.1 days), P value 0.553 The trial authors reported a hazard ratio estimation of 1.1 (95% CI 0.8 to 1.5), P value 0.451, and stated that findings were similar with adjustment for study centre and prognostic index (statistics not provided) Mean percentage change in ulcer area at 12 weeks: Group 1: -65.5% Group 2: -74.1% The trial authors reported a difference in means of 8.6% (95% CI 23.9% to -4.7%), P value 0.186, and stated that findings were similar with adjustment for study centre and prognostic index (statistics not provided) Secondary outcomes: Numbers (%) of participants with incident ulcer infection, diagnosed by clinical assessment or wound swab: Group 1: 40/181 (22) Group 2: 32/187 (17) The trial authors reported an absolute difference of 5% (95% CI -3.1% to 13.1%), P value 0.228 Number of episodes of infection: Group 1: 49 Group 2: 37 The trial authors reported P value 0.449 for the between-group difference Numbers (%) of participants reporting one or more adverse events: Group 1: 84/181 (46) Group 2: 111/187 (59) The trial authors reported a risk ratio of 1.3 (95% CI 1.1 to 1.6), P value 0.013 Numbers (%) of participants reporting local adverse events:

Group 1: pain 18 (10); bleeding 3 (2); dermatitis 8 (4); deterioration of ulcer 9 (5); erythema 4 (2); oedema 1 (< 1); increased exudate 1 (< 1); deterioration of surrounding skin 3 (2); new ulceration 15 (8); other 3 (2)

Group 2: pain 47 (25); bleeding 3 (2); dermatitis 8 (4); deterioration of ulcer 19 (10); erythema 6 (3); oedema 4 (2); increased exudate 5 (3); deterioration of surrounding skin 5 (3); new ulceration 16 (9); other 6 (3)

The trial authors reported that the between-group difference in pain was statistically significant, P value 0.001. All other between-group differences were not statistically significant (reported P values all > 0.06)

Numbers (%) of participants reporting systemic adverse events:

Group 1: cardiovascular 3 (2); cancer 2 (1); neurological 1 (< 1); gastrointestinal 2 (1); injury 9 (5); musculoskeletal 9 (5); respiratory 3 (2); other 7 (4)

Group 2: cardiovascular 4 (2); cancer 2 (1); neurological 4 (2); gastrointestinal 4 (2); injury 10 (5); musculoskeletal 13 (7); respiratory 6 (3); other 3 (2)

All between-group differences were not statistically significant (reported P values all > 0.18)

Health-related quality of life assessed with SF-36 (8 domains scored on a scale of 1 to 100, with higher scores representing better perceived health, 100 being the best possible score):

SF-36 physical component mean summary score at 12 weeks:

Group 1: 37.9 (n = 174)

Group 2: 39.0 (n = 186)

The trial authors reported a difference in means of 1.1 (95% CI -0.8 to 3.0), P value 0.256 (not stated whether adjusted for baseline values)

SF-36 mental component mean summary score at 12 weeks:

Group 1: 50.4 (n = 174)

Group 2: 51.1 (n = 186)

The trial authors reported a difference in means of 0.7 (95% CI -1.1 to 2.4), P value 0.437 (not stated whether adjusted for baseline values)

Health-related quality of life assessed with CXVUQ (Charing Cross Venous Ulcer Questionnaire comprising four domains scored from 0 to 100, higher scores reflecting greater affliction, 100 being the worst possible score):

CXVUQ mean overall score at 12 weeks:

Group 1: 35.1 (n = 174)

Group 2: 33.5 (n = 186)

The trial authors reported a difference in means of -1.6 (95% CI -4.2 to 0.9), P value 0.204 (not stated whether adjusted for baseline values)

Health-related quality of life assessed with EQ-5D visual analogue scale (scale from 0 to 100, 0 = worst imaginable health state to 100 = best imaginable health state):

EQ-5D VAS mean score at 12 weeks:

Group 1: 73.5 (n = 174)

Group 2: 75.1 (n = 186)

The trial authors reported a difference in means of 1.6 (95% CI -1.5 to 4.7), P value 0.313 (not stated whether adjusted for baseline values)

Cost-effectiveness analysis, base case analysis of mean total health service costs per participant:

Group 1: NZD 972.68

	Group 2: NZD 917.00 The trial authors reported that the ICER (incremental cost-effectiveness ratio) was -NZD 9.45 (95% CI -NZD 39.63 to NZD 16.07) favouring Group 2. Exclusion of hospitalisation costs (six participants hospitalised for a total of 40 days in Group 1 and three participants hospitalised for a total of 10 days in Group 2) reversed the ICER to NZD 11.34 (95% CI -NZD 2.24 to NZD 26.25) in favour of Group 1
Notes	This is the HALT Trial (ISRCTN 06161544) In participants with multiple ulcers, the largest was used as the reference ulcer, and all ulcers for that participant were treated with the allocated intervention Numbers (%) of participants lost to follow-up (reasons): Group 1: 6/181 (3) (2 died, 3 moved, 1 uncontactable) Group 2: 0/187 (0) Numbers (%) of participants withdrawing from treatment (reasons): Group 1: 0/181 (0) Group 2: 31/187 (17) (8 deterioration of ulcer or surrounding skin, 7 healthcare professional's advice, 7 ulcer infection, 4 ulcer pain, 3 participant's choice, 1 ulcer bleeding, 1 dressing not available)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly assigned to one of two groups by an independent central telephone service. The allocation sequence was stratified by study centre and the Margolis Index using minimisation" Comment: the method of random sequence generation was deemed satisfactory
Allocation concealment (selection bias)	Low risk	Quote: "Participants were randomly assigned to one of two groups by an independent central telephone service. The allocation sequence was stratified by study centre and the Margolis Index using minimisation" Comment: the method of allocation concealment was deemed satisfactory
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Trial described as "open label" but no further information provided about blinding participants
Blinding (performance bias and detection bias)	Low risk	Quote: "Outcome assessment could not be blinded. However, re-analysis of the primary outcome using healing state determined

Outcome assessor blinded to the intervention		from blinded review of ulcer photographs did not affect the study findings" Comment: The above information suggests low risk of bias in relation to blinding of outcome assessment
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Numbers withdrawing, with reasons reported for both groups
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Withdrawal rate less then 20% in both groups, with patients discontinuing treatment followed up
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Quote: "Intention-to-treat analysis was undertaken with the inclusion of all participants randomised" Comment: all participants were included in the analysis
Baseline factors comparable	Low risk	The median ulcer size and the median ulcer duration appear comparable at baseline

Jørgensen 2005

Methods	Randomised controlled trial (multi-centre, 15 centres in 7 countries, including Canada, Denmark, Germany, Italy, Netherlands, UK and USA)
Participants	129 participants with chronic venous or mixed venous/arterial leg ulcers (ABPI ≥ 0.65) were recruited with the following characteristics: moderately or highly exuding ulcer; minimum ulcer size of 2 cm^2 and maximum size not exceeding the 10 × 10-cm dressing; delayed healing (defined as area reduction 0.5 cm^2 or less during the previous 4 weeks); at least 1 clinical sign of critical colonisation (including increased exudate during previous 4 weeks, increased wound pain during previous 4 weeks, discolouration of granulation tissue or foul odour as assessed by study staff); use of compression therapy for 4 weeks before randomisation Patients who had the following were excluded: clinical infection (including erysipelas and cellulitis of peri-ulcer skin); concomitant treatment with antibiotics or antiseptics during the week before randomisation; concomitant treatment with systemic corticosteroids exceeding 10 mg/d or other immunosuppressants from 4 weeks before randomisation; uncontrolled diabetes (HbA_{1c} > 10%); and diseases that may interfere with ulcer healing (e.g. vasculitis, rheumatoid arthritis, severe kidney or heart disease) Group 1: 64 participants Group 2: 65 participants Baseline ulcer area, median cm^2 (range): Group 1: 6.7 (1.3 to 50.6) Group 2: 6.1 (1.1 to 53.4) Duration of ulcer at baseline, median years (range):

	Group 1: 1.0 (0.1 to 10.0) Group 2: 1.1 (0.1 to 32.0) Numbers (%) of participants with ulcer infections during the previous year: Group 1: 40/64 (62) Group 2: 44/65 (67) Health-related quality of life baseline score, assessed with EQ-5D (EUROQoL): Group 1: median 0.71 Group 2: median 0.69
Interventions	Group 1: hydrocellular foam dressing 10 × 10 cm (Allevyn) Group 2: silver foam dressing 10 × 10 cm (Contreet Ag) All participants received wound cleansing with saline or tap water; securing of dressings with gauze or adhesive tape; treatment of peri-ulcer skin, as necessary, with a mild zinc cream or a topical steroid ointment; compression therapy according to the clinical practice of the centre, with the system unchanged throughout the trial period; dressings left in place for as long as clinically possible, to a maximum of 7 days; and weekly evaluation. Participants were treated for 4 weeks unless complete wound healing or withdrawal occurred sooner. Participants were withdrawn if treated with antibiotics or antiseptics during the trial
Outcomes	Primary outcomes: Numbers (%) of ulcers healed at 4 weeks: Group 1: 5/64 (8) Group 2: 5/65 (8) Mean ulcer area remaining relative to baseline at 4 weeks % ± SD (median, range): Group 1: 71.0 ± 38.9 (74.6, 100 to 148) Group 2: 53.3 ± 34.6 (54.8, 100 to 126) Median % change in ulcer area at 4 weeks: Group 1: -25 Group 2: -45 Weekly % wound reduction rate median (mean): Group 1: not reported Group 2: 11.3 (11.2) Secondary outcomes: Health-related quality of life scores - EQ-5D (EUROQoL) at week 4 (1 = perfect health, 0 = death): Group 1: median 0.79 Group 2: median 0.79 Numbers (%) of participants reporting adverse events and type of events: Group 1: 3/64 (5) device-related skin reactions: maceration, eczema and satellite ulcer Group 2: 4/65 (6) device-related skin reactions: satellite ulcer and deterioration of peri-ulcer skin Proportion of participants developing peri-ulcer maceration after 1 week/4 weeks of treatment: Group 1: 55%/48% Group 2: 34%/37%

	The trial authors reported the between-group difference at 1 week as statistically significant (P value 0.008) but did not report a test of statistical significance for the 4-week data The trial authors reported that participants in both groups indicated a decrease in pain during the treatment period, but no data are presented
Notes	Numbers (%) of participants withdrawing (reasons): Group 1: 7 (11) (5 protocol violation, e.g. ulcer did not meet defined size limits; 1 treated with antibiotics unrelated to study ulcer; 1 other protocol violation, not defined) Group 2: 13 (20) (7 protocol violation, e.g. ulcer did not meet defined size limits; 3 treated with antibiotics unrelated to study ulcer; 2 treated with antibiotics for study ulcer infection; 1 other protocol violation, not defined)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to treatment with either Contreet Foam or Allevyn Hydrocellular by computer generated randomisation" Comment: This was judged to be a satisfactory method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomised to treatment with either Contreet Foam or Allevyn Hydrocellular by computer generated randomisation" Comment: No information regarding group allocation was provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Quote: "The study was designed as a multicenter, open, block-randomised and controlled study" Comment: No mention was made of participants being blind to treatment allocation
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "The study was designed as a multicenter, open, block-randomised and controlled study" Quote: "The study personnel evaluated the patients weekly at the clinic or hospital throughout the study" Comment: No mention was made of outcome assessors being blind to treatment allocation
Incomplete outcome data (attrition bias)	Low risk	Comment: Numbers withdrawing and reasons are reported for both groups

Drop out rate described		
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Comment: A greater proportion of participants withdrew from the silver dressing group: Group 1: n = 7 (11%) Group 2: n = 13 (20%)
Incomplete outcome data (attrition bias) ITT analysis	High risk	Quote: "Intention-to-treat analyses were performed in connection with the safety parameters, whereas per-protocol analyses were applied for the performance parameters" Comment: Analysis of healing outcomes was undertaken on a per-protocol basis
Baseline factors comparable	Low risk	Comment: Baseline ulcer size and duration appear comparable. Similar rates of infection were reported per group during previous year

Kerihuel 2010

Methods	Two separate randomised controlled trials, 1 in venous leg ulcer patients with 7 participating hospitals in France, the other in pressure ulcers. The trial authors stated that no a priori power calculation was undertaken
Participants	Leg ulcer study: 60 participants were randomly assigned, with ulcers of primarily venous origin (ABPI > 0.7), of ≤ 12 months' duration, area 5 to 100 cm^2 and necrotic tissue covering ≥ 50% of wound bed, not contraindicated to compression bandaging. Participants with diabetes were eligible for inclusion. Participants with infected ulcers requiring systemic antibiotics were excluded: Group 1: 30 (9 had some arterial disease) Group 2: 30 (8 had some arterial disease) Numbers (%) of participants with wound duration > 1 month: Group 1: 11 (37) Group 2: 10 (33) Numbers (%) of participants with wound duration > 3 months: Group 1: 1 (3) Group 2: 9 (30) Wound area cm^2 mean ± SD (median): Group 1: 17.5 ± 24.4 (8.2) Group 2: 18.1 ± 18.2 (12.1)
Interventions	Group 1: hydrocolloid dressing (Duoderm) Group 2: charcoal dressing impregnated with silver (Actisorb 220 silver) All participants received sharp debridement of necrotic tissue; wound cleansing with sterile saline; dressing changes 2 to 3 times per week or more frequently in cases of abundant exudate; recommendation to wear elastic compression bandage (Biflex 16) daily; and weekly assessment

	Numbers (%) of participants complying with use of compression: Group 1: 15/30 (50) Group 2: 12/30 (40) Treatment duration was 4 weeks
Outcomes	Change in wound area, cm^2 median (range) at week 4: Group 1: -3.5 (-53.3 to 18.5) Group 2: -4.5 (-30.9 to 22.5) P value for between-group difference at 4 weeks not provided Percentage change at week 4, median (range): Group 1: -40.9 (-100.0 to 308.3) Group 2: -35.6 (-100.0 to 182.1) P value for between-group difference at 4 weeks not provided Numbers (%) of participants reporting adverse events (reasons): Group 1: 20/30 (67) (9 maceration/high exudation, 1 wound infection, 5 eczema, 1 pain, 3 skin irritation, 1 bleeding at dressing removal) Group 2: 5/30 (17) (1 wound infection, 2 wound aggravation, 1 pain, 1 skin irritation)
Notes	One ulcer per participant was included in the study; it was not reported how the reference wound was selected in participants with multiple wounds Numbers (%) of participants withdrawing (reasons): Group 1: 6/30 (20) (2 local adverse event—eczema; 1 died; 2 withdrew consent; 1 was discharged home) Group 2: 1/30 (3) (hospitalisation for heart failure)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was by blocks of four: identical sealed boxes containing the allocated dressings, gauze and saline were randomly allocated to each patient. The box reference number indicated which study arm the patient had been allocated to, although this was unknown to the patient and investigator. The box reference numbers were verified by a co-ordinating centre before allocation" Comment: Although the method of random sequence generation is not specifically stated, the details provided suggest that a satisfactory method was likely to have been used and that the trial is likely to be at low risk of bias for this domain
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was by blocks of four: identical sealed boxes containing the allocated dressings, gauze and saline were randomly allocated to each patient. The box reference number indicated which study arm the patient had been allocated to, although this was unknown to the patient and investigator. The box reference numbers were verified by a co-ordinating centre before allocation"

		Comment: The details provided suggest a satisfactory method of allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: no details provided about blinding of participants
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Low risk	Quote: "All wound tracings were measured by two independent, experienced clinicians who were unaware of the treatment allocation" Comment: The method of blinded outcome assessment was deemed satisfactory
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: The numbers of withdrawals and reasons are reported for both groups
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	11.7% withdrew overall, but proportions differed between groups: Group 1: 6/30 (20%) Group 2: 1/30 (3%)
Incomplete outcome data (attrition bias) ITT analysis	Low risk	"All analyses used data from the intention-to-treat population (defined as all randomised patients whose wounds were traced in at least one assessment during the first four weeks of the study)" Comment: The presentation of results suggested that all randomly assigned participants had been included in all analyses
Baseline factors comparable	Unclear risk	Although between-group wound surface area appears broadly comparable, it is difficult to judge wound duration comparability (categorical data only provided)

Kero 1987

Methods	Randomised controlled trial conducted in Finland
Participants	27 people over 18 years of age with venous leg ulcers recruited Group 1: 13 people Group 2: 14 people Mean ± SD (range) baseline ulcer duration in months: Group 1: 12.2 ± 23.0 (1 to 72); Group 2: 54.8 ± 108.7 (1 to 360)

	Baseline ulcer area and infection status were not reported
Interventions	1. Ulcer surface cleansed with normal saline, mechanical wound cleansing procedure carried out, dextranomer applied to ulcer surface, dry compress cover applied, and conventional compression bandage applied 2. Same as above but cadexomer iodine used
Outcomes	Complete healing at 8 weeks: 1. 5/13 (38%) 2. 7/14 (50%) Trial authors did not report a P value for this comparison Mean reduction in ulcer area at 8 weeks: 1. 35% 2. 81% Between-group difference reported as non-significant but P value not presented Secondary outcomes: Adverse events: Group 1: pain (1) Group 2: erythema (1); pain (1); stinging sensation (1)
Notes	Withdrawals: Group 1: Drug-related S/Es (1); infection (2) Group 2: Drug-related S/Es (1); infection (2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The trial was conducted under open design using random allocation to treatment with either cadexomer iodine or dextranomer" "Each patient was allocated to the treatment by using a sealed enclosure envelope containing the treatment code of the individual patient" Information taken from secondary publication (Tarvainen 1988)
Allocation concealment (selection bias)	Unclear risk	"The trial was conducted under open design using random allocation to treatment with either cadexomer iodine or dextranomer" "Each patient was allocated to the treatment by using a sealed enclosure envelope containing the treatment code of the individual patient" Information taken from secondary publication (Tarvainen 1988)
Blinding (performance bias	Unclear risk	"The trial was conducted under open design..." Information taken from secondary publication (Tarvainen 1988)

and detection bias) Participant blinded to the intervention		
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"The trial was conducted under open design..." Information taken from secondary publication (Tarvainen 1988)
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	"Two patients (one in each group) withdrew because of drug related side effects"
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Dropout rate less than 20%
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	"Two patients, one in each group were excluded from the evaluation of ulcer size because of infection that made cessation of therapy necessary. Two more patients, one in each group, were also excluded because of adverse reactions"
Baseline factors comparable	High risk	Ulcer duration appeared longer in the group receiving cadexomer iodine. No information about baseline ulcer area or wound infection status

Kuznetsov 2009

Methods	Randomised controlled trial conducted in Russia
Participants	30 participants with venous leg ulcers recruited from surgical outpatient clinic in Moscow, Russia Group 1: 15 participants Group 2: 15 participants Numbers (%) of participants with aetiological factors for VLUs: Group 1: 11 (73) participants with varicose vein disease; 4 (27) participants post thrombophlebitis Group 2: 12 (80) participants with varicose vein disease; 3 (20) participants post thrombophlebitis Mean size of ulcer at baseline cm^2 ± SD (range): Group 1: 14.8 ± 3.4 (2.5 to 50.3) Group 2: 17.4 ± 6.4 (2.2 to 99.5) Numbers (%) of participants with ulcers > $20cm^2$: Group 1: 5 (33) Group 2: 4 (27) Numbers (%) of participants with microbiological isolates:

	Group 1: *Staphylococcus aureus* 10 (67); *Pseudomonas aeruginosa* 1 (6.7); *Escherichia coli* 1 (6.7) Group 2: *Staphylococcus aureus* 9 (60); *Pseudomonas aeruginosa* 4 (27); *Proteus* species 1 (6.7)
Interventions	Group 1: 10% povidone-iodine dressing (Betadine), changed daily Group 2: different dressings used according to ulcer status. If necrotic tissue present, a moist wound dressing was used (TenderWet 24). This is a wound dressing pad used in combination with Ringer's solution to continuously irrigate the wound bed for 24 hours, changed daily. Once the necrotic tissue was cleared, a foam dressing (PermaFoam) was applied and was changed every 5th day or sooner. In the case of resistant infection, the foam dressing was combined with tulle dressing containing silver (Atrauman Ag) Both groups received short-stretch compression bandaging (Pütter-Verband, Hartmann). No participants underwent surgery Biological and cytological assessment was undertaken at baseline and on days 7, 14 and 21 The duration of treatment was 28 days or until complete healing (whichever came first)
Outcomes	Primary outcomes: Numbers (%) of participants with complete healing at 21 days: Group 1: 1/15 (7) Group 2: 4/15 (27) Numbers (%) of participants with complete healing at 28 days: Group 1: 2/15 (13) Group 2: 5/15 (33) Mean change in ulcer size in cm^2 at 7 days: Group 1: -0.35 Group 2: -2.09 Mean change in ulcer size in cm^2 at 21 days: Group 1: -1.27 Group 2: -5.03 Mean rate of healing in cm^2/d: Group 1: -0.06 Group 2: -0.24 The study authors reported that the between-group difference was statistically significant (P value < 0.05) Secondary outcomes: Numbers (%) of participants with microbiological isolates at 21 days: Group 1: *Staphylococcus aureus* 7 (47), *Pseudomonas aeruginosa* 1 (6.7), *Escherichia coli* 1 (6.7) Group 2: *Staphylococcus aureus* 5 (33), *Pseudomonas aeruginosa 3* (20), *Proteus* species 1 (6.7) Mean cost of complete course of treatment per group (RUB): Group 1: 6,669.84

	Group 2: 14,360.15 Mean cost of treatment per participant, per day (RUB): Group 1: 16.47 Group 2: 36.82
Notes	Article translated from Russian Unit of randomisation and analysis was the participant Withdrawals not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: Translation indicates that participants were randomly assigned to groups, but no details of randomisation methods were provided
Allocation concealment (selection bias)	Unclear risk	Comment: The report contained no statement regarding the group allocation process
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: The trial was described as "open", but no details of blinding of participants were provided
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Comment: The trial was described as "open", but no details of blinding of outcome assessors were provided
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: The trial report indicates that all randomly assigned participants completed treatment
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Comment: The trial report indicates that all randomly assigned participants completed treatment

Incomplete outcome data (attrition bias) ITT analysis	Low risk	Comment: The trial report indicates that all randomly assigned participants completed treatment
Baseline factors comparable	Unclear risk	The upper end of the ulcer area range is larger in Group 2. No information was provided about baseline ulcer duration

Laudanska 1988

Methods	Randomised controlled trial conducted in Poland
Participants	67 people with venous leg ulcers who failed to respond to outpatient treatment (dressings and compression bandages) were recruited; data from 60 people were analysed by the trial authors. Those with ulcers of diameter < 2 cm were excluded: 1. 33 people 2. 33 people 1 patient was excluded from the trial authors' analyses, for whom the treatment group was not specified Mean ± SE baseline ulcer area, cm^2: Group 1: 35.2 ± 8.1; Group 2: 27.5 ± 7.0 Mean ± SE baseline ulcer duration, months: Group 1: 15.0 ± 3.1; Group 2: 19.1 ± 4.3 No information about ulcer infection status at baseline (but it appeared that those with infected ulcers might have been allowed into the trial).
Interventions	1. Ulcers cleansed with dilute hydrogen peroxide and covered with zinc paste dressing. The following were also used if deemed necessary by the clinician: saline dressing; dilute potassium permanganate solution; and gentian violet solution 2. Cadexomer iodine applied in a 3 to 4 mm layer All participants were treated in a hospital inpatient setting and received daily dressing changes; a light elastic bandage to keep the dressing in place; and bed rest for the 6 weeks' duration of the trial; allowed out of bed for meals and toileting
Outcomes	Primary outcomes: Complete healing or very superficial wound remaining at 6 weeks: 1. 7/33 2. 16/33 Mean ulcer area reduction at 6 weeks: 1. 54% 2. 71% P value < 0.01 (reported by trial authors) Secondary outcomes: Pain assessed using 100=cm visual analogue scale: Figure presented in paper indicates reduction in pain at 6 weeks in both groups relative to baseline, but figure not detailed enough for values to be read. The trial authors reported that pain reduction occurred more rapidly in Group 2, and that relative to Group 1, significantly less pain was reported within 1 week of commencement of treatment (P value < 0.01) Numbers (%) of participants reporting adverse events (description): 1. 1/30 (3%) (stinging sensation in the ulcer when dressing applied)

	2. 6/30 (20%) (1 peri-ulcer erythema; 5 stinging sensation in the ulcer when dressing applied) Elevation of serum concentrations of protein-bound iodine occurred after treatment with cadexomer iodine in participants with large ulcers, but tests of thyroid function showed no changes associated with the use of cadexomer iodine
Notes	Overall, 7/67 (10%) participants withdrew. 4 participants (2 per group) withdrew before the first assessment (social reasons 3 and heart failure 1; reasons not presented per group) A further 3 participants completed the trial but were excluded from analysis, 2 because of difficulty in measuring the ulcer because of large size (1 per group) and 1 because of having an ulcer associated with severe rheumatoid arthritis, which interfered with assessment (group not stated)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly allocated to treatment with either cadexomer iodine or the standard local dressing regime" Comment: It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Treatment code not broken until study was completed" Comment: No measures were described to prevent foreseeing the intervention allocation
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	No information provided
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Quote: "A single observer made all assessments in every patient throughout the trial and treatment code not broken until study completed" Comment: It was not stated whether this observer was blind to treatment allocation
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Quote: "Two patients in each treatment group dropped out of the trial before the first assessment. In three instances this was due to social reasons and in one case because of cardiac failure not due to treatment..." Quote: "The results obtained from three patients, all of whom responded to treatment, were excluded from the analysis"

		Comment: Some information on withdrawals (numbers/reasons) was given in relation to the whole sample, not per treatment group
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Comment: Overall withdrawal rate was less than 20%
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Quote: "The results obtained from three patients, all of whom responded to treatment, were excluded from the analysis" Comment: Analysis was based on 60/67 participants. It is unclear how these withdrawals might have impacted estimates of treatment effect (this is a small RCT)
Baseline factors comparable	Unclear risk	Difficult to judge baseline comparability, as mean values, rather than medians, were provided

Lazareth 2008

Methods	Multi-centre randomised controlled trial (24 centres in France, including hospital dermatology and vascular medicine outpatient clinics). A minimum sample size of 96 participants was determined a priori to have 80% power to detect, at 8 weeks, 15% superiority of the silver dressing if relative wound area regression in the non-silver group was within a 20% to 25% range, with an expected standard deviation of 26% and a two-tailed 5% significance level
Participants	102 participants with venous leg ulcers (ABPI > 0.8), ulcer duration < 24 months, wound area 5 to 40 cm^2 and presence of at least 3 of 5 clinical signs of heavy bacterial load (pain at dressing change, peri-ulcer erythema, oedema, foul odour, and heavy exudate). Patients with diabetes were eligible for inclusion. Patients with the following were excluded: current (or within previous week) usage of local or systemic antibiotics; clinically infected wound; erysipelas; malignant wound; recent deep vein thrombosis or venous surgery; neoplastic lesion treated by radiotherapy or chemotherapy; and ongoing treatment with immunosuppressive agents or high dose corticosteroids Group 1: 50 participants Group 2: 52 participants Mean duration of ulcer months ± SD (median) Group 1: 10 ± 8 (9.0) Group 2: 11 ± 8 (9.5) Mean ulcer area, cm^2 ± SD (median) Group 1: 17.5 ± 14.4 (12.6) Group 2: 22.3 ± 20.4 (16.3) 71% of patients were outpatients at recruitment
Interventions	Group 1: contact layer dressing (Restore)—similar to test dressing, the only difference being the absence of silver

	Group 2: contact layer silver dressing (Restore Silver)—non-adhesive, non-occlusive, polyester mesh impregnated with hydrocolloid particles and Vaseline. Silver incorporated as silver sulphate that releases over 7 days. 10 × 10-cm dressing All participants received wound cleansing with normal saline; mechanical debridement, where necessary, to remove slough and necrotic tissue; secondary foam dressings (Ultrasorb); compression therapy selected by the investigators; and dressing changes every other day or less frequently, depending on the clinical condition of the wound and the volume of exudate. Local use of antiseptics (but not antibiotics) was permitted Investigators withdrew participants from the study if dressing-related adverse events occurred, or if they considered that a different treatment was warranted (e.g. systemic antibiotics) Treatment duration was 4 weeks, after which all participants received the non-silver dressing for a further 4 weeks
Outcomes	Primary outcomes: Mean change in ulcer area at 4 weeks, cm^2 ± SD (median): Group 1: -1.3 ± 9.0 (-1.1), n = 48 Group 2: -6.5 ± 13.4 (-4.2), n = 51 The trial authors reported that the between-group difference was statistically significant (P value 0.023) Mean relative change in ulcer size at 4 weeks % ± SD (median): Group 1: -8.6 ± 54.6 (-9.5), n = 48 Group 2: -28.1 ± 36.7 (-29.1), n = 51 No P value reported for between-group difference Mean healing rate, cm^2/day ± SD (median) at 4 weeks: Group 1: -0.08 ± 0.56 (-0.04), n = 48 Group 2: -0.20 ± 0.42 (-0.15), n = 51 The trial authors reported that the between-group difference was statistically significant (P value 0.009) Secondary outcomes: Numbers (%) of participants with no clinical signs of bacterial colonisation at 4 weeks: Group 1: 8/50 (17) Group 2: 20/52 (39) Numbers (%) of participants with adverse events at 4 weeks (event type): Group 1: 11/50 (22) (2 erythema/oedema, 1 infection, 4 peri-ulcer skin irritation, 1 pain, 1 over granulation, 2 other). 5 participants withdrew because of adverse events (types not specified) Group 2: 11/52 (21) (1 erythema/oedema, 2 infection, 4 peri-ulcer skin irritation, 2 pain, 2 other). 4 participants withdrew because of adverse events (types not specified)
Notes	Numbers (%) of participants withdrawing up to week 4 (reasons): Group 1: 14 (28) (4 ulcer aggravation, 9 local adverse event, 1 other event) Group 2: 3 (6) (1 consent withdrawal, 2 ulcer aggravation) Further follow-up data were reported at 8 weeks, but data here were only recorded at 4 weeks to reflect the period of the controlled study
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A random list balanced by blocks of 4 patients was used" Comment: no statement on how randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Each centre received at least 4 sealed envelopes with a number corresponding to the chronological order of patients' inclusion. According to the centre recruitment capacities, more than one block could be provided. No randomization error or deviation was detected by the on-site audits held during the study" Comment: not stated whether envelopes were opaque
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: trial described as "open-label". No information about blinding of participants
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Low risk	Quote: "The wound area tracings were measured by an independent person who was unaware of the test dressings. Furthermore, a blind review of the planimetric and photographic data was performed at the end of the study to validate the investigators' evaluations, by 2 independent and experienced physicians. These reviewers did not know the received dressings and classified the final target ulcer status according to a 7-point scale (from "leg ulcer strongly improved" or "healed", to leg ulcer "strongly aggravated"). This review detected no difference between investigators and reviewers evaluations and confirmed that the decision rules followed by the investigators when the treatment was prematurely discontinued were no different for patients treated with the silver releasing dressing or the control." Comment: The details provided were judged as indicating a low risk of bias for this domain
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: Numbers withdrawing and reasons are reported for both groups
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Group 1: 14 (28%) Group 2: 3 (6%) Comment: Withdrawal rates differed between groups, and Group 1 had withdrawal rate > 20%
Incomplete outcome data	Low risk	

(attrition bias) ITT analysis		Quote: "All analyses were conducted on the intent-to-treat population defined as all randomised patients with at least one follow-up planimetry value" Quote: "...the efficacy analysis on the ITT population included 99 subjects (51 patients treated with the silver sequential strategy [CLS] and 48 patients with the continuous strategy with the control dressing [CL])" Comment: Presentation of data in the trial report indicated that analyses had been conducted according to intention-to-treat, as defined above
Baseline factors comparable	Low risk	Baseline ulcer characteristics appear comparable across groups

Lindsay 1986

Methods	Randomised controlled trial conducted in the UK. Trial was of cross-over design with cross-over point at 4 weeks
Participants	28 females over 30 years of age with exuding venous leg ulcers were recruited. Patients with insulin-dependent diabetes were excluded Group 1: 14 randomly assigned, 13 completed Group 2: 14 randomly assigned, 12 completed Mean ulcer area, mm^2 (read from graph): Group 1: 1300 Group 2: 1250 Mean baseline ulcer duration: 20.1 months (breakdown per group not reported) Not stated whether wounds were clinically infected at baseline (but it appeared that those with infected ulcers might have been allowed into the trial).
Interventions	1. Standard treatment consisting of sterile, non-adherent dressing plus support bandaging or stocking changed on alternate days. Other treatments were also allowed, including topical antimicrobials 2. Ulcer cleansed with sterile saline swabs or water or saline irrigation; cadexomer iodine applied to ulcer surface in a 3-mm layer; dry sterile dressing applied and secured with support bandaging or stocking. The dressing was changed on alternate days All participants had ulcers managed in the community by general practitioners. After 4 weeks, participants were switched to the alternative treatment or were withdrawn from the trial according to the clinician's judgement The duration of the trial was 10 weeks
Outcomes	Primary outcomes: Complete healing at 4 weeks: 1. 1/14 2. 4/14 Mean reduction in ulcer area at 4 weeks: 1. 4.2% 2. 33.6% P value < 0.005 (reported by trial authors)

	Secondary outcomes: Ulcer pain assessed with 10-cm visual analogue scale. The trial authors reported that Group 2 had significantly better results for pain after 4 weeks (P value < 0.002) but no further information presented Infection assessed using swab taken before ulcer cleansing: the trial authors reported that the most frequently isolated organisms during the trial were Enterobacteriaceae, usually polymicrobial infections. The second most frequently occurring group was *Staphylococcus aureus,* and 4 participants were colonised by *Pseudomonas* species. Streptococci groups C and G were also isolated but were quickly eliminated. Cadeomer iodine treatment resulted in elimination or decrease of organisms in most cases. These data appear to relate to the first 4 weeks of the trial, but further information and breakdown by group not provided
Notes	Numbers of participants who withdrew, with reasons: Group 1: peripheral vascular disease (1) Group 2: allergy (1); itching and irritation (1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients were randomised to receive either standard dressing or cadexomer iodine"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	"The patient or whoever was to manage the patient was instructed how to treat the ulcer"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information provided
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	28 participants were randomly assigned, of whom 3 withdrew, one from Group 1 (because of peripheral vascular disease) and two from Group 2 (allergic reaction, skin irritation/itching)

Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Dropout rate less than 20% in each group
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	"Statistical analysis at four weeks was performed on 12 assigned to cadexomer iodine and 13 patient assigned to standard treatment." This suggests that 25 participants were analysed out of 28 recruited to the trial. It is unclear how these withdrawals might have impacted estimates of treatment effect (this is a small RCT)
Baseline factors comparable	Unclear risk	Limited data available

Meaume 2005

Methods	Randomised controlled trial (multi-centre, involving 13 study centres in France). Sample size estimation was described, although not in relation to healing outcomes (it was in relation to a risk of wound infection score—mASEPSIS)
Participants	99 patients with venous leg ulcers (ABPI > 0.7) or pressure ulcers were recruited who were hospitalised or who could be seen daily for 14 days. To be eligible, wounds had to be 2 to 20 cm in one dimension; have at least one of the following signs—covered with > 50% yellow slough, discoloured or friable granulation tissue, pocketing or undermining at the base of the wound, or foul odour; have at least two of the following signs of critical colonisation present—continuous pain, erythema, oedema, heat and moderate to high levels of exudate. Patients with diabetes were eligible for inclusion Patients with the following were excluded: clear signs of ulcer infection requiring antibiotics, or lymphangitis and/or fever; poor life expectancy; clinical condition that might interfere with wound healing; receiving systemic antibiotics during previous 5 days; or receiving a topical chemical debridement agent during previous 7 days Group 1: 48 participants (33 had VLU) Group 2: 51 participants (38 had VLU) Mean ulcer duration of VLU participants, months ± SD (median): Group 1: 25.0 ± 37.2 (7.0) Group 2: 42.5 ± 96.0 (12.0) Mean ulcer area of VLU participants, cm^2 ± SD (median): Group 1: 24.5 ± 21.3 (16.1) Group 2: 44.8 ± 46.3 (25.7)
Interventions	Group 1: pure calcium alginate dressing (Algosteril) Group 2: silver-releasing hydro alginate dressing (Silvercel) All participants received wound cleansing with sterile saline; debridement as necessary, using surgical or mechanical methods; sterile pads as secondary dressings secured with hypoallergenic adhesives; systemic antibiotic therapy in cases of wound infection; at least 5 dressing changes per week during the first 2 weeks, and at least every 2 to 3 days thereafter. All participants with venous leg ulcers were treated with compression bandaging designed to provide 15 to 35 mmHg initial ankle pressure

	(French classification II to III). Wound cultures were taken at the investigators' discretion, but methods used were not reported Treatment duration was two weeks. Participants were followed up whenever possible for an additional two weeks to evaluate change in wound surface area and to continue monitoring dressing acceptability and tolerability
Outcomes	Primary outcomes: Mean ± SD change in ulcer area (cm^2, VLU participants only) at week 4: Group 1: -6.0 ± 11.7 Group 2: -9.5 ± 17.9 The trial authors did not report a P value for the between-group difference Mean ± SD percentage change in ulcer area (VLU participants only) at week 4: Group 1: -28.5 ± 37.0 Group 2: -21.0 ± 45.4 The trial authors did not report a P value for the between-group difference Mean ± SD healing rate over 4 weeks (cm^2/d, VLU participants only): Group 1: 0.21 ± 0.42 Group 2: 0.34 ± 0.64 The trial authors did not report a P value for the between-group difference Secondary outcomes: Mean ± SD mASEPSIS index (ITT population, VLU participants only), follow-up point unclear: Group 1: 86.3 ± 51.0 (n = 33) Group 2: 111.8 ± 79.1 (n = 38) Note: The mASEPSIS index is an evaluation of the risk of wound infection, with higher scores indicating higher risk of infection. The trial authors reported that the between-group difference was not statistically significant (P value not provided) and that findings were similar for VLU participants between ITT and per protocol populations NB: The following findings apply to all participants, separate data not available for VLU participants: Numbers (%) of wounds in all participants who developed a clinical infection during the 4-week follow-up: Group 1; 23/51 (46) Group 2: 16/48 (33) The trial authors reported that the between-group difference was not statistically significant (P value 0.223) Numbers (%) of all participants requiring systemic antibiotics during the 4-week follow-up: Group 1: 4/51 (8) Group 2: 5/48 (10) The trial authors reported that the between-group difference was not statistically significant (P value 0.736) Numbers (%) of all participants with adverse events (event type): Group 1: 5/48 (10)—all were VLU participants (1 pain during dressing change; 1 peri-ulcer eczema; 1 burning sensation following dressing change; 1 increased wound size and pain; 1 erythema and pain)

	Group 2: 5/51 (8)—4 were VLU participants (1 peri-ulcer eczema; 1 peri-wound irritation due to maceration; 1 extension of slough and dry wound; 1 pruritis and pain; 1 pain during dressing change, peri-ulcer erythema and pruritus)
Notes	Numbers (%) of all participants withdrawing (reasons): Group 1: 9/48 (19) (1 alginate dressing no longer indicated, as wound had become dry; 1 intercurrent event; 1 wound grafting; 2 wound infection; 4 wound aggravation) Group 2: 10/51 (20) (1 alginate dressing no longer indicated, as wound had become dry; 1 consent withdrawal; 4 intercurrent event; 1 wound grafting; 1 wound infection; 2 wound aggravation) Numbers (%) of VLU participants withdrawing: Group 1: 6/33 (18) Group 2: 9/38 (24)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Two *a priori* randomisation lists were prepared and balanced by blocks of six" Comment: no statement on how the randomisation sequence was generated
Allocation concealment (selection bias)	Unclear risk	Quote: "Two *a priori* randomisation lists were prepared and balanced by blocks of six" Comment: no information on group allocation concealment provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: trial described as "open-label" with no information about participant blinding
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Comment: trial described as "open-label" with no information about outcome assessor blinding
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: The numbers withdrawing and the reasons for withdrawal were reported for both groups

Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	Group 1: 6/33 VLU participants (18%) Group 2: 9/38 VLU participants (24%) Comment: A larger proportion of VLU participants in Group 2 withdrew; withdrawal rate of VLU participants in Group 2 was > 20%
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Quote: "All patients received at least one application of the allocated dressings and had at least one clinical evaluation (ITT population)" Comment: both ITT and per-protocol analyses presented, and clear that all randomly assigned participants included in the ITT population
Baseline factors comparable	High risk	Comment: Median baseline ulcer area and duration are comparatively greater in Group 2 than in Group 1

Michaels 2009

Methods	Multi-centre pragmatic randomised controlled trial conducted in the UK. Initial sample size requirement was for 300 participants, including loss to follow-up and withdrawal; this was revised to 212 participants after slow recruitment resulting in an extension to the trial's duration, and information from an interim analysis
Participants	Patients with active ulceration of the lower leg ≥ 1 cm in diameter that had been present for longer than 6 weeks were included. Patients with the following were excluded: ABPI < 0.8 in the affected leg; systemic antibiotic use; and insulin-controlled diabetes mellitus Group 1: 106 participants Group 2: 107 participants Numbers (%) of participants with ulcer size ≤ 3 cm in diameter: Group 1: 76 (72) Group 2: 77 (72) Numbers (%) of participants with ulcer size > 3 cm in diameter: Group 1: 30 (28) Group 2: 30 (28) Numbers (%) of participants with previous ulcer in either leg: Group 1: 52 (49) Group 2: 61 (57) Median baseline ulcer size, cm^2 (from figure): Group 1: 2.5 Group 2: 2.5 Numbers (%) of participants with ulcer present > 12 weeks: Group 1: 43 (40) Group 2: 39 (36) Mean EQ-5D health state scores: Group 1: 0.6536 (n = 94)

	Group 2: 0.6446 (n = 98) Mean SF-6D health state scores: Group 1: 0.6792 (n = 83) Group 2: 0.6544 (n = 89) No information on signs of ulcer infection or colonisation reported, but patients were excluded if using antibiotics
Interventions	Group 1: non-antimicrobial low-adherent dressing from any manufacturer (most were knitted viscose dressings) Group 2: approved silver-donating dressings including silver-impregnated foam, alginate, hydrocolloid, low-adherent and non-adherent dressings (Aquacel Ag, Acticoat, Acticoat 7, Acticoat Absorbant, Contreet Ag or Urgotel SSD). The most commonly used dressings were Urgotel SSD, Acticoat 7 and Aquacel Ag. Most participants remained on the same dressing during the treatment period The choice of the specific silver-donating or non-silver dressing was the responsibility of the clinician. In both groups, the allocated dressing was placed beneath multi-layer compression, applied by a nurse trained in the technique. Dressings were changed and bandages reapplied on a weekly basis unless clinicians believed that more frequent changes were necessary. The choice of compression was based on local practice. After healing, a compression stocking was recommended. Other interventions such as debridement were used if needed Treatment duration was until the ulcers were fully healed, or for the 12-week treatment period of the trial. Follow-up was at 1, 3, 6 and 12 months. If active ulceration was still present after 12 weeks, the decision regarding continuation or change of the dressing was made by the clinician
Outcomes	Primary outcomes: Median time to healing, days (95% CI): Group 1: 58 (43 to 73) Group 2: 67 (54 to 80) The trial authors reported that the between-group difference was not statistically significant (P value 0.408, Cox proportional hazards model) The trial authors reported the following hazard ratio estimate for silver versus control dressings: 1.13 (95% CI 0.85 to 1.15) Numbers (%) of participants with complete ulcer healing at 12 weeks: Group 1: 59/106 (56) Group 2: 62/107 (58) Numbers (%) of participants with complete ulcer healing at 6 months: Group 1: 78/106 (74) Group 2: 87/107 (81) Numbers (%) of participants with complete ulcer healing at 12 months: Group 1: 90/106 (85) Group 2: 95/107 (89) Secondary outcomes: Recurrence rates within first year.: Group 1: 13 (14%) of 90 participants who were healed within the first year Group 2: 11 (12%) of 95 participants who were healed within the first year

	Health-related quality of life: Mean EQ-5D health state scores at 12 weeks/1 year (adjusted for baseline EQ-5D score): Group 1: 0.7004 (n = 76)/0.6752 (n = 58) Group 2: 0.7255 (n = 81)/0.7526 (n = 61) Mean SF-6D health state scores at 12 weeks/1 year (adjusted for baseline SF-6D score): Group 1: 0.7029 (n = 68)/0.662 (n = 53) Group 2: 0.6864 (n = 73)/0.7092 (n = 55) The trial authors reported no significant between-group differences at any of the follow-up times (baseline, 1, 3, 6 and 12 months) in the EQ-5D and SF-6D mean utility scores. No significant difference between groups was noted with respect to mean follow-up after adjustment for age. This was also true when the mean scores for the eight SF-36 dimensions were compared. Adverse events: The trial authors reported no adverse events identified as being related to the dressings, although 1 participant in Group 2 stopped treatment at week 4 because of skin irritation. Also, 4 participants in each group died during the 1-year follow-up period, but after the 12-week treatment period Costs and resource use, price year 2007: Mean cost of clinic visits GBP (95% CI): Group 1: 196.06 (156.95 to 235.18) (n = 67) Group 2: 275.39 (236.83 to 313.95) (n = 74) Mean cost per dressing GBP (95% CI): Group 1: 5.73 (2.96 to 8.49) (n = 67) Group 2: 30.62 (25.47 to 35.78) (n = 74) Mean total cost per participant based on cost of clinic visits, home visits, dressings, bandages, GP and chiropody contacts, compression hosiery, antibiotics and other medicines GBP (95% CI): Group 1: 320.12 (277.42 to 362.82) (n = 67) Group 2: 417.97 (375.01 to 460.93) (n = 74) Cost-effectiveness: Silver dressings were associated with an incremental cost in GBP of 97·85 and an incremental QALY (quality-adjusted life-year) gain of 0·0002 compared with control dressings. The ICER for silver dressings was GBP 489,250 per QALY gained. Based on these data and additional sensitivity analyses, the trial authors concluded that silver dressings were unlikely to be cost-effective
Notes	In participants with bilateral ulceration, the leg with the greatest total ulcer area was the study limb, but the allocated treatment was used for both legs Numbers (%) of participants withdrawing (reasons): Group 1: 5 (5) (2 lost to follow-up; 3 received silver dressing; 1 was by participant request and 2 by nurses' choice) Group 2: 8 (7) (3 lost to follow-up; 4 did not receive a silver dressing; 1 case was due to non-availability of dressing and 3 were unexplained; 1 case of skin irritation) Numbers (%) of participants who did not receive the allocated dressing: Group 1: 3/106 (3)—treated with silver-donating dressings

	Group 2: 4/107 (4)—1 healed before dressing became available, 3 unexplained breach of protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocation was carried out using a computer program to generate stratified block randomisation with variable block size" Comment: The details provided suggested a satisfactory method of random sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "Trial numbers and randomisation were allocated through a telephone-based service which recorded details of the patient and which proffered a checklist of questions to confirm eligibility" Comment: The details provided suggested a satisfactory method of allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	Quote: "It was not possible to blind either the patients or the nurses applying the dressings, because each type of dressing had different physical characteristics" Comment: It is clear from the details provided that participants were not blind to treatment allocation
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Low risk	Quote: "The research staff dealing with postal questionnaires, the staff measuring ulcer sizes based upon tracings, and the staff carrying out initial data entry and analysis were all blinded to the treatment allocation of the patient" Comment: It is clear from the details provided that outcome assessors were blind to treatment allocation
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: The numbers of participants withdrawing from each group were reported, along with reasons for withdrawal
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Group 1: 5/106 (5%) Group 2: 8/107 (7%) Comment: Withdrawal rates were low and similar between groups
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Quote: "Analysis of all outcomes was on an intention-to-treat basis" Comment: It is clear from the trial report that an intention-to-treat analysis was conducted

Baseline factors comparable	Unclear risk	The information provided on baseline ulcer area suggests between-group comparability, but the only information on baseline ulcer duration was the number of participants in each group with ulcers present > 12 weeks

Miller 2010

Methods	Randomised controlled trial (multi-centre involving 2 not-for-profit community nursing services in Australia). Sample size calculation estimation was reported, but the number of patients recruited was less than the estimated number (281 vs 360)
Participants	281 participants with venous or mixed venous/arterial aetiology leg ulcers (ABPI ≥ 0.6) and ≤ 15 cm in diameter were randomly assigned. Ulcers had to present at least one of the following signs of infection or critical colonisation: cellulitis, suppuration, lymphangitis, sepsis, bacteraemia, changes in granulation tissue, increased or malodorous exudate, new areas of slough or wound breakdown, impaired healing, increased or new pain. Patients with/receiving the following were excluded: diabetes; malignant leg ulcer; topical antiseptics within 1 week of recruitment; antibiotics within 48 hours of recruitment; systemic steroids; or palliative care 74% of recruited participants had venous leg ulceration; the remainder had mixed disease (data per group not provided): Group 1: 140 participants Group 2: 141 participants Mean baseline ulcer area reported for participants included in final analysis (cm^2 ± SD): Group 1: 59.7 ± 63.2 (n = 133) Group 2: 81.2 ± 107.0 (n = 133) Mean baseline ulcer duration reported for participants included in final analysis (weeks ± SD): Group 1: 58.1 ± 260.6 (n = 133) Group 2: 49.4 ± 165.9 (n = 133)
Interventions	Group 1: silver-donating dressings (Acticoat, Acticoat Absorbant or Acticoat 7) Group 2: cadexomer iodine dressings (Iodosorb ointment or Iodosor powder) All participants received dressing choice determined by clinician, according to individual wound characteristics such as moisture levels; and four-layer compression bandaging (Profore or Profore Lite). Dressings in both groups were provided until all signs of critical colonisation and infection had been absent for 1 week, after which a non-antimicrobial dressing was applied according to the clinician's judgement. If signs of critical colonisation or infection recurred, the original randomised dressing was reinstated Fifty-five participants received antibiotic treatment during the 12-week study period. Breakdown by group not reported Duration of treatment was 12 weeks
Outcomes	Primary outcomes: Time to healing:

Estimates not provided; the trial authors reported that the between-group difference was not statistically significant (P value 0.70, log rank test; and P value 0.80 Wilcoxon test)

Numbers (%) of ulcers healed at week 12:

Group 1: 85/140 (61)

Group 2: 84/141 (60)

Mean percentage daily healing rate ± SD:

Group 1: -2.10 ± 1.89 (n = 133)

Group 2: -1.69 ± 2.46 (n = 133)

Secondary outcomes:

Numbers of adverse events reported:

Group 1: 13

Group 2: 8

Details of the adverse events not provided; unclear whether the numbers provided refer to the numbers of participants reporting adverse events, or the number of adverse events in the group.

Bacterial profile of wounds obtained by swab, using a rotating, 10-point zigzag technique while avoiding necrotic tissue, across wound bed, which had been cleansed with sterile water before specimen collection. Gram stain and semi-quantitative analyses were conducted to identify the species and level of bacteria present. The bacterial burden was classified as nil/scant, low, moderate or heavy. In assessing the semi-quantitative bacteriology results for each swab, the highest level of growth for bacilli positive, bacilli negative, cocci positive or cocci negative was used, regardless of which organism was isolated from the wound culture. Swab data obtained from 278 participants, breakdown per group not provided

Numbers (%) of participants with nil/scant/low and mod/high degree of bacterial growth during the first 2 weeks of treatment:

Leucocytes:

Group 1: 116 nil/scant/ low; 16 mod/high

Group 2: 110 nil/scant/ low; 17 mod/high

Gram-postive bacilli:

Group 1: 90 nil/scant/ low; 5 mod/high

Group 2: 90 nil/scant/ low; 1 mod/high

Gram-negative bacilli:

Group 1: 62 nil/scant/ low; 43 mod/high

Group 2: 64 nil/scant/ low; 32 mod/high

Gram-positive cocci:

Group 1: 72 nil/scant/ low; 41 mod/high

Group 2: 73 nil/scant/ low; 35 mod/high

Gram-negative cocci:

Group 1: 87 nil/scant/ low; 0 mod/high

Group 2: 83 nil/scant/ low; 0 mod/high

Staphylococcus aureus was the most commonly isolated organism overall (isolated from around 90% of ulcers, further data and breakdown per group not provided). 16 swabs were identified with methicillin-resistant *Staphylococcus aureus* (not explained how many participants this relates to, nor which treatment groups)

	The trial authors reported that when moderate to heavy growth was identified, no differences in healing rates were noted between treatment groups. When nil/scant or low bacterial growth was identified, Group 1 had a significantly faster healing rate compared with Group 2 in relation to leucocytes (P value < 0.01), Gram-positive bacilli (P value < 0.05), Gram-positive cocci (P value < 0.01) and Gram-negative cocci (P value < 0.05) within the first 2 weeks Healing rates in light of bacterial colony and degree of bacterial burden were not examined for the entire 12-week study period because of variations in the timing of swabs; the baseline swab was the only consistent time when all study participants were swabbed Dressing acceptability as rated by participants with a 4-point questionnaire—completely agree, moderately agree, moderately disagree, completely disagree that the dressing was acceptable Proportion of participants who completely or moderately agreed that the dressing was acceptable overall: Group 1: 91.6% (n = 107) Group 2: 88.9% (n = 100)
Notes	The trial authors reported that baseline differences in wound size were adjusted for in the analysis. Numbers (%) of participants withdrawing (reasons): Group 1: 7 (5) (1 lost to follow-up, 5 withdrawn and insufficient data for analysis, 1 died) Group 2: 8 (6) (3 lost to follow-up, 5 withdrawn and insufficient data for analysis) When participants had multiple wounds, the wound with the most signs of critical colonisation or infection was studied, but the same randomly assigned treatment was applied to all wounds for that participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomization lists were generated using the random number function generator in Microsoft Excel" Comment: The details provided suggested a satisfactory method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Following recruitment, clients were randomized to their treatment group by the nurse opening the next numbered envelope in which the group allocation was concealed" Comment: not stated whether envelopes were sealed or opaque
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	Quote: "The design of this trial could have been strengthened by participant and data collector blinding. However, presentation of the two antimicrobial treatments was quite distinctive and might have been discerned by sensation alone" Comment: It was clear that participants were not blind to treatment allocation

Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	High risk	Quote: "The design of this trial could have been strengthened by participant and data collector blinding. However, presentation of the two antimicrobial treatments was quite distinctive and might have been discerned by sensation alone" Comment: It was clear that outcome assessors were not blind to treatment allocation
Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Comment: Numbers of participants lost to follow-up, withdrawing or died are given for each group, but reasons for withdrawal are not reported
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Group 1: 7/140 (5%) Group 2: 8/141 (6%) Comment: The withdrawal rates are low and similar between groups
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Quote: "In accordance with the intention-to-treat principle, once the client was randomized to a treatment, they remained in the study regardless of variations to their treatment and completed all data collection including monitoring the treatment provided" Quote: "All clients with at least two wound size measurements at any time during the 12-week period, for whom a healing rate could therefore be calculated, were included in the final analysis in the treatment arm to which they were randomized, even if a change in treatment had occurred. With a total of 15 clients excluded from the analysis due to missing data or loss to follow-up (seven from the silver treatment group and eight from the iodine treatment group), 266 clients (95%) were included in the final analysis" Comment: Some randomly assigned participants were excluded from the analysis. It is unclear how these withdrawals might have impacted estimates of treatment effect
Baseline factors comparable	Unclear risk	Difficult to judge between-group baseline comparability of ulcer size or duration, as data are reported only for participants included in the final analysis (not all participants randomly assigned). Values are reported as mean ± SD (medians are not reported)

Morias 1979

Methods	Randomised controlled trial conducted in Belgium
Participants	59 people with chronic leg ulcers, 45/59 (76%) of venous aetiology, were recruited Group 1: 29 people Group 2: 30 people Median (range) baseline ulcer area (mm^2): Group 1: 100 (4 to 3300); Group 2: 100 (3 to 4400) No information about baseline ulcer duration or infection status of wounds

Interventions	1. Placebo tablet identical in appearance to levamisole 2. Levamisole dosed according to body weight ranging from 100 to 250 mg, given on 2 consecutive days every week until cure or failure or for 20 weeks Previously used topical treatment was continued for all participants; no information about whether this included compression
Outcomes	At 20 weeks Number of ulcers cured 1. 22/29 (76%) 2. 30/30 (100%) Secondary outcomes: Adverse effects 1. Group 1: 0/29 (0%) 2. Group 2: 3/30 (10%) - all were gastric complaints
Notes	Group 1: evident failure (8) Group 2: evident failure (2) The trial authors state that double-blind treatment was stopped before the end of the trial in eight participants in Group 1 and two participants in Group 2 because of "evident failure" (defined as no improvement). However, other information in the trial report suggests that all 59 participants were followed up for 20 weeks

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"All patients were sequentially numbered and received a bottle bearing their individual sequence number and containing double-blind tablets. These tablets randomly contained either 50 mg of levamisole (30 patients) or a placebo (29 patients) and were identical in appearance." It was not stated how the randomisation sequence was generated
Allocation concealment (selection bias)	Low risk	Reports "sequentially numbered drug containers of identical appearance"
Blinding (performance bias and detection bias) Participant blinded to the intervention	Low risk	"these tablets randomly contained either 50mg of levamisole or a placebo and were identical in appearance"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	No information provided

Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Participants complete at analysis; no dropouts or withdrawals reported
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	No withdrawals reported
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Participants complete, no exclusions
Baseline factors comparable	Unclear risk	The two groups appeared comparable for baseline ulcer area. However, no information about baseline ulcer duration was available, and it was not stated whether wounds were clinically infected

Moss 1987

Methods	Randomised controlled trial conducted in the UK, cross-over design (with cross-over point at 6 weeks)
Participants	43 outpatients with venous leg ulcers of > 3 months' duration, unresponsive to topical treatment, were randomly assigned. Some participants also had arterial disease, and no further information was provided. Data reported on 42 participants: Group 1: 21 completers Group 2: 21 completers Median ± SD baseline ulcer area (cm^2): Group 1: 25.5 ± 29.5; Group 2: 19.7 ± 19.8 Median ± SD baseline ulcer duration (months): Group 1: 61.0 ± 68.0; Group 2: 75.0 ± 127.0 No information about whether wounds were clinically infected at baseline
Interventions	1. Ulcers cleansed with normal saline, filled with dextranomer powder, non-adhesive pad, cotton wool wadding, stockinet and a firm elastic bandage applied 2. As above, but cadexomer iodine powder used instead All participants were allowed to receive a 2-week course of oral antibiotics during the trial for clinical infection of ulcers After 6 weeks of randomly assigned treatment, those not improving could be changed to the other treatment for the remaining 20 weeks of the trial
Outcomes	Primary outcomes: At 6 weeks: Mean percentage area change: Group 1: -2%; Group 2: -3% (values read from graph) No significant difference between groups (P value not reported)

	Secondary outcomes: Numbers (%) of participants requiring antibiotics up to week 6: 1. 5/21 (24); 3 for infection in trial ulcer and 2 for infection in another ulcer 2. 5/21 (24); 4 for infection in trial ulcer; 1 for chest infection Proportion of participants acquiring organisms during 6 weeks of treatment (values read from graph): 1. Beta-haemolytic *Streptococcus* 35%; *Staphylococcus aureus* 18%; *Pseudomonas* species 10%; *Proteus* species 10% 2. Beta-haemolytic *Streptococcus* 20%; *Staphylococcus aureus* 15%; *Pseudomonas* species 0%; *Proteus* species 0% Proportions of participants eradicating organisms during 6 weeks of treatment (values read from graph): 1. Beta-haemolytic *Streptococcus* 0%; *Staphylococcus aureus* 42%; *Pseudomonas* species 10%; *Proteus* species 25% 2. Beta-haemolytic *Streptococcus* 40%; *Staphylococcus aureus* 0%; *Pseudomonas* species 35%; *Proteus* species 50% Link between bacteriology and wound healing: Complete eradication of bacteria during the 6-week trial was associated with a reduction in mean ulcer size in both treatment groups. In terms of specific isolates, this association was statistically significant for *Pseudomonas* species (P value < 0.05)
Notes	1 participant was withdrawn because of poor compliance (group allocation not stated) Bacterial profile assessed by wound swab

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"n=42 were randomly allocated to treatment"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	Not reported that allocation was concealed
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	"...the trial was not blind because the treatments can easily be distinguished by colour..."
Blinding (performance bias and detection bias) Outcome assessor	High risk	"All assessments were performed by CM or AT, but could not be blind because after the dressing were removed differences in colour were still apparent"

blinded to the intervention		
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Dropout rate described (1 participant from unspecified group, because of "poor compliance")
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Dropout rate < 20%
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	One participant dropped out, and it is not clear whether that participant was included in the 6-week analysis
Baseline factors comparable	High risk	Ulcers in Group 1 were of shorter duration but larger area compared with Group 2. It is not clear whether wounds were clinically infected at baseline

Münter 2006

Methods	Randomised controlled trial. Multi-centre—80 study centres, 9 countries (Belgium, Brazil, Canada, Denmark, Germany, Italy, Slovenia, Switzerland, UK). From an interim analysis, a sample of 272 participants per treatment group was estimated as required to detect a difference in means of 17.1 relative surface area with standard deviation 71.0, at 80% power and 5% significance level. To ensure adequate recruitment, while allowing for a withdrawal rate of 15%, a target of "over 600" was set
Participants	619 participants with chronic wounds exhibiting delayed healing and producing moderate to high levels of exudate were recruited. Ulcers had to be < 0.5 cm in depth and characterised by at least one of the following: delayed healing due to bacteria (< 0.5 cm ulcer reduction or no change or increase in wound volume or surface area over past 4 weeks); being at risk of infection (such as diabetic wounds or sacral pressure ulcers); discolouration of granulation tissue; malodour; or clinical infection requiring treatment with systemic antibiotics Group 1: 293 participants Group 2: 326 participants Breakdown of proportions of participants according to wound type: Group 1: venous leg ulcers 50%; mixed venous/arterial leg ulcers 17%; pressure ulcers 7%; diabetic foot ulcers 8%; other wounds 18% Group 2: venous leg ulcers 46%; mixed venous/arterial leg ulcers 21%; pressure ulcers 8%; diabetic foot ulcers 8%; other wounds 17% Numbers of participants with leg ulcers, with breakdown according to aetiology: Group 1: 197—venous 147/197 (75%); venous/arterial 50/197 (25%) Group 2: 218—venous 150/218 (69%); venous/arterial 68/218 (31%) Mean baseline ulcer size in cm^2 ± SD (median, range) for all wound types (separate data not presented for participants with leg ulcers): Group 1: 36.6 ± 64.4 (12.0, 0.1 to 400)

	Group 2: 52.9 ± 90.0 (20.0, 0.1 to 700) No data on baseline wound duration were provided Participants with clinically infected wounds, or wounds deemed at risk of infection, were eligible for inclusion, but no data related to prevalence of infection at baseline were presented
Interventions	Group 1: local best practice, including the following dressings—foams/alginates (53%), hydrocolloids (12%), gauze (3%), silver dressings (17%), other antimicrobial dressings (9%), other active dressings (6%) Group 2: silver-donating foam dressing (Contreet Ag). Both adhesive and non-adhesive versions of the dressing were used Wound management for all participants (including compression therapy) was performed in line with local protocols, guidelines and dressing manufacturers' instructions. All dressings were changed between weekly assessments when judged necessary by the wound care practitioners Duration of treatment was 4 weeks
Outcomes	Primary outcomes: Median percentage change in ulcer area at 4 weeks for venous and venous/arterial leg ulcer participants: Group 1: -28.8 (n = 197) Group 2: -45.5 (n = 218) The trial authors reported that the between-group difference was statistically significant (P value 0.0001) Median percentage change in ulcer area at 4 weeks for venous leg ulcer participants: Group 1: -26.9 (n = 147) Group 2: -46.2 (n = 150) The trial authors reported that the between-group difference was statistically significant (P value 0.0001) Secondary outcomes: Numbers (%) of participants with pain at dressing change for venous and venous/arterial leg ulcers: Group 1: 2/197 (1%) Group 2: 1/218 (< 1%) The trial authors reported that the between-group difference was statistically significant (P value < 0.0001) Numbers (%) of participants with ulcer pain between dressing changes for venous and venous/arterial leg ulcers: Group 1: 2/197 (1%) Group 2: 1/218 (< 1%) The trial authors reported that the between-group difference was statistically significant (P value 0.0003) Adverse events—numbers (%) of participants with macerated peri-ulcer skin at 4 weeks for venous and venous/arterial leg ulcer participants: Group 1: 27/197 (13.7%) (22.1% at baseline) Group 2. 26/218 (12.0%) (28.6% at baseline)

	The trial authors reported that the between-group difference at week 4 was not statistically significant, but no P value was provided Health-related quality of life (EQ-5D) for venous leg ulcer participants: The trial authors reported that the between-group difference for the overall EQ-5D score at 4 weeks was not statistically significant, but no data were provided apart from the P value (P value 0.0878) When analysed separately, significantly less pain/discomfort was reported in Group 2 compared with Group 1; again, no data shown other than the P value (P value 0.0426). Not stated whether values were adjusted for baseline scores (and no baseline scores were presented) Cost-effectiveness parameters—mean wear time of dressing for venous and venous/arterial leg ulcer participants: Group 1: 2.1 days Group 2: 3.5 days The trial authors reported that the between-group difference was statistically significant (P value < 0.0001)
Notes	No outcome data on infection-related or microbiological outcomes were presented No information about withdrawals was provided Note: 17% of participants in the control group received silver dressings

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a computer-generated list in sealed envelopes, patients were randomly assigned to a four-week treatment period of either silver foam or LBP" Comment: The above information suggested a satisfactory method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "Using a computer-generated list in sealed envelopes, patients were randomly assigned to a four-week treatment period of either silver foam or LBP" Comment: No statement was made as to whether envelopes were opaque
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: The trial was described as "open", and no mention was made of participant blinding
Blinding (performance bias and detection bias) Outcome	Unclear risk	Quote: "The study personnel at the participating centres completed the data collection forms" Comment: The trial was described as "open", and no mention was made of outcome assessor blinding

assessor blinded to the intervention		
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Comment: Although no explicit statement is made, tabulated outcome data for leg ulcers indicate that analyses were based on all participants
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Comment: Although no explicit statement is made, tabulated outcome data for leg ulcers indicate that analyses were based on all participants
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Quote: "Data were analysed on the principle of last observation carried forward" Quote: "The obtained data were analysed as intention to treat (ITT)" Comment: Although no explicit statement is made, tabulated outcome data for leg ulcers indicate that analyses were based on all participants
Baseline factors comparable	Unclear risk	Baseline ulcer size was reported for all wound types together, not separately for the leg ulcer participants. For the overall group, the baseline ulcer size was larger in Group 2. No information on baseline ulcer duration was provided

Ormiston 1985

Methods	Randomised controlled trial conducted in the UK with optional cross-over point at 12 weeks
Participants	61 participants with chronic venous ulcers (ABPI ≥ 0.7) were recruited; the trial authors presented data on 60 participants Group 1: 30 participants Group 2: 31 participants Mean ± SD baseline ulcer area (cm^2): Group 1: 10.2 ± 8.7; Group 2: 12.1 ± 13.9 Median [10th to 90th percentile] (range) baseline duration of ulcer (months): Group 1: 6.0 [4 to 36] (3 to 96); Group 2: 8.5 [3 to 144] (3 to 517) No information about ulcer infection status at baseline (but it appeared that those with infected ulcers might have been allowed into the trial).
Interventions	1. Ulcers cleansed with saline; polymyxin and bacitracin ointment (Polyfax) and gentian violet applied; ulcer covered with non-adherent dressing (Melolin) 2. Ulcers cleansed with saline; cadexomer iodine powder sprinkled in a layer 3 to 5 mm deep; ulcer covered with gauze pad All participants were treated at home; were trained by study nurses how to dress and bandage their ulcers; changed dressings and bandages daily; and received below-knee bandaging with a crepe bandage followed by a cotton crepe compression bandage

Outcomes	Primary outcomes: At 12 weeks: Complete healing: 1. 7/30 2. 12/31 Mean ± SEM healing rate (cm^2/wk): 1. 0.46 ± 0.1 2. 0.89 ± 0.1 P value 0.0001 (reported by trial authors) Mean healing rate (cm^2/wk/cm circumference) 1. 0.03 ± 0.004 2. 0.06 ± 0.005 P value 0.0001 (reported by trial authors) Secondary outcomes: No significant difference in improvement in pain, erythema, exudate, oedema, pus/debris and granulation between both groups of the study The trial authors reported no significant effect of treatment on bacterial colonisation, but no data were presented Numbers of participants reporting adverse events: 1. Eczema, pruritus, rashes (2) 2. Difficulty in removing cadexomer iodine from ulcer (2—not stated whether 1 of these participants was the one who withdrew); stinging or itching on application of cadexomer iodine (3); eczema, pruritus, rashes (5)	
Notes	Withdrawals: Group 1: none Group 2: Death (1, included in analysis) Difficulty in removing cadexomer iodine from ulcer (1, included in analysis) Admitted to hospital for routine surgery and received inappropriate dressing (1, excluded from analysis) Total = 3	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"subjects were randomised to treatment with cadexomer iodine or standard"; it was not stated how the sequence was generated
Allocation concealment (selection bias)	Low risk	"patients were then allocated a code number according to sequence of selection for the trial. for each number there was a double sealed envelope that contained a paper stating which treatment the patient should receive. The sequence of treatments was randomised, and the code of randomisation was not available to the investigators"
Blinding (performance bias and	High risk	"A nurse specially attached to the study taught the patients how to dress and bandage their ulcers..."

detection bias) Participant blinded to the intervention		
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"At the 12th week each case was reviewed by a clinician not associated with the routine assessment of the ulcer to see whether it was healing satisfactorily." Not stated whether clinician was blind to treatment allocation
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	"Sixty one patients entered this study. One patient receiving cadexomer iodine was admitted to hospital for routine surgery and his ulcer was dressed inappropriately.He was withdrawn from the trial" Study further describes 2 participants who failed to complete the study
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Dropout rate acceptable
Incomplete outcome data (attrition bias) ITT analysis	Low risk	"Sixty one patients entered this study. One patient receiving cadexomer iodine was admitted to hospital for routine surgery and his ulcer was dressed inappropriately. He was withdrawn from the trial. This left 30 in each group. Two patients, both receiving cadexomer iodine, failed to complete the study. One died of a perforated ulcer and the other had difficulty removing the cadexomer iodine from the ulcer. The data on these two patient were included in the analysis." It is unlikely that exclusion of one participant from the analysis had an important impact on estimates of treatment effect
Baseline factors comparable	High risk	Median values indicate that ulcers in Group 2 were of longer duration than those in Group 1. It is difficult to interpret comparability for ulcer area, as mean rather than median values are presented. It is unclear whether ulcers were clinically infected at baseline

Skog 1983

Methods	Randomised controlled trial conducted in Sweden (multi-centre, 10 study centres), with optional cross-over point at 6 weeks
Participants	95 participants with chronic infected venous ulcers of ≥ 3 months' duration, ≥ 2 cm diameter and ≥ 3 cm^2 surface area were recruited, of whom 21 were excluded from analyses. Some included participants had mixed venous/arterial aetiology leg ulcers Group 1: 45 randomly assigned, 36 analysed Group 2: 50 randomly assigned, 38 analysed Numbers (%) of participants with venous/mixed venous/arterial leg ulcers:

	Group 1: 30/36 (83)/6/36 (17) Group 2: 37/38 (97)/1 (3) Mean ± SEM baseline ulcer area, cm^2: Group 1: 34.0 ± 5.7 (n = 36) Group 2: 20.1 ± 4.4 (n = 38) Mean ± SEM baseline ulcer duration, months: Group 1: 22.2 ± 14.3 (n = 36) Group 2: 26.5 ± 18.3 (n = 38) Mean ± SEM baseline pain score (assessed by 100-point visual analogue scale divided into increments of 10, where 0 = no pain and 100 = severe pain): Group 1: 33.0 ± 4.3 (n = 36) Group 2: 32.0 ± 4.7 (n = 38) All participants had infected ulcers at baseline (infection was defined as a colony count of +++ using a standard plating technique).
Interventions	1. Ulcers cleansed daily with dilute hydrogen peroxide or dilute potassium permanganate baths, then non-adherent dressing applied (most commonly paraffin-impregnated dressings, also saline dressings and bland ointments used). Other treatments were allowed, including systemic antibiotics 2. Ulcers cleansed with running water, then cadexomer iodine powder applied to a depth of 3 mm followed by application of a dry dressing All participants received care at home or at a hospital clinic; compression bandages (system unspecified, applied by nurse or participant); twice-daily dressing changes, if necessary, during the first few days of the trial, thereafter once-daily changes. If no improvement in the ulcer was noted at 6 weeks, the participant was switched to the other treatment for a further 12 weeks
Outcomes	Primary outcomes: At 6 weeks: Mean (SEM) percentage change in ulcer area (SEM values read from figure): Group 1: increase of 5% (SEM 15) (n = 36) Group 2: reduction of 34% (SEM 5) (n = 38) The trial authors reported that the between-group difference was statistically significant (P value < 0.02) Secondary outcomes: Numbers of participants with eradication or reduction of staphylococcal infection/infection persisted or new infection during treatment: Group 1: 0/18 Group 2: 16/7 The trial authors reported that the between-group difference was statistically significant (P value < 0.001) Numbers of participants with eradication or improvement of *Pseudomonas aeruginosa* infection/infection persisted or new infection during treatment: Group 1: 1/6 Group 2: 3/0 The trial authors reported that the between-group difference was statistically significant (P value < 0.05)

	Numbers of participants with eradication or improvement of infection from other pathogenic organisms *(Streptococcus, Proteus, Enterococcus, Enterobacteria* and *Klebsiella*)/infection persisted or new infection during treatment: Group 1: 3/17 Group 2: 15/5 The trial authors reported that the between-group difference was statistically significant (P value < 0.01) Relationship between ulcer healing and bacteriological response to treatment: The trial authors reported that a statistically significant association was evident between eradication of *Staphylococcus aureus* and a more rapid rate of healing (P value < 0.002). Figure presented in a secondary reference, but no detailed description of methods or outcomes was provided to allow assessment of this association Mean ± SEM pain score at 6 weeks (assessed by 100-point visual analogue scale divided into increments of 10, where 0 = no pain and 100 = severe pain) [change in means relative to baseline, calculated by review authors]: Group 1: 23.0 ± 3.7 [-10] (n = 36) Group 2: 10.0 ± 2.5 [-22] (n = 38) The trial authors reported that the between-group difference was statistically significant (P value < 0.01) Numbers of participants (%) with adverse events with description: 1. 1/36 (3%) pain following application of dressing 2. 4/38 (11%) pain following application of dressing; 1/38 (3%) itching in the peri-ulcer area; 1/38 (3%) rash resulting in withdrawal
Notes	Bacteriological outcomes assessed by wound swab (further details of specimen acquisition not provided) Numbers of participants who withdrew: Group 1: Ineligible (3); beta-haemolytic strep. infection (4); squamous cell cancer (1); dramatic increase in ulcer size (1) total = 9 Group 2: Ineligible (4); beta-haemolytic strep. infection (2); rash (1); holiday (2); missing information (2); recurrence of pain (1) total = 12

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were allocated blindly and at random to the standard treatment or to cadexomer iodine." It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	"Patients were allocated blindly and at random to the standard treatment or to cadexomer iodine." The method of allocation concealment was not stated
Blinding (performance bias and detection	Unclear risk	No information was provided

bias) Participant blinded to the intervention		
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"at each centre the same observer always made these observations"; it was not stated whether observer was blinded
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Study reported number of dropouts and provided reasons
Incomplete outcome data (attrition bias) Drop out rate acceptable	High risk	21/95 withdrew overall (22%)
Incomplete outcome data (attrition bias) ITT analysis	High risk	"ninety five sets of data were received for evaluation, of which 21 were excluded from the statistical analysis"
Baseline factors comparable	Unclear risk	Mean values were reported for ulcer area and ulcer duration; therefore it was difficult to assess comparability

Smith 1992

Methods	Randomised controlled trial conducted in the UK
Participants	200 people with venous leg ulcers (ABPI ≥ 0.75) ≥ 2 cm in diameter were recruited. Those with the following were excluded: diabetes; rheumatoid arthritis; infected ulcers requiring treatment that precluded dressings being left in situ; infection requiring immediate antibiotics; known intolerance to iodine; and neurological disease causing tropic impairment Group 1: 99 Group 2: 101 Participants with smaller baseline ulcer diameter (2 to 4 cm) Group 1a: 64 Group 2a: 62 Participants with larger baseline ulcer diameter > 4 cm Group 1b: 35 Group 2b: 39

	Median (interquartile range) baseline ulcer area (cm^2) in participants with smaller/larger ulcers: Group 1: 3.1 (2.0 to 5.0)/13.3 (9.0 to 27.0); Group 2: 2.6 (2.0 to 4.0)/17.6 (9.0 to 38.0) Median (interquartile range) baseline ulcer duration (months) in participants with smaller/larger ulcers: Group 1: 5 (3 to 9)/14 (2 to 45); Group 2: 3 (2 to 10)/17 (6 to 58) Ulcers were not clinically infected at baseline. Most had bacteria present at initial assessment
Interventions	1. Ulcers cleansed with sterile isotonic saline and ulcers filled with hydrocolloid powder (Biofilm powder) until level with the ulcer margins, before a hydrocolloid dressing (Biofilm dressing) was applied. Participants were allowed to remove their compression bandages and bathe or shower with the dressing in place 2. Ulcers cleansed with sterile isotonic saline, then povidone-iodine dressing applied (Betadine), cut to fit exactly the shape of the ulcer, and an absorbent pad placed over. Participants could not bathe or shower with the dressing in place All participants were treated in a community setting and received graduated compression in the form of an elasticated tubular bandage (2 layers of shaped Tubigrip) or a stocking (Venosan 2002)
Outcomes	Frequency of complete healing at 4 months: 1a: 38/64 (59%) 2a: 43/62 (69%) P value 0.27 1b: 12/35 (34%) 2b: 4/39 (10%) P value 0.02 (reported by trial authors) Cox proportional hazards model found that the following 4 variables were significant independent predictors of time to healing (P value < 0.01): baseline ulcer area, ulcer duration, age, deep vein involvement. No significant interaction was detected between treatment and baseline ulcer area. Hazard ratio estimate of treatment effect not reported Median (interquartile range) healing rate (cm^2/d) at 1 month (analysis based on 151 participants): 1a(50 participants analysed): 0.056 (0.027 to 0.085) 2a (52 participants analysed): 0.062 (0.039 to 0.086) P value 0.40 Mann-Whitney U-test 1b (25 participants analysed): 0.184 (0.115 to 0.338) 2b (24 participants analysed): 0.017 (0.001 to 0.267) P value 0.09 Mann-Whitney U-test Numbers (%) of participants reporting moderate or severe ulcer pain, assessed using 5-point scale (1 = no pain and 5 = worst pain) at 1 month (analysis based on 123 participants): 1a: 6/34 (18%) 2a: 16/36 (44%) P value 0.02 1b: 12/27 (44%) 2b: 14/26 (54%) P value 0.02 Estimated cost of dressings and nursing time over 4 months (GBP, price year not stated, analysis based on all 200 participants):

	Participants with smaller wounds, defined as baseline diameter < 6 cm: 1a: 48.96 2a: 38.95 Participants with large wounds, defined as baseline diameter ≥ 6 cm: 1b: 526.63 2b: 183.75
Notes	In participants with bilateral ulceration, the right leg was included as the study limb Numbers of participants (%) who withdrew, with reasons: Group 1: total = 27/99 (27%) Refused treatment (12); acute infection (1); admission (7); allergy (6); moved (1) Group 2: total = 33/101 (33%) Refused treatment (11); acute infection (12); admission (5); allergy (2); died (2); moved (1)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"200 patients with VLUs assessed by continuous wave ultrasound and plethysmography were randomly allocated to each treatment group, stratified by initial maximum ulcer diameter 2-4 cm and >4 cm, using a block length of 4 within each strata." It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	"this was not a blind study"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	High risk	"this was not a blind study"
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	Dropout rate described (60/200 participants)
Incomplete outcome data (attrition bias)	High risk	"70% completed the trial"

Drop out rate acceptable		
Incomplete outcome data (attrition bias) ITT analysis	High risk	"Five patients did not receive their randomly allocated treatment because of clerical errors. Two patients received biofilm instead of Betadine and three patients received Betadine instead of biofilm. Statistical analysis was performed on basis of treatment received"
Baseline factors comparable	High risk	Of those with larger ulcers at baseline (> 4 cm diameter), Group 2 included more participants with larger ulcers and wounds of longer duration

Steele 1986

Methods	Randomised controlled trial conducted in the UK (Northern Ireland)
Participants	60 participants with active venous leg ulcers for at least 3 months and at least 2 cm^2 surface area were recruited; data on 57 participants are presented: Group 1: 29 (completers) Group 2: 28 (completers) Mean ± standard error baseline ulcer area, mm^2: Group 1: 1759 ± 397; Group 2: 1264 ± 291 Mean ± standard error baseline ulcer duration, months: Group 1: 16.3 ± 2.5; Group 2: 16.6 ± 2.7 Day-to-day ulcer pain reported as none/mild/moderate/severe at baseline: Group 1: 12/5/3/9 (n = 29) Group 2: 9/8/4/7 (n = 28) Unclear whether wounds were clinically infected at baseline (but it appeared that those with infected ulcers might have been allowed into the trial).
Interventions	1. Various topical agents including antibiotics, antiseptics, hydrophilic agents, topical steroids and bland agents. Compression bandage applied to the whole leg, and changes occurred 3 times a week 2. Ulcer cleaned with normal saline, sprinkled with cadexomer iodine and dressed with gauze. Compression bandage applied to whole leg, and changes occurred 3 times a week All patients were treated in a community setting
Outcomes	Primary outcomes: Complete healing at 6 weeks: 1: 1/29 2: 3/28 Mean percentage change in ulcer area at 6 weeks (values read from figure): 1. -18% (n = 29) 2. -22% (n = 28) The trial authors reported that the between-group difference was not statistically significant (P value 0.31) Secondary outcomes:

	Numbers of participants reporting pain after treatment at 2/4/6 weeks: 1. 2/2/4 2. 14/11/11 The trial authors reported that between-group differences were statistically significant at 2 weeks (P value 0.001), 4 weeks (P value 0.008) and 6 weeks (P value 0.032) Day-to-day ulcer pain reported as none/mild/moderate/severe at 2 weeks: Group 1: 7/4/9/9 (n = 29) Group 2: 10/13/1/4 (n = 28) The trial authors reported that the between-group difference was statistically significant (P value 0.03) Day-to-day ulcer pain reported as none/mild/moderate/severe at 4 weeks: Group 1: 8/7/8/6 (n = 29) Group 2: 15/7/3/3 (n = 28) The trial authors reported that the between-group difference was not statistically significant (P value 0.17) Day-to-day ulcer pain reported as none/mild/moderate/severe at 6 weeks: Group 1: 9/8/6/6 (n = 29) Group 2: 16/4/3/5 (n = 28) The trial authors reported that the between-group difference was not statistically significant (P value 0.31)
Notes	Three withdrawals were reported overall. Reasons for withdrawal were given as hospital admission and lack of cooperation, but breakdown of numbers/reasons per group was not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"patients were divided into 2 groups using random numbers"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	High risk	"cadexomer iodine did not lend itself to a double blind trial"
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	High risk	"Measurements were recorded on the Proforma at 0, 2, 4 and 6 weeks by each patient's nurse." "Cadexomer iodine did not lend itself to a double blind trial"

Incomplete outcome data (attrition bias) Drop out rate described	Low risk	"57 of the 60 patients completed the trial"; reasons given for the three withdrawals were hospital admission and lack of cooperation
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Withdrawal rate 5%
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Analyses were based on 57 of 60 randomly assigned participants. It is unclear how these withdrawals might have impacted estimates of treatment effect (this is a small RCT)
Baseline factors comparable	Unclear risk	Mean, rather than median, values were reported for baseline ulcer area and ulcer duration and so it is difficult to judge comparability

Valtonen 1989

Methods	Randomised controlled trial conducted in Finland
Participants	27 participants with *Pseudomonas aeruginosa* or other Gram-negative rod colonised chronic leg ulcers of ≥ 2 months' duration were recruited. Patients with diabetes were eligible for inclusion. Those with ulcer flora resistant to ciprofloxacin were excluded: Group 1: 8 participants Group 2: 18 participants Numbers (%) of participants with venous/arterial insufficiency: Group 1: 6/8 (75%); 8/8 (100%) Group 2: 16/18 (89%); 13/18 (72%) Mean ± SD sum of maximum length plus width of ulcer (cm) at baseline: Group 1: 16.9 ± 11.4; Group 2: 16.7 ± 8.2 Range for baseline ulcer duration, months: Group 1: 29 to 35; Group 2: 60 to 71 Proportions of participants with isolation of *Pseudomonas aeruginosa* at baseline: Group 1: 63%; Group 2: 61% Unclear whether wounds had signs and symptoms of clinical infection at baseline or whether just colonised
Interventions	1. Standard care consisting of: daily ulcer cleansing with warm water and disinfectants (chlorhexidine or potassium permanganate); mechanical or enzymatic debridement; coverage with dextranomer paste or hydrocolloid (DuoDerm) dressing. Topical antibiotic creams were not used 2. Oral ciprofloxacin 750 mg twice daily for 3 months in addition to standard care as above. Some participants received a lower dose as the study progressed (250 or 500 mg twice daily) to achieve a maximum serum level of 2 to 4 mg/L. All participants were treated as inpatients or outpatients according to clinical status; additional systemic antibiotics based on clinical features of infection, and the resistance pattern of the bacteria isolated. Use of compression not mentioned

Outcomes	Primary outcomes: Numbers (%) of participants with complete healing at 3 months: 1. 0/8 (0) 2. 3/18 (17) Numbers (%) of participants with clinical improvement (defined as those with complete healing plus those with reduction of at least 10% of sum of maximum length and width of ulcer) at 3 months: 1. 1/8 (13) 2. 12/18 (67) Secondary outcomes: Numbers of participants with adverse events: Group 1: (0) Group 2: mild, transient nausea that did not result in discontinuation of treatment (3) Numbers (%) of participants who needed extra antimicrobial treatment during the trial: 1. 6/8 (75) 2. 3/18 (17) Numbers (%) of participants with bacterial eradication or no bacteriological growth during trial: 1. 1/8 (13) 2. 6/18 (33) Numbers (%) of participants with eradication of original strain during trial: 1. 2/8 (25) 2. 15/18 (83) Numbers (%) of participants with ciprofloxacin-resistant strain in ulcer during trial: 1. 0/8 (0) 2. 12/18 (67)
Notes	One participant excluded from analysis because of malignant tumour in leg ulcer (group allocation not stated)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to two treatment groups." It was not stated how the sequence was generated
Allocation concealment (selection bias)	Unclear risk	No information was provided
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	"We have studied, using an open, comparative study design, the efficacy of..."

Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	"We have studied, using an open, comparative study design, the efficacy of..."
Incomplete outcome data (attrition bias) Drop out rate described	Low risk	"Altogether 27 patients enrolled..." One was excluded from analysis
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	One participant was excluded because of malignancy in ulcer
Incomplete outcome data (attrition bias) ITT analysis	Low risk	Participants were analysed in the groups into which they were enrolled at the beginning of the study
Baseline factors comparable	High risk	Longer baseline ulcer duration in ciprofloxacin group

Wunderlich 1991

Methods	Randomised controlled trial conducted in Germany
Participants	40 participants with venous leg ulcers were recruited: Group 1: 20 participants Group 2: 20 participants Mean ulcer duration in years: Group 1: 7.9 Group 2: 7.6 Mean ulcer area in mm^2 (values taken from graph): Group 1: 2000 Group 2: 3000 No information about ulcer infection/colonisation status at baseline
Interventions	Group 1: various topical agents used for different stages of wound healing, including mineral oil or mixture of sea salt and povidone-iodine paste for granulation phase; and paraffin-impregnated gauze or oil-and-water emulsion with panthenol for epithelialisation phase Group 2: silver-impregnated activated charcoal dressing (Actisorb plus, Johnson & Johnson) used for all stages of wound healing All participants received initial debridement (mechanical or enzymatic) for 5 days; intermittent debridement as necessary during the trial (up to 4 times in 6 weeks) for large ulcers; and daily dressing changes. No mention was made of using compression therapy

	Treatment duration was 6 weeks
Outcomes	Primary outcomes: Numbers (%) ulcers healed at 6 weeks: Group 1: 2/20 (10) Group 2: 6/20 (30) Median percentage change in ulcer area at 6 weeks (from graph): Group 1: -60% Group 2: -75% The trial authors did not report P values for between-group differences Secondary outcomes: Semi-quantitive bacterial colony growth was assessed at weeks 2, 4 and 6 (details of method not reported). Assessment was reported on a scale: 0 = no growth, 1 = low growth, 2 = medium growth, 3 = high growth. The trial authors reported a non-significant reduction in colonisation over the whole study period in Group 2 and a reduction only at week 2 in Group 1. No data were presented
Notes	Translated from German One withdrawal per group (reasons not reported)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote, from translation: "Randomized in each group were 20 patients treated with SIAX or with conventional control therapy" Comment: no information regarding the method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote, from translation: "Randomized in each group were 20 patients treated with SIAX or with conventional control therapy" Comment: no information regarding allocation concealment
Blinding (performance bias and detection bias) Participant blinded to the intervention	Unclear risk	Comment: The trial was described as "an open randomised study", but no participant blinding was described
Blinding (performance bias and detection bias) Outcome assessor blinded to the intervention	Unclear risk	Comment: The trial was described as "an open randomised study" but no description of outcome assessor blinding was provided

Incomplete outcome data (attrition bias) Drop out rate described	Unclear risk	Comment: The trial authors report that 19 of the 20 participants in each arm completed the study, but no details of the participants not completing are reported
Incomplete outcome data (attrition bias) Drop out rate acceptable	Low risk	Group 1: 1/20 (5%) Group 2: 1/20 (5%) Comment: Withdrawal rates are low in both groups, with identical rates
Incomplete outcome data (attrition bias) ITT analysis	Unclear risk	Comment: The trial authors report that the analyses were undertaken on 19/20 participants randomly assigned to each arm, but no analysis methods were reported
Baseline factors comparable	Unclear risk	Comment: Limited information was presented on baseline ulcer area and duration

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Allen 1980	Not RCT
Allen 1996	No healing outcomes reported
Altman 1976	Primary outcomes not reported
Anonymous 1982	Not an RCT
Bazzigaluppi 1991	No control group
Beele 2010	Patients with various wound types recruited. Results not available for VLU patients only (communication with study author)
Beitner 1985c	No antimicrobial intervention evaluated (comparison was vehicle of benzoyl peroxide lotion versus saline solution). Two other RCTs were reported in the same paper, and are included in this review (Beitner 1985a; Beitner 1985b)
Bender 1982	Not RCT (confirmed by translator)
Bourgeois 1963	No control group
Brauman 2008	Not RCT (confirmed by study author)
Brzeziska 1990	Not an RCT

Study	Reason for exclusion
Castellano 2007	Not an RCT
Chaparro 2003	CCT
Chaudhary 2008	Not an RCT
Cherry 2003	Not an RCT - single arm study
Chirwa 2010	Mixed wound aetiologies, 20% of patients had venous leg ulcers. Conference abstract with no further details available (unable to establish contact with trial authors)
Colombo 1993	Participants with various wound types recruited, unclear if venous leg ulcers included. No objective healing outcomes reported
Colonna 2004	Mixed wound aetiologies, 28% of patients had venous leg ulcers. Conference abstract with no further details available following contact with trial authors
Contretas-Ruiz 2004	Antimicrobial intervention is not the only systematic difference between treatment groups; different methods of debridement are used (confirmed through contact with trial authors)
Coutts 2005	Not an RCT
Daltrey 1981	Primary outcomes not reported
Danielsen 1997	No control group
Dharap 2008	No control group
Ferra 2007	Interventions evaluated do not include antimicrobials
Fox 1966	CCT
Friedman 1984	Mixed aetiologies, minority venous, CCT
Garcia 1984	Antimicrobial intervention not clearly defined
Gottrup 2003	Not RCT.
Haler 1964	Not randomised, no objective outcomes of healing reported
Hanft 2006	Available only as conference abstracts with no outcome data. Unable to establish contact with the trial authors in order to request further information
Heggers 2003	Not a controlled trial
Howell-Jones 2005	Not a controlled trial

Study	Reason for exclusion
Hutchinson 1993	No healing outcomes reported
Ivins 2006	Not an RCT (random allocation of only some patients from one treatment group of a previously reported trial to receive either the treatment or comparator for a further 4 weeks)
Karap 2008	Not an RCT (confirmed by study author)
Karas 1984	No control group
Katelaris 1987	CCT
Kordestani 2008	Quasi randomised, intervention not antimicrobial
Kosicek 2004	CCT
Lanzara 2008	Available only as a conference abstract. Unable to establish contact with the trial authors in order to request further information
Lischka 1980	CCT
Locati 1994	No control group, mixed aetiology
Magana Lozano 1980	Primary outcome not reported
Maiques Nadal 1976	Case series
Mancuso 1994	Primary outcomes not reported
Markoishvili 2002	No control group
Marzin 1982	CCT
McKnight 1965	No control group
Mehtar S 1988	Mixed aetiology
Mogabgab 1984	Soft tissue infections, not venous leg ulcers
Morely de Benzaquen 1990	From abstract, appears to be RCT evaluating silver sulphadiazine versus placebo in participants with lower limb ulcers. Not clear if venous leg ulcers included or if healing reported. Full study report unavailable from overseas and unable to locate contact details for study authors
Motta 2004	Not venous leg ulcers
Nakagawa 1997	Mixed aetiology, no control group

Study	Reason for exclusion
Ouvry 1989	Not an RCT
Pardes 1993	Primary outcome not reported
Paul 1990	Not an RCT
Pegum 1968	CCT
Pereira 2004	Mixed aetiology, primary outcome not reported
Pierard-Franchimont 1997	CCT
Planinsek 2006	Available only as a conference abstract. Unable to establish contact with the trial authors in order to request further information
Pollice 1989	CCT
Privat 1979	No control group
Robson 2009	Patients with various types of wounds recruited. Less than 75% had leg ulcers, and aetiology of leg ulcers not explained. Unable to obtain further information from trial authors
Rogers 2000	Not RCT
Romanelli 2010	Insufficient report of outcomes and unable to obtain further information from trial authors.
Rubisz Brzeziska 87	Not RCT.
Rucigaj 2007a	Available only as a conference abstract. Unable to establish contact with the trial authors in order to request further information
Rucigaj 2007b	Intervention has no microbial properties
Salim 1991	No antibacterial or antiseptic intervention
Sanchez-Vasquez 2008	Isosorbide dinitrate spray, not antibiotic
Serra 2005	Not randomised (confirmed by translator - paper published in Spanish)
Sibbald 2007	Intervention not antimicrobial
Sibbald 2011	

Study	Reason for exclusion
	Partcicipants with various types of wounds recruited. Less than 75% had leg ulcers, and aetiology of leg ulcers not explained. Unable to obtain further information from trial authors
Steenvoorde 2007	Not an RCT
Subrahmanyam 1993	Unable to obtain data for VLU patients only. Confirmed by study author (email communication)
Thebbe 1996	Mixed aetiology, silver used
Thorne 1965	No control group
Wuite 1974	No healing outcomes reported

References

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