National Institute for Health and Care Excellence

Final

Infected leg ulcer: antimicrobial prescribing guideline

Evidence review

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1 Context

1.1 Background

A leg ulcer is a long-lasting (chronic) sore that takes more than four to six weeks to heal. They usually develop on the inside of the leg, just above the ankle. The symptoms of a venous leg ulcer include pain, itching and swelling in the affected leg. There may also be discoloured or hardened skin around the ulcer, and the sore may produce a foul-smelling discharge (NHS: Venous leg ulcer). Arterial ulcers differ from venous leg ulcers in cause (lack of adequate blood supply) that can cause the affected area to be cool, they may be painful particularly at night.

A UK Study (Callam et al 1987) examined 600 people with leg ulceration and found that 76% of those with ulcerated legs had evidence of venous disease and 22% had evidence of arterial disease. Ten to 20% of people had both arterial and venous disease. Nine per cent of those with ulcerated legs were people with rheumatoid arthritis. Five per cent of the people in the study had diabetes. A more recent study (Guest et al 2015) estimated that 1.5% of the UK adult population had a leg ulcer in 2012/2013, with 1 in 170 adults having a diagnosed venous leg ulcer.

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 (O'Meara et al 2014).

Findings from microbiological studies suggest that 80% to 100% of leg ulcers may be colonised with bacteria (Halbert 1992; Brook 1998 and Harker 2001). In leg ulcer infection, the most common causative pathogens are *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Alinovi 1986; Kontiainen 1988; Halbert 1992; Brook 1998; Harker 2001 and Moore 2010).

The diagnosis of infection in a leg ulcer may be difficult given that most are colonised, and the classic symptoms and signs of infection may not always be present.

1.2 Antimicrobial stewardship

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, and for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and

returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks. This guideline also recommends that safety netting advice should be given to everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include how long symptoms are likely to last with antimicrobials, what to do if symptoms get worse, what to do if they experience adverse effects from the treatment, and when they should ask again for medical advice.

In line with the Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship , intravenous antibiotic prescriptions should be reviewed at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.3 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2019 reported that antimicrobial prescribing has been decreasing since its peak in 2014, with the total consumption of antibiotics in primary and secondary care (measured in terms of new defined daily doses) declining by 9.0% from 2014 to 2018. This reflected a 16.7% decrease in primary care and a 2.8% increase in secondary care prescribing. In 2018, the most commonly used antibiotic groups were penicillins (38.4%), tetracyclines (25.2%) and macrolides (15.8%).

Over the 5-year period from 2014 to 2018, significant declining trends of use were seen for penicillins, first and second-generation cephalosporins, tetracyclines, macrolides, sulfonamides and trimethoprim, and oral metronidazole. In contrast, use of third, fourth and fifth generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

In the 5-year period from 2014 to 2018, use of penicillins declined by 14.2% in the GP setting and by 18.4% in the dental setting, but increased by 32.3% in other community settings and by 7.9% in hospital inpatients. Prescribing of co-amoxiclav and amoxicillin between 2014 and 2018 decreased by 9.9% and 16.7%, respectively. The use of pivmecillinam increased steadily, most likely for use in urinary tract infection; and piperacillin with tazobactam use decreased by 31.7% over the 5-year period, with a sharp reduction in 2017 due to the shortage of international supply and a subsequent 6.4% increase from 2017 to 2018.

Overall use of tetracyclines reduced slightly (by 6.8%) between 2014 and 2018, but doxycycline use in particular increased. Macrolide use declined by 14.6% from 2014 to 2018, largely because of a decrease in erythromycin use. Azithromycin use, however, continued to increase. Oral metronidazole use also declined by 19.1%, mainly because of declining use in GP and dental settings.

Total cephalosporin use decreased by 20.2% between 2014 and 2018, largely due to decreasing use of first-generation cephalosporins (such as cefalexin). However, use of the third-generation cephalosporins, ceftazidime and ceftriaxone, increased significantly over the 5-year period.

Fluoroquinolone use declined by 3.9% between 2014 and 2016, but then increased by 4.8% from 2016 to 2018, with levofloxacin use consistently increasing from 2014 to 2018.

There was an 8.4% rise in aminoglycoside use between 2014 and 2018; and a 25.3% increase in the use of parenteral glycopeptides (vancomycin and teicoplanin) and daptomycin.

For the 7 priority bacterial pathogens reported, the rate of bloodstream infection in 2018 was 145 per 100,000 of the population (a 22% increase from 2014). However, *Escherichia coli* was the most common cause of blood stream infection (76.0 cases per 100,000 population). For the most common causative pathogens in leg ulcer infection – *Staphylococcus aureus* and *Pseudomonas aeruginosa* – ESPAUR 2019 reports that there was little change in the proportion of *Staphylococcus aureus* blood stream infections that were methicillin-resistant between 2014 (7.5%) and 2018 (6.7%). Resistance to daptomycin and linezolid remained low in *Staphylococcus aureus* bacteraemia in 2018, with less than 1% resistance reported for both antibiotics. The proportion of isolates of *Pseudomonas* species resistant to key antibiotics remained stable or decreased slightly between 2014 and 2018.

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for leg ulcers.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing infected leg ulcers (see appendix C: literature search strategy for full details). The literature search identified 2,158 references. These references were screened using their titles and abstracts and 79 full text references were obtained and assessed for relevance. Two full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). 10% percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. One of the 2 references was prioritised by the committee as the best available evidence and was included in this evidence review (see appendix F: included studies).

One reference was not prioritised for inclusion. In summary, the reason that the RCT was deprioritised was that it was retracted due to errors in the data. A full list of studies that were not prioritised for inclusion are listed in appendix I: not prioritised studies, with reasons. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 77 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in **Table 1.** Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies. No evidence was found for antibiotic prescribing strategies, antibiotic dose, antibiotic course length, antibiotic dose frequency or antibiotic route of administration.

The review protocol (appendix B) outlines that the population was adults, young people and children with an infected leg ulcer. There was minimal evidence for people with infected leg ulcers (2 small studies), therefore the population was expanded to people with leg ulcers that had an unclear infection status or were not infected. For the interventions (antiseptics and antibiotics), the results have been presented as subgroups for infected leg ulcer, leg ulcer with unclear infection status and uninfected leg ulcers.

No studies included in the review stated that they included children in their population. The committee discussed that leg ulcer infection in children and young people is extremely rare, and usually a result of an underlying illness that requires specialist management. Therefore,

the committee considered that the evidence presented here applied only to an adult population; the evidence was not extrapolated to a population of children and young people and no recommendations were made for children and young people.

Table 1: Summary of included studies: antibiotic choice

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
O'Meara et al 2014 Systematic review and meta-analysis Multiple countries.	45 RCTs n=4,486	Adults with venous leg ulceration (ages not defined in the review).	Systemic antibiotic (co-trimoxazole, gentamicin, amikacin or ciprofloxacin), topical antibiotic (mupirocin) or topical disinfectant or antiseptic (iodine, honey, silver).	Any other active comparator, placebo or standard care.	Any objective assessment of wound healing (for example frequency of complete healing or the proportion of ulcers healed at a specific time point).
Abbreviations: RCTs, Randomised controlled trial.					

3 Evidence summary

Full details of the evidence are shown in appendix H: GRADE profiles.

The main results are summarised below for adults with infected leg ulcers, adults with unclear leg ulcer infection status and adults with uninfected leg ulcers. The committee asked for the evidence for antibiotics and antiseptics/disinfectants in people with unclear leg ulcer infection status or non-infected leg ulcer to be included so that they could look at inappropriate or overuse of these interventions in line with the aims of antimicrobial stewardship. The search found no evidence for people aged under 16 years.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on drug interactions, contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

Population in the included study

The systematic review (O'Meara et al 2014) included 45 randomised controlled trials (RCTs) reporting 53 comparisons and recruiting a total of 4486 participants.

Seven RCTs included in this review were in adults with an 'infected' leg ulcer. However, in 5 RCTs the definition of infection was uncertain:

- Daroczy 2006 compared povidone-iodine with amoxicillin, the population was described as infected, but no further details were provided, and it is not clear if this referred to baseline status or incidence during the trial.
- Kuznetsov 2009 compared povidone-iodine with standard care the population was mixed (adults with infected and uninfected leg ulcers were allowed into the trial) but the results for each group are not presented separately.
- Miller 2006 compared silver dressings with cadexomer-iodine and included adults with infection or critical colonization (not defined), however it excluded adults using either topical antiseptics within 1 week of recruitment or antibiotics within 48 hours of recruitment.
- Münter 2006 compared silver dressing with standard care and included participants with clinically infected wounds, or wounds deemed at risk of infection, but no data related to prevalence of infection at baseline was presented.
- Valtonen 1989 compared ciprofloxacin with standard care and may have included adults with signs and symptoms of leg ulcer infection at baseline or they may have been just colonised, although participants were given additional systemic antibiotics based on clinical features of infection.

Only in 2 RCTs comparing non-adhesive silver dressing vs. non-adhesive foam dressing (Dimakakos 2009) and cadexomer-iodine vs. standard care (Skog 1983) were all participants leg ulcers described as infected.

Fourteen RCTs included in this review were in adults with an unclear leg ulcer infection status, in which, adults with an infected leg ulcer may have been admitted to the trial but no information about infection status was reported. Fourteen RCTs included in this review stated adults had uninfected leg ulcers (described as

uninfected at baseline, although in many cases leg ulcers were colonised). In 3 trials antibiotics were given prior to enrolment to ensure no infection at baseline.
The search for this evidence review included children, however we found no evidence in this population. Only 4 RCTs reported the age of the included populations (2 RCTs included people aged 30 years or over, 1 RCT included people aged 18 years or older and 1 RCT included people aged 16 years or older). No RCT within the SR reported including children in their population. Only 1 RCT reported the gender of the population (all female, n=28). Very little information about comorbidity is presented for the included population: Two RCTs reported that people with diabetes were included and 3 RCTs reported that people with diabetes were excluded.

The systematic review included both acute or new ulcers and chronic ulceration the baseline duration of ulceration varied markedly, by RCT, from 1.1 months (±0.2 standard deviation [SD]) to over 9 years.

Comparisons included in O'Meara (2014) where the intervention or comparator are not available in the UK clinical setting were not reported in the evidence review.

3.1 Topical antiseptics in adults with leg ulcer

The evidence for antiseptics versus other interventions comes from 1 systematic review (O'Meara et al 2014).

3.1.1 Iodine based preparations

Infected leg ulcer

Cadexomer-iodine compared with standard care in adults

One randomised controlled trial [RCT] (Skog et al 1983) included in the systematic review was adults with infected leg ulcer and was explored for additional outcomes data. The RCT included 95 adults with chronic infected (colony count +++ using standard plating technique, no report of clinical symptoms or signs) ulcers of ≥3 month's duration. Ulcers were venous/arterial/ or mixed. The intervention was cadexomer-iodine powder applied to a depth of 3 mm followed by the application of a dry dressing. Standard care was daily cleansing with dilute hydrogen peroxide or dilute potassium permanganate bath, then a non-adherent dressing applied. Other treatments, including systemic antibiotics, were allowed in the standard care group. All participants were treated at home or as an outpatient and received compression bandages.

Cadexomer-iodine significantly reduced the mean ulcer size (mean percentage change in ulcer area) compared with standard care at 6 weeks (1 RCT, n=74, cadexomer-iodine mean percentage reduction of 34% versus standard care mean percentage increase of 5%, mean difference [MD] −0.39, 95% confidence interval [CI] −0.70 to −0.08; moderate quality evidence). Cadexomer-iodine significantly lowered pain (measured using 100-point visual analogue scale) at 6 weeks compared with standard care (1 RCT, n=74, 23.0±3.7 [mean±standard error of the mean] versus 10.0±2.5, MD −13.0, 95% CI −21.75 to −4.25; low quality evidence).

Cadexomer-iodine was more effective than standard care at reducing or eliminating *Staphylococcus aureus* during treatment (p<0.001, Chi-square test with Yates' correction; very low-quality evidence). Cadexomer-iodine was also more effective for infections that cleared or persisted, or new infection during treatment than standard care (p<0.001, Chi-square test with Yates' correction; very low-quality evidence).

Staphylococcus aureus accounted for 77% of all species found on culture in the RCT.

Cadexomer-iodine increased the percentage of adults experiencing adverse effects (pain, itching or rash) although the increase was not significant (1 RCT, n=74, 10.5% versus 2.7%, relative risk [RR] 3.79, 95% confidence interval [CI] 0.44 to 32.32; very low-quality evidence).

See GRADE table 4.

Cadexomer-iodine compared with silver dressing for adults

Cadexomer-iodine was not significantly different compared with silver dressing for the frequency of complete healing at 12 weeks (1 RCT, n=281, 59.6% versus 60.7%, RR 0.98, 95% CI 0.81 to 1.19; low quality evidence) and for participant satisfaction (evaluation time point not reported) in 1 RCT (n=207, 89% versus 91.6%, RR 0.97, 95% CI 0.89 to 1.06; low quality evidence). Neither group reported any adverse effects and adults with leg ulcers in this study had to present at least 1 sign of infection or critical colonisation, results for those categorised as infected not presented separately.

See GRADE table 7.

Povidone-iodine plus compression compared with other dressings plus compression for adults

Povidone-iodine plus compression was not significantly different to moist or foam dressings plus compression for complete healing at 4 months (1 RCT, n=30, 13.3% versus 33.3%, RR 0.40, 95% CI 0.09 to 1.75; very low-quality evidence). Although microbiological isolates were reported, no data is given for ulcer infection status.

See GRADE table 8.

Unclear leg ulcer infection status

Cadexomer-iodine compared with standard care in adults

Cadexomer-iodine (topical application) was significantly better compared with standard care (varied by RCT) for the frequency of complete healing at 4 to 12 weeks (4 RCTs, n=212, 33% versus 15.1%, RR 2.17, 95% CI 1.30 to 3.60, number needed to treat [NNT] 6, 95% CI 4 to 15; low quality evidence). No information was given about infection status of the ulcer in 1 RCT, in the other 3 RCTs the infection status was unclear.

Cadexomer-iodine improved the mean percentage change ulcer area (1 RCT, n=72, p<0.01, no effect size reported; very low quality evidence) and mean rate of ulcer healing (1 RCT, n=75, p=0.0025, no effect size reported; very low quality evidence) compared with standard care.

However, adverse events were significantly more common in the cadexomer-iodine group (1 RCT, n=60, 33% versus 6.7%, RR 5.0, 95% CI 1.19 to 20.92, number needed to harm [NNH] 4, 95% CI 2 to 13; very low quality evidence). The infection status of the ulcers in 1 RCT was unknown. In 2 other RCTs adverse effects (mostly itching, burning or pain) were more common in the cadexomer-iodine group compared with standard care (no adverse effects reported in either RCT) but due to insufficient data (denominators not defined) an effect size could not be calculated.

See GRADE table 5.

Uninfected leg ulcer

Cadexomer-iodine compared with other dressings for adults

Cadexomer-iodine was not significantly different compared with hydrocolloid dressing for the frequency of complete healing at 12 weeks (1 RCT, n=104, 14.3% versus 10.4%, RR 1.37, 95% CI 0.48 to 3.91; very low-quality evidence). Neither group reported any adverse effects.

Cadexomer-iodine was not significantly different compared with paraffin gauze dressing for the frequency of complete healing at 12 weeks (1 RCT, n=105, 14.3% versus 14.3%, RR 1.00, 95% CI 0.39 to 2.56; very low-quality evidence). Neither group reported any adverse effects.

See GRADE table 6.

Povidone-iodine plus compression compared with other dressings plus compression for adults

Povidone-iodine plus compression was not significantly different to hydrocolloid plus compression for the frequency of complete healing at 4 months (1 RCT, n=200, 46.5% versus 50.5%, RR 0.92, 95% CI 0.69 to 1.23; very low-quality evidence).

Povidone-iodine 10% solution plus compression was significantly better for time to healing compared with hydrocolloid plus compression (1 RCT, n=17, p<0.01, no effect size presented, very low-quality evidence).

See GRADE table 9.

3.1.2 Peroxide- based preparations

unclear leg ulcer infection status

Benzoyl peroxide-based topical preparation compared with saline soak for adults

Benzoyl peroxide (10%) dressing was significantly better than a saline (0.9%) dressing for reducing ulcer size (mean percentage ulcer area remaining) at 42 days (1 RCT, n=20, 64.3%±14 [mean±standard deviation, SD] versus 94.7%±12.3, mean difference [MD] −30.4%, 95% CI −42.1% to −18.7%; low quality evidence). Benzoyl peroxide (20%) dressing was significantly better than a saline (0.9%) dressing for reducing ulcer size (mean percentage ulcer area remaining) at 42 days (1 RCT, n=20, 59.6%±12.3 [mean±SD] versus 93.7%±15.2, MD −34.10%, 95% CI −46.2% to −21.98%; low quality evidence). Data on adverse effects were limited and poorly reported.

See GRADE table 10.

uninfected leg ulcer

Hydrogen peroxide cream compared with placebo cream for adults

Hydrogen peroxide 1% cream was significantly better for median [range] decrease in ulcer area compared with placebo cream at 10 days follow-up (1 RCT, n=20, 35% [12% to 44%] versus 11% [0% to 23.5%], p<0.05; very low quality evidence; 1 RCT, n=32, 44.8% [15% to 57%] versus 32% [15% to 44%], p<0.005; very low quality evidence).

See GRADE table 11.

3.1.3 Honey- based preparations

The evidence for honey versus standard care comes from 1 systematic review (O'Meara et al 2014). The systematic review includes 2 RCTs of honey as an intervention (Gethin 2009; Jull et al 2008). This review largely presents data from the later RCT (Jull et al 2008), as the Gethin et al (2008) RCT paper has been subsequently withdrawn from publication, an additional paper for the same RCT by the same authors published the same year has been included for another outcome (Meticillin-resistant *Staphylococcus aureus* [MRSA] eradication).

unclear leg ulcer infection status

Honey compared with standard care for adults with

Honey (calcium alginate dressing impregnated with Manuka honey) was not significantly different compared with standard care for complete healing at 12 weeks (1 RCT, n=368, 55.6% versus 49.7%, RR 1.12, 95% CI 0.92 to 1.38; very low-quality evidence). Similarly, there was no significant difference for honey compared with standard care for incidence of ulcer infection during treatment for 12 weeks (1 RCT, n=368, 17.1% versus 22.1%, RR 0.77, 95% CI 0.51 to 1.18; very low-quality evidence). The number of adults with signs and symptoms at baseline in this study was not reported. However, in this RCT there were significantly more adverse effects in the honey group than the standard care group, but details of the adverse effects were not reported (1 RCT, n=368, 59.4% versus 46.4%, RR 1.28, 95% CI 1.05 to 1.56; very low-quality evidence).

See GRADE table 12.

uninfected leg ulcer

Honey compared with standard care for adults

Honey (topical Manuka honey) was not significantly different to hydrogel (3 g/20 cm^2 applied weekly) for the eradication of MRSA at 4 weeks (1 RCT, n=16, 70% versus 16.7%, RR 4.20, 95% CI 0.67 to 26.3; very low-quality evidence).

See GRADE table 13.

3.1.4 Silver- based preparations

Infected leg ulcers

Silver impregnated dressing versus non-adhesive dressing in adults with infected leg ulcer

One RCT (Dimakakos et al 2009) included only adults with infected leg ulcer and was explored for additional outcomes data. The RCT included 42 adults with an infected (all ulcers had signs of clinical inflammation). The intervention was non-adhesive silver foam dressing plus compression. Standard care was a non-adhesive foam dressing plus compression. Treatment duration was 9 weeks.

Silver dressing plus compression was significantly better compared with non-adhesive plus compression dressing for complete healing at 9 weeks (1 RCT, n=42, 81% versus 47.6%, RR 1.70, 95% CI 1.04 to 2.79, NNT 4, 95% CI 2 to 17; low

quality evidence). Silver dressing plus compression was also significantly better compared with non-adhesive dressing plus compression for the proportion of adults who were pain free at the end of the trial (1 RCT, n=42, 100% versus 61.9%, RR 1.59, 95% CI 1.14 to 2.23, NNT 3, 95% CI 2 to 6; low-quality evidence).

Silver dressings were not significantly different to non-adhesive dressings for adverse effects (2 RCTs, n=457, 10.9% versus 12.4%, RR 0.87, 95% CI 0.53 to 1.44; low-quality evidence).

See GRADE table 16.

Unclear leg ulcer infection status

Topical silver sulfadiazine cream compared with non-adherent dressing for adults

Silver sulfadiazine (1% cream) plus compression was not significantly different to non-adherent dressing plus compression for complete healing at 12 weeks (1 RCT, n=60, 63.3% versus 80%, RR 0.79, 95% CI 0.57 to 1.10: very low-quality evidence). The RCT reported that all wounds were 'contaminated' with 80% of wounds growing more than 1 organism, but infection status of the ulcers is unclear.

See GRADE table 14.

Silver impregnated dressing compared with silver impregnated or other non-antimicrobial dressings for adults

Silver impregnated dressings (with or without compression) was not significantly different to non-antimicrobial dressings (with or without compression) for complete healing at 4-12 weeks (2 RCTs, n=169, 12.9% versus 8.3%, RR 1.56, 95% CI 0.64 to 3.8: very low-quality evidence).

Silver-impregnated polyurethane foam dressing plus compression was not significantly different compared with 5-layer silver impregnated dressing plus compression for complete healing at 12 weeks (1 RCT, n=40, 50% versus 35%, RR 1.43, 95% CI 0.68 to 3.00; very low-quality evidence). The clinical infection status of the ulcers in RCT was unclear.

Silver dressings were not significantly different to non-antimicrobial dressings for adverse effects (1 RCT, n=129, 6.1% versus 4.7%, RR 1.31, 95% CI 0.31 to 5.63; very low-quality evidence).

See GRADE table 17.

Uninfected leg ulcers

Topical silver sulfadiazine cream compared with placebo or standard care for adults

Silver sulfadiazine (1% cream) with non-adherent dressing and compression was not significantly different to placebo cream with non-adherent dressing and compression for complete healing at 4 weeks (1 RCT, n=61, 19.4% versus 3.3%, RR 5.81, 95% CI 0.74 to 45.4; very low-quality evidence). Adults with $>10^5$ bacteria/gram ulcer tissue (confirmed by tissue biopsy) were excluded from this RCT as were those with systemic sepsis or bone infection.

Silver sulfadiazine (1% cream) was not significantly different to standard care for median [range] time to healing (1 RCT, n=17, 15 weeks [7 to 23 weeks] versus 16 weeks [9 to 22 weeks], p value not reported; very low-quality evidence).

See GRADE table 15.

Silver impregnated dressing versus silver impregnated or other dressing for adults

Silver dressing plus compression was not significantly different compared with low adherent dressing for complete healing at 4 to 12 weeks (1 RCT, n=213, 57.9% versus 55.6%, RR 1.04, 95% CI 0.82 to 1.32; very low quality evidence); 6 months (1 RCT, n=213, 81.3% versus 73.6%, RR 1.10, 95% CI 0.96 to 1.28; very low-quality evidence) or 12 months (1 RCT, n=213, 88.8% versus 84.9%, RR 1.05, 95% CI 0.94 to 1.16; low quality evidence). There was also no significant difference in ulcer recurrence within 12 months (1 RCT, n=185, 11.6% versus 14.4%, RR 0.80, 95% CI 0.38 to 1.70; very low-quality evidence).

Silver dressings plus compression was significantly better compared with non-antimicrobial dressings plus compression for reducing ulcer surface area when measured using cm^2 at 4 weeks (2 RCTs, n=170, MD -4.70, 95% CI -8.46 to -0.94; very low quality evidence) but was not significantly different when measured as a percentage change (2 RCTs, n=170, MD -6.13, 95% CI -32.59 to 20.32; very low quality evidence). The healing rate (cm^2 per day) in these 2 RCTs was not significantly different.

Silver dressings were not significantly different compared with non-antimicrobial dressings for adverse effects (evaluation time point not reported) in 2 RCTs (n=164, 19.5% versus 37.8%, RR 0.50, 95% CI 0.13 to 1.87; very low-quality evidence).

See GRADE table 18.

3.2 Antibiotics in adults with leg ulcer

3.2.1 Antibiotic prescribing strategies in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.2 Efficacy of antibiotics in adults with leg ulcer

The evidence for efficacy of antibiotics comes from 1 systematic review (O'Meara et al 2014).

Infected leg ulcers

Antibiotics compared with standard care for adults

Ciprofloxacin was not significantly different to standard care for the frequency of complete healing (1 RCT, n=26, 16.6% versus 0%, RR 3.32, 95% CI 0.19 to 57.61; very low-quality evidence), emergence of antibiotic resistant strains (1 RCT, n=26, 66.7% versus 0%, RR 11.84, 95% CI 0.79 to 178.54; very low-quality evidence) or bacterial eradication (1 RCT, n=26, 33.3% versus 12.5%, RR 2.67, 95% CI 0.38 to 18.67; very low-quality evidence) at 3 months.

See GRADE table 19.

Unclear leg ulcer infection status

Antibiotics compared with placebo for adults

Ciprofloxacin was not significantly different to placebo for the frequency of complete healing (unclear follow-up time) for adults with unclear leg ulcer infection status (1 RCT, n=24, 38.4% versus 27.3%, RR 1.41, 95% CI 0.43 to 4.61; very low-quality evidence). Emergence of resistance was significantly higher with ciprofloxacin compared to placebo for adults with unclear leg ulcer infection status (1 RCT, n=22, 66.7% versus 10%, RR 6.67, 95% CI 1.0 to 44.66; very low-quality evidence).

Trimethoprim was not significantly different to placebo for the frequency of complete healing (unclear follow-up time) for adults with unclear leg ulcer infection status (1 RCT, n=23, 25% versus 27.3%, RR 0.92, 95% CI 0.23 to 3.63; very low-quality evidence). There was no significant difference in the emergence of resistance with trimethoprim compared to placebo for adults with unclear leg ulcer infection status.

See GRADE table 20.

Uninfected leg ulcers

Antibiotics compared with standard care for adults

Systemic antibiotics (co-trimoxazole, gentamicin or amikacin according to sensitivities) were not significantly different compared with standard care for complete healing at 3 weeks (1 RCT, n=56, 16.7% versus 26.9%, RR 0.62, 95% CI 0.22 to 1.72; very low-quality evidence). In the same RCT there was also no significant difference for the outcomes of complete eventual healing or bacterial eradication (evaluation time point not reported). No dose or route of administration details were reported, additionally no information on how the wound samples were obtained were reported.

See GRADE table 21.

Topical antibiotic (mupirocin) compared with standard care for adults

Mupirocin was not significantly different to standard care for frequency of complete healing at 12 weeks (1 RCT, n=30, 53.3% versus 46.7%, RR 1.14, 95% CI 0.56 to 2.35; very low-quality evidence). There was also no significant difference for the eradication of gram-positive bacteria (evaluation time point not reported).

See GRADE table 22.

3.2.3 Antibiotic compared with other antiseptics in adults with leg ulcer

infected leg ulcer

Amoxicillin compared with povidone-iodine for adults

Systemic amoxicillin with compression was not significantly different for the outcome of complete healing at 12 weeks compared with either povidone-iodine alone (1 RCT, n=42, 85.7% versus 61.9%, RR 1.38, 95% CI 0.95 to 2.02; very low quality evidence) or with compression (1 RCT, n=42, 85.7% versus 81%, RR 1.06, 95% CI 0.81 to 1.39; very low quality evidence). The dose, route of administration and frequency of administration of amoxicillin were not reported. Ulcers were described as infected, but no further details were provided, and it is not clear if this referred to baseline status or incidence of infection during the RCT.

See GRADE table 23.

3.2.4 Choice of antibiotic in adults with leg ulcer

unclear leg ulcer infection status

Ciprofloxacin compared with trimethoprim for adults

Ciprofloxacin (750 mg twice daily, course length unclear) was not significantly different to trimethoprim (160 mg twice daily, course length unclear) for frequency of complete healing in 1 RCT (n=25, 38.5% versus 25%, RR 1.54, 95% CI 0.46 to 5.09; very low-quality evidence). Emergence of resistance was not significantly different at follow-up. Route of administration details and the evaluation time point were not reported.

See GRADE table 24.

3.2.5 Antibiotic dosage in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.6 Antibiotic course length in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.7 Antibiotic route of administration in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

4 Terms used in the guideline

Standard care

Standard care is the care given in addition to the intervention and/or the control. In the included studies this varied widely. The definition of standard care for each included study is given in the footnotes of the GRADE tables.

Appendices

Appendix A: **Evidence sources**

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• Brook & Frazier (1998) Aerobic and anaerobic microbiology of chronic venous ulcers • Callam et al (1987) Arterial disease in chronic leg ulceration: an underestimated hazard? Lothian and Forth Valley leg ulcer study • Halbert et al (1992) The effect of bacterial colonization on venous ulcer healing • Harker (2001) The effect of bacteria on leg ulcer healing • NHS Choices Venous leg ulcer (2019) • O'Meara et al (2014) Antibiotics and antiseptics for venous leg ulcers
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• Alinovi et al (1986) Systemic administration of antibiotics in the management of venous ulcers: a randomized clinical trial • Brook & Frazier (1998) Aerobic and anaerobic microbiology of chronic venous ulcers • Chief medical officer (CMO) report (2011) • Halbert et al (1992) The effect of bacterial colonization on venous ulcer healing

Key area	Key question(s)	Evidence sources
		• Harker (2001) The effect of bacteria on leg ulcer healing • Kontiainen & Rinne (1988) Bacteria in ulcera crurum Acta Dermato-Venereologica; 68(3):240–4. • Moore et al (2010) Surface bacteriology of venous leg ulcers and healing outcome • NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary (BNF) June 2018 • BNF for children (BNF-C) June 2018 • Summary of product characteristics

Appendix B: **Review protocol**

Review question	What antimicrobial interventions are effective in managing leg ulcer infection?
Types of review question	Intervention questions will primarily be addressed through the search.
Objective of the review	To determine the effectiveness of antimicrobial interventions in managing leg ulcer infection to address antimicrobial resistance. In line with the major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.
Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Adults and children (aged 72 hours and older) with leg ulcer infection of any severity[1].
Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Antimicrobial pharmacological interventions[2]. For the treatment of leg ulcer infection in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).
Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo, no treatment or usual care. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.
Outcomes and prioritisation	a) Clinical outcomes such as: • mortality

[1] Due to the paucity of evidence in people with infected leg ulcers, a post-hoc decision was made to include people with unclear leg ulcer infection status and uninfected leg ulcer in the review.

[2] Antimicrobial pharmacological interventions include: antiseptics, medicated antibiotic or antiseptic dressings, delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy

	• infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. c) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. d) Ability to carry out activities of daily living. e) Service user experience. f) Health and social care related quality of life, including long-term harm or disability. g) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).
Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Cohort studies • Pre and post intervention studies (before and after) • Time series studies.
Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers • non-antimicrobial and non-pharmacological interventions • general management of leg ulcer (as an intervention): for example cleansing, wound debridement, wound dressings (non-antiseptic and non-antimicrobial) or compression stockings.

Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.
Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.
Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following sources will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process via Ovid The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries

	• conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from 2000 to the present day The results will be downloaded in the following mutually exclusive sets: • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results See Appendix for further details on the search strategy. Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.
Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk
Highlight if amendment to previous protocol	For details please see the interim process guide (2017).
Search strategy – for one database	For details see appendix C.
Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.
Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.
Methods for assessing bias at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).
Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).

Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).
Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).
Rationale/ context – Current management	For details please see the interim process guide (2017).
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence and conducted meta-analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	Developed and funded by NICE.
Name of sponsor	Developed and funded by NICE.
Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.

Appendix C: **Literature search strategy**

Search format

The main search strategy will take the following format:

Leg ulcers

AND (Named Antibiotics OR Classes of Antibiotics OR Prescribing Strategies OR Antiseptics)

AND (Systematic Reviews OR Randomised Controlled Trials OR Observational Studies)

AND Limits

The strategy includes a top up search for the following terms:

Leg ulcers

AND General term “Antibiotics”

AND Systematic Reviews

Main concepts	Concept	Proposed search terms
Condition	Leg ulcers	exp Leg Ulcer/ ((varicose or vein* or venous or leg* or stasis or crural or crurus or lower extremit*) adj4 (ulcer* or sore*)).tw.
Named Antibiotics	Amikacin	Amikacin/ Amikacin.ti,ab.
	Amoxicillin	exp Amoxicillin/ Amoxicillin.ti,ab.
	Ampicillin	Ampicillin/ Ampicillin*.ti,ab
	Azithromycin	Azithromycin/ (Azithromycin* or Azithromicin* or Zithromax*).ti,ab

	Benzylpenicillin sodium	Penicillin G/ (Benzylpenicillin* or "Penicillin G").ti,ab
	Ceftaroline fosamil	(Ceftaroline* or Zinforo*).ti,ab
	Clarithromycin	Clarithromycin/ (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab
	Chloramphenicol	Chloramphenicol/ (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.
	Clindamycin	Clindamycin/ (Clindamycin* or Dalacin* or Zindaclin*).ti,ab
	Co-amoxiclav	Amoxicillin-Potassium Clavulanate Combination/ (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab
	Daptomycin	Daptomycin/ (Daptomycin* or Cubicin*).ti.ab
	Doxycycline	Doxycycline/ (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab
	Ertapenem	(Ertapenem* or Invanz*).ti,ab
	Erythromycin	Erythromycin/ Erythromycin Estolate/ Erythromycin Ethylsuccinate/ (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab
	Flucloxacillin	Floxacillin/ (Floxacillin* or Flucloxacillin*).ti,ab.
	Framycetin	Framycetin/ Framycetin.ti,ab
	Fusidic acid	Fusidic Acid/ ("Fusidic acid" or fusidate or Fucidin).ti,ab.
	Gentamicin	Gentamicins/ (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab
	Imipenem	Imipenem/ (Imipenem* or Primaxin*).ti,ab
	Levamisole	Levamisole/ (Levamisole OR ergamisol).ti,ab
	Levofloxacin	Levofloxacin/ (Levofloxacin* or Evoxil* or Tavanic*).ti,ab.

	Linezolid	Linezolid/ (Linezolid* or Zyvox*).ti,ab
	Meropenem	(Meropenem*).ti,ab
	Metronidazole	Metronidazole/ Metronidazole.ti,ab.
	Neomycin	exp Neomycin/ (neom?cin or "Neo-Fradin").ti,ab.
	Mupirocin	Mupirocin/ (Mupirocin or Bactroban).ti,ab.
	Ofloxacin	Ofloxacin/ (Ofloxacin* or Tarivid*).ti,ab
	Phenoxymethylpenicillin (penicillin V)	Penicillin V/ (Phenoxymethylpenicillin or "Penicillin V").ti,ab.
	Piperacillin with Tazobactam	Piperacillin/ (Piperacillin* or Tazobactam* or Tazocin*).ti,ab
	Teicoplanin	Teicoplanin/ (Teicoplanin* or Targocid*).ti,ab
	Tedizolid	Tedizolid.ti,ab
	Temocillin	Temocillin/ (Temocillin* or Negaban*).ti.ab
	Tigecycline	(Tigecycline* or Tygacil*).ti,ab
	Vancomycin	Vancomycin/ (Vancomycin* or Vancomicin* or Vancocin*).ti,ab
Classes of Antibiotics	Aminoglycoside	exp Aminoglycosides/ Aminoglycoside*.ti,ab
	Antipseudomonal penicillin	exp Penicillins/ Penicillin*.ti,ab
	Beta-lactamase	exp beta-Lactamases/ ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. exp beta-Lactamase inhibitors/
	Beta-lactam (stable)	beta-Lactams/ (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab.
	Carbapenems	exp Carbapenems/ Carbapenem*.ti,ab
	Cephalosporins	exp Cephalosporins/ Cephalosporin*.ti,ab
	Fluoroquinolones	exp Fluoroquinolones/

		Fluoroquinolone*.ti,ab
	Macrolides	exp Macrolides/ macrolide*.ti,ab
	Polymyxins	Polymyxins/ Polymyxin*.ti,ab
	Quinolones	exp Quinolones/ Quinolone*.ti,ab
	Tetracyclines	exp Tetracyclines/ Tetracycline*.ti,ab
	General terms	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ (antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.
Interventions – specific antiseptics	Chlorhexidine	Chlorhexidine/ (Chlorhexidine or Unisept or Hibiscrub or Hydrex or Hibi or HiBiTane).ti,ab.
	Dialkylcarbamoyl chloride	Dialkylcarbamoyl chloride/ (“Dialkylcarbamoyl chloride” or “Cutimed Sorbact”).ti.ab.
	Glucose oxidase	Glucose oxidase/ (“Glucose oxidase” or Flaminal*).ti.ab
	Hydrogen peroxide	Hydrogen Peroxide/ ("Hydrogen peroxide" or crystacide).ti,ab.
	Lactoperoxidase	Lactoperoxidase/ (Lactoperoxidase* or Flaminal*).ti.ab
	Octenidine	Octenidine/ (Octenidine* or Octenilin*).ti.ab.
	Polihexanide	Polihexanide/ (Polihexanide* or Suprasorb*).ti.ab.
	Povidone-iodine	Povidone-Iodine/ (Povidone-Iodine or Betadine or Videne).ti,ab.
	Potassium permanganate	Potassium Permanganate/ ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab.
	Proflavine	Proflavine/ proflavine.ti,ab.
	Silver sulfadiazine	Silver Sulfadiazine/ (Silver Sulfadiazine or Flamazine).ti,ab.
	Antimicrobial reactive oxygen gel/reactive oxygen therapy	(reactive oxygen or surgihoney*).ti,ab

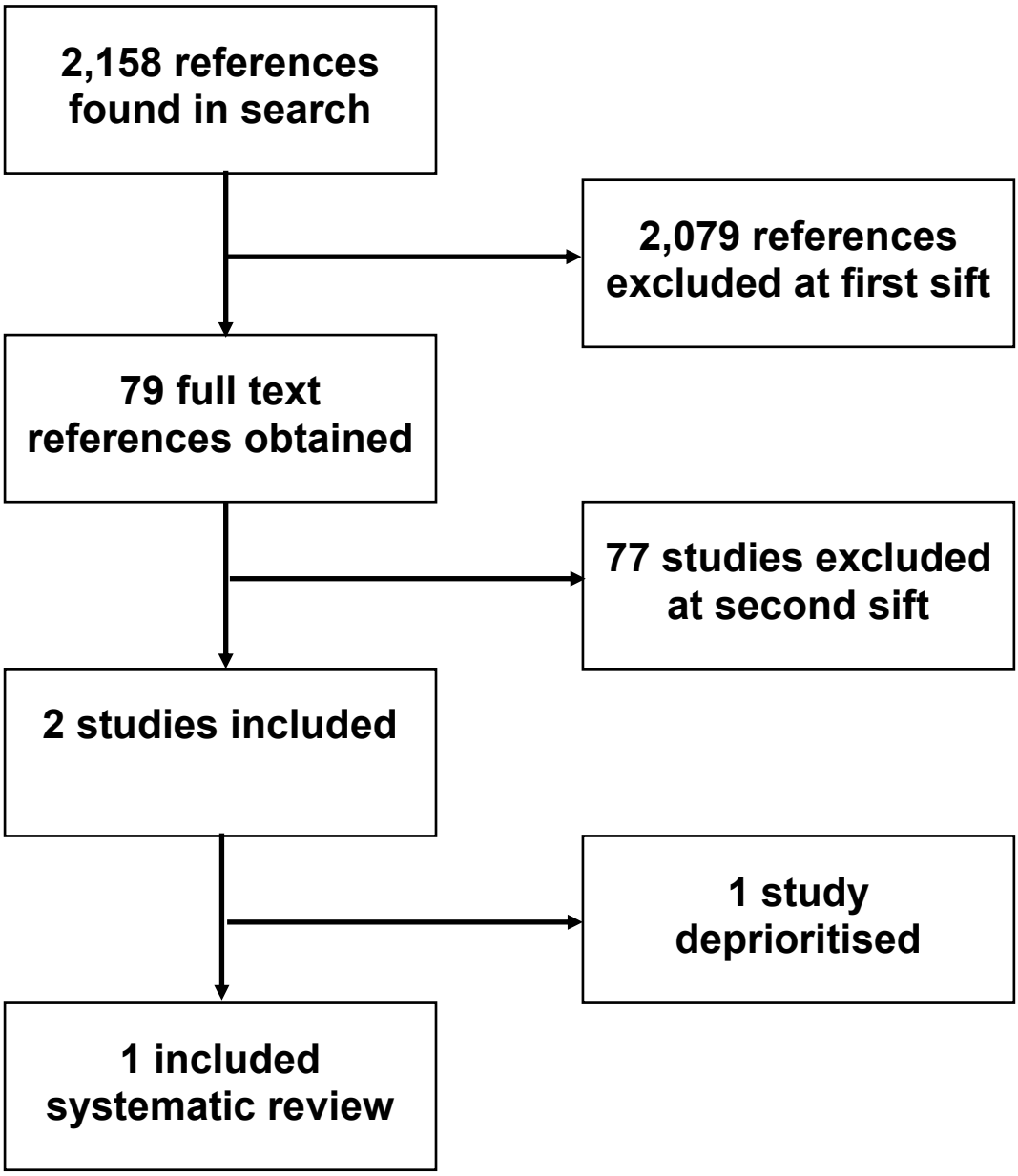
	Iodine	Iodine/ Iodine.ti,ab
	Honey-based topical application	Honey/ or Apitherapy/ (Honey* or L-Mesitran or MANUKApli or Medihoney or Melladerm or Mesitran).ti,ab
Interventions – general antiseptic terms	General antiseptic terms	exp anti-infective agents, local/ (Antiseptic* or anti-infective* or anti infective or antiinfective or microbicide*).ti,ab.
Prescribing Strategies	Active surveillance No intervention Watchful waiting	watchful waiting/ "no intervention*".ti,ab (watchful* adj2 wait*).ti,ab. (wait adj2 see).ti,ab (expectant* adj2 manage*).ti,ab (active* adj2 surveillance*).ti,ab
	Prescribing times Delayed treatment	((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv*)).ti,ab ((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*").ti,ab Inappropriate prescribing/
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Standard search filter
Randomised Controlled Trials	Controlled Clinical Trials Cross over studies Randomised controlled trials (rcts)	Standard search filter

Observational Studies	Case-Control Studies Cohort Studies Controlled Before-After Studies Cross-Sectional Studies Epidemiologic Studies Observational Study	Standard search filter
Limits	Exclude Animal studies Exclude letters, editorials and letters Limit date to 2006-Current	Standard search limits

Key to search operators for above table

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

Appendix D:**Study flow diagram**



Appendix E: **Evidence prioritisation**

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Which antibiotic is most effective in adults with leg ulcers?						
O'Meara et al 2014	Systematic review	Antibiotic (systemic or topical)	Standard care or placebo	Healing (frequency or rate) Development of resistance	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Is silver effective in adults with leg ulcers?						
O'Meara et al 2014	Systematic review	Silver (dressing or topical)	Standard care or other silver dressing	Healing (frequency or rate)	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Is honey effective in adults with leg ulcers?						
O'Meara et al 2014	Systematic review	Honey (dressing or topical)	Standard care	Healing (rate)	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Gethin et al 2009	RCT	Honey (topical)	Standard care	Healing (rate)	Not prioritised	RCT retracted due to data errors
Is povidone-iodine or cadexomer-iodine effective in adults with leg ulcers?						
O'Meara et al 2014	Systematic review	Topical iodine	Standard care or antibiotic	Healing (frequency or rate)	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Is peroxide effective in adults with leg ulcers?						
O'Meara et al 2014	Systematic review	Benzoyl peroxide	Saline dressing	Healing rate	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison

Appendix F: **Included studies**

O'Meara S, Al-Kurdi D, Ologun Y et al. Antibiotics and antiseptics for venous leg ulcers. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD003557.

Appendix G: **Quality assessment of included studies**

G.1 Antibiotic prescribing strategy in adults with leg ulcers

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.2 Antibiotic efficacy and choice in adults with leg ulcers

Table 2: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	O'Meara et al 2014
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes[a]
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

[a] No RCT included within the systematic review was assessed by the Cochrane authors as at low risk of bias

NB. The same systematic review was used for the other interventions in this evidence review.

G.3 Antibiotic dose in adults with leg ulcers

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.4 Antibiotic course length in adults with leg ulcers

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.5 Antibiotic route of administration in population

No systematic reviews or randomised controlled trials met the inclusion criteria.

G.6 Antiseptics for adults with leg ulcer

Table 3: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	O'Meara et al 2014
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes[a]
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a] No RCT included within the systematic review was assessed by the Cochrane authors as at low risk of bias NB. The same systematic review was used for the other interventions in this evidence review.	

Appendix H: **GRADE profiles**

H.1 Topical antiseptics in adults with leg ulcer

H.1.1 Iodine in adults with leg ulcer

Table 4: GRADE profile – cadexomer-iodine vs standard care for adults with infected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cadexomer-iodine	Standard care	Relative (95% CI)	Absolute		
Pain measured with 100-point VAS -divided into increments of 10 (follow-up 6 weeks; measured with cadexomer-iodine versus standard care; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	n=38[4] mean 23.0 SEM±3.7	n=36[5] mean 10.0 SEM±2.5	-	MD 13.00 lower (21.75 to 4.25 lower)	⊕⊕OO LOW	CRITICAL
Mean percentage change in ulcer area (follow-up 6 weeks; measured with cadexomer-iodine versus standard care; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	none	none	n=38[4] -34% SEM±5	n=36[5] +5% SEM±15	-	MD 0.39 lower (0.70 to 0.08 lower)[6]	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological findings (*Staphylococcus aureus*) (follow-up unclear[7]; assessed with cadexomer-iodine versus standard care)- infected leg ulcer												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[8]	none	n=38[4]	n=36[5]	*Staphylococcus aureus* accounted for 77% of all species in cultures. Standard care was less effective than cadexomer iodine at reducing or eliminating *Staphylococcus aureus* during treatment (p<0.001, Chi-square test with Yates' correction). Standard care was less effective for infection cleared or persisted or new infection[17] during treatment than cadexomer-iodine (16 cleared/7 persisted or new infection) (p<0.001, Chi-square test with Yates' correction).	⊕OOO VERY LOW	IMPORTANT
Bacteriological findings (*Pseudomonas aeruginosa*) (follow-up unclear[7]; assessed with cadexomer-iodine versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[8]	none	0/38 (0%)[4]	0/36 (0%)[5]	Standard care was less effective (6 persisted or new infection) than cadexomer-iodine (0 new, 3 improved or cleared) (p<0.05, Fishers exact).		⊕OOO VERY LOW	IMPORTANT

Bacteriological findings (Other organisms[9]) (follow-up unclear[7]; assessed with: cadexomer-iodine versus standard care)- infected leg ulcer												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[8]	none	0/38 (0%)[4]	0/36 (0%)[5]	Standard care was less effective (not defined) for other organisms (p<0.001, Chi-square test).		⊕OOO VERY LOW	IMPORTANT
Adverse effects[10] (follow-up unclear; assessed with cadexomer-iodine versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[11]	none	4/38 (10.5%)	1/36 (2.7%)	RR 3.79 (0.44 to 32.32)	78 more pre 1000 (from 16 fewer to 870 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; VAS, Visual analogue scale; MD, Mean difference; RCT, Randomised controlled trial, p, P value; SEM, Standard error of the mean.												

[1] O'Meara et al 2014, the included RCT (Skog et al 1983) was identified for further exploration as the population was adults with an infected leg ulcer.
[2] Downgraded 1 level - no RCT was assessed by the Cochrane reviewers as at low risk of bias.
[3] Downgraded 1 level - at a minimal important difference of 0.5 SD of the control arm (11.1) data are consistent with no meaningful difference or appreciable benefit with cadexomer-iodine powder.
[4] Intervention was ulcers cleansed with running water, then cadexomer-iodine powder applied to a depth of 3 mm followed by application of a dry dressing.
[5] Control was daily cleansing with dilute hydrogen peroxide or potassium permanganate baths, non-adherent dressing applied (other treatments including antibiotics were allowed). All participants had compression.
[6] Cadexomer-iodine also significantly reduced the following wound healing secondary outcomes compared to standard care at 6 weeks: Pus and debris (p<.005); Exudate (p<0.005); Erythema (p<0.005). It significantly improved granulation (p<0.05) compared to standard care. Within groups (standard care and cadexomer-iodine) all outcomes improved significantly compared to baseline. Although cadexomer-iodine reduced oedema compared to baseline (within group test) it was not significantly different to standard care at 6 weeks.
[7] Follow-up period not reported.
[8] Downgraded 2 levels - unable to recalculate authors reported statistical significance due to unreported denominators.
[9] Includes beta-haemolytic *Streptococcus*, *Proteus, Enterobacteria, and Klebsiella*.
[10] Adverse effects were pain itching or rash.
[11] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with cadexomer-iodine, and no meaningful difference or appreciable benefit with standard care.

Table 5: GRADE profile – cadexomer-iodine vs standard care for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cadexomer-iodine**	**Standard care**	**Relative (95% CI)**	**Absolute**		
Frequency of complete healing (follow-up 4 to 12 weeks; assessed with cadexomer-iodine versus standard care)												
4[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	35/106 (33%)[4]	16/106 (15.1%)[5]	RR 2.17 (1.3 to 3.6)	177 more per 1000 (from 45 more to 392 more)	⊕⊕OO LOW	CRITICAL
Adverse effects[6] (follow-up time point unclear; assessed with cadexomer-iodine versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	serious[7]	serious[8]	none	10/30[9] (33%)	2/30[10] (6.7%)	RR 5.0 (1.19 to 20.92)	267 more per 1000 (from 13 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Mean percentage change in ulcer area (follow-up at 4 weeks; assessed with cadexomer-iodine versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	serious[7]	serious[11]	none	41[12]	31[13]	Percentage reduction in ulcer size with cadexomer 31.7% Percentage reduction in ulcer size with standard care 10% p<0.01.		⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up time point up to 6 weeks; assessed with cadexomer-iodine versus standard care)												

1[1]	randomised trials	serious[2]	not applicable	serious[7]	serious[11]	none	41[12]	31[13]	Withdrawal due to adverse effects with cadexomer-iodine: 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 No adverse effects reported in the control group.	⊕OOO VERY LOW	CRITICAL
Mean (standard error of the mean) rate of ulcer healing (cm²/wk) (follow-up at 24 weeks; assessed with cadexomer-iodine versus standard care)											
1[1]	randomised trials	serious[2]	not applicable	serious[7]	serious[11]	none	38[14]	37[15]	Mean (SEM) rate of ulcer healing with cadexomer 0.41 (0.13) Mean (SEM) rate of ulcer healing with standard care 0.95 (0.12) p=0.0025	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up time point unclear; assessed with cadexomer-iodine versus standard care)											
1[1]	randomised trials	serious[2]	not applicable	serious[7]	serious[11]	none	38[14]	37[15]	Adverse effects with cadexomer (burning, itching or pain n=6) Adverse effects with control (n=0)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; p, P value; SEM, Standard error of the mean.											

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT was assessed by the Cochrane reviewers as at low risk of bias.
[3] Downgraded 1 level - in all the RCTs it is uncertain whether the participants had an infected ulcer either at baseline or follow-up. In the meta-analysis only 1 of the 4 RCTs reported bacterial growth (Lindsay 1986) 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.
[4] Intervention was cadexomer-iodine powder in 2 RCTs and unclear cadexomer-iodine preparation in 2 RCTs. Cadexomer iodine was applied in 3 to 5 mm depth in 3 RCTs, unclear depth in 1 RCT, covered with a gauze dressing. Compression was used in 2 RCTs and light elastic bandage or support stocking in 2 RCTs. Dressing changes were daily or every other day. Cleaning with saline, saline swab or water.
[5] The control (standard care) varied both within and between studies from sterile non-adherent dressing in 1 RCT changed on alternate days, to cleaning with dilute hydrogen peroxide and covered with zinc paste (some adults had saline dressing, dilute potassium permanganate solution or gentian violet applied at clinicians discretion) in 1 RCT, cleaned with saline and polymixin/bacitracin ointment plus gentian violet in 1 RCT and 1 RCT which allowed any standard treatment (including topical antibiotics, antiseptics, hydrophilic agents, topical steroids, bland agents) plus compression.
[6] Adverse effects were eczema, pruritus or rash following use and difficulty in removing powder, itching or stinging during application of powder
[7] Downgraded 1 level - it is uncertain whether the participants had an infected ulcer either at baseline or follow-up.
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with cadexomer-iodine.
[9] Intervention was Cadexomer iodine was applied in 3 to 5 mm depth then gauze and compression.
[10] Control was ulcer cleaned with saline and polymixin/bacitracin ointment plus gentian violet plus non adherent dressing.
[11] Downgraded 1 level – insufficient data to recalculate effect size, for example denominators for those completing treatment unclear.
[12] Intervention was 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.
[13] Control was support bandaging or stocking with a dry dressing. Multiple treatment modalities used.
[14] Intervention was ulcer was 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.
[15] Control was wet-to-dry dressings with saline-soaked gauze pads changed by the participant daily plus toe-to-knee elastic compression bandage.

Table 6: GRADE profile – Cadexomer-iodine versus other dressing for adults uninfected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cadexomer-iodine	Other dressing	Relative (95% CI)	Absolute		
Frequency of complete healing (follow-up 12 weeks; assessed with cadexomer-iodine versus hydrocolloid dressing)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	very serious[4]	none	8/56 (14.3%)[5]	5/48 (10.4%)[6]	RR 1.37 (0.48 to 3.91)	39 more per 1000 (from 54 fewer to 303 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up unclear; assessed with cadexomer-iodine versus hydrocolloid dressing)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	serious[7]	none	19[5]	33[6]	UTD[8]	-	⊕OOO VERY LOW	CRITICAL
Frequency of complete healing (follow-up 12 weeks; assessed with cadexomer-iodine versus paraffin gauze)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	very serious[9]	none	8/56 (14.3%)[5]	7/49 (14.3%)[10]	RR 1.00 (0.39 to 2.56)	0 fewer per 1000 (from 87 fewer to 223 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up unclear; assessed with cadexomer-iodine versus paraffin gauze)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	serious[7]	none	19[5]	26[6]	UTD[8]	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk, UTD, Unable to determine.												

[1] O'Meara et al 2014
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias
[3] Downgraded 2 levels - participants with clinically infected ulcers were excluded from the trial
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with cadexomer-iodine paste, and no meaningful difference or appreciable harm with hydrocolloid dressing
[5] Intervention was cadexomer-iodine paste (changed when moisture saturated), all participants received compression therapy.
[6] Control was hydrocolloid dressing changed when saturated or leaking, all participants received compression therapy.
[7] Downgraded 1 level - unable to determine
[8] Unable to calculate as denominator unclear
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with cadexomer-iodine paste, and no meaningful difference or appreciable harm with paraffin gauze dressing
[10] Control was paraffin gauze dressing changed when saturated or leaking

Table 7: GRADE profile – Cadexomer-iodine versus silver dressing for adults with infected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cadexomer-iodine	Other dressing	Relative (95% CI)	Absolute		
Frequency of complete healing (follow-up 12 weeks; assessed with cadexomer-iodine versus silver dressing)												

1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	84/141 (59.6%)[4]	85/140 (60.7%)[5]	RR 0.98 (0.81 to 1.19)	12 fewer per 1000 (from 115 fewer to 115 more)	⊕⊕OO LOW	CRITICAL
Participant satisfaction (follow-up unclear; assessed with cadexomer-iodine versus silver dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	89/100 (89%)[4]	98/107 (91.6%)[5]	RR 0.97 (0.89 to 1.06)	27 fewer per 1000 (from 101 fewer to 55 more)	⊕⊕OO LOW	IMPORTANT
Adverse effects (follow-up unclear; assessed with cadexomer-iodine versus silver dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[6]	none	8[4]	13[5]	UTD[7]	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk, UTD, Unable to determine.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - participants had to have at least one sign (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) of infection or 'critical colonisation' (poorly defined term) and it was unclear how many participants were adjudged to have either infection or critical colonisation.
[4] Intervention was cadexomer-iodine dressing (ointment or powder), compression was allowed.
[5] Control was silver-donating dressings, compression was allowed.
[6] Downgraded 1 level - unable to determine.
[7] Unable to calculate as denominator unclear.

Table 8: GRADE profile – povidone-iodine plus compression versus other dressing plus compression for adults with infected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Povidone-iodine plus compression**	**Other dressing plus compression**	**Relative (95% CI)**	**Absolute**		
Complete healing (follow-up 4 weeks; assessed with povidone-iodine plus compression versus moist or foam dressings plus compression)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	2/15 (13.3%)[5]	5/15 (33.3%)[6]	RR 0.40 (0.09 to 1.75)	200 fewer per 1000 (from 303 fewer to 250 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - unclear if wounds were clinically infected at baseline although most had bacterial growth and the study included protocols for infected leg ulcers.
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with povidone-iodine, and no meaningful difference or appreciable harm with moist or foam dressing
[5] Intervention was 10% povidone-iodine dressing changed daily
[6] Control was (according to ulcer status) moist wound dressing (with Ringer's solution to continuously irrigate the wound bed) changed daily for necrotic tissue; foam dressing once necrotic tissue removed changed every 5th day (or sooner) or if infected a silver containing dressing plus compression.

Table 9: GRADE profile – povidone-iodine plus compression versus other dressing plus compression for adults with uninfected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Povidone-iodine plus compression	Other dressing plus compression	Relative (95% CI)	Absolute		
Frequency of complete healing (follow-up 4 months; assessed with povidone-iodine plus compression versus hydrocolloid plus compression)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	47/101 (46.5%)[5]	50/99 (50.5%)[6]	RR 0.92 (0.69 to 1.23)	40 fewer per 1000 (from 157 fewer to 116 more)	⊕OOO VERY LOW	CRITICAL
Time to healing (follow-up unclear; assessed with 10% povidone-iodine solution plus compression versus with hydrocolloid plus compression)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[7]	none	n=17[8, 9]	n=17[8, 10]	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).		⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - participants had ulcers not clinically infected at baseline although most had bacteria present at initial assessment.
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with povidone-iodine
[5] Intervention was ulcer cleaning with sterile isotonic saline, povidone-iodine dressing and an absorbent pad plus compression.
[6] Control was ulcer cleaning with sterile isotonic saline, ulcer filled with hydrocolloid powder until level with ulcer margin then hydrocolloid dressing plus compression.
[7] Downgraded 1 level – data insufficient to recalculate, the Cochrane authors advise this finding should be treated with caution because of the small number of participants recruited.
[8] Overall n=17 each with 2 ulcers acting as their own control.
[9] Intervention was one ulcer per participant was randomly assigned to receive 10% povidone-iodine solution plus standard treatment ((comprised saline cleansing, hydrocolloid dressing and a 'compressive bandage').
[10] Control was the other ulcer was treated with standard treatment alone (comprised saline cleansing, hydrocolloid dressing and a 'compressive bandage').

H.1.2 Peroxide in adults with leg ulcer

Table 10: GRADE profile – peroxide-based topical preparation versus saline soak for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Peroxide-based topical preparation (mean%±SD)	Saline soak (mean%±SD)	Relative (95% CI)	Absolute		
Mean percentage ulcer area remaining (follow-up 42 days; measured with: 10% peroxide-based topical preparation versus saline soak; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	10[4] 64.3±14	10[5] 94.7±12.7	-	MD 30.40 lower (42.12 to 18.68 lower)	⊕⊕OO LOW	CRITICAL
Mean percentage ulcer area remaining (follow-up 42 days; measured with: 20% peroxide-based topical preparation versus saline soak; Better indicated by lower values)												

1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	10[6] 59.6±12.3	10[5] 93.7±15.2	-	MD 34.10 lower (46.22 to 21.98 lower)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; MD, Mean difference.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - the infection status of the ulcers was unclear.
[4] Intervention was ulcer treated with 10% benzoyl peroxide lotion, with sponge dressing, gauze pad and support bandage changed 3 times weekly for 42 days. NB the intervention is not available in the same strength, formulation and is off license use for leg ulcer treatment.
[5] Control was normal saline solution with sponge dressing, gauze pad and support bandage changed 3 times weekly for 42 days.
[6] Intervention was ulcer treated with 20% benzoyl peroxide lotion, with sponge dressing, gauze pad and support bandage changed 3 times weekly for 42 days. NB the intervention is not available in the same strength, formulation and is off license use for leg ulcer treatment.

Table 11: GRADE profile – peroxide-based topical preparation versus placebo for adults with uninfected leg ulcer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Peroxide cream (median decrease and range)**	**Placebo (median decrease and range)**	**Relative (95% CI)**	**Absolute**		
Median decrease in ulcer area (follow-up 10 days; measured with: 1% hydrogen peroxide-based cream versus placebo cream; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	n=10[5] 35% (12% to 44%)	n=10[6] 11% (0% to 23.5%)	-	Favours peroxide p<0.05	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	n=18[5] 44.8% (15% to 57%)	n=14[6] 32% (15% to 44%)	-	Favours peroxide p<0.005	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; p, P value.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT was assessed by the Cochrane reviewers as at low risk of bias.
[3] Downgraded 1 level – both RCTs had an initial run-in period involved administration of systemic antibiotics for 15 to 20 days to clear any underlying infection.
[4] Downgraded 1 level – insufficient data to calculate effect size.
[5] The lower limb and the area of ulceration were cleaned with water and neutral soap; skin was dried with tissue paper; 2 g hydrogen peroxide cream 1% was applied to the ulcerated area and surrounding skin and compression below-knee stockings were applied.
[6] Instead of peroxide cream 2 g of placebo cream was applied.

H.1.3 Honey in adults with leg ulcer

Table 12: GRADE profile – honey versus standard care for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Honey**	**standard care**	**Relative (95% CI)**	**Absolute**		

Complete healing (follow-up 12 weeks; assessed with honey impregnated dressing versus standard care)											
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	104/187 (55.6%)[5]	90/181 (49.7%)[6]	RR 1.12 (0.92 to 1.38)[7]	60 more per 1000 (from 40 fewer to 189 more)	⊕OOO VERY LOW	CRITICAL
Incidence of ulcer infection during follow-up (follow-up 12 weeks; assessed with honey impregnated dressing versus standard care)											
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[8]	none	32/187 (17.1%)[5]	40/181 (22.1%)[6]	RR 0.77 (0.51 to 1.18)[7]	51 fewer per 1000 (from 108 fewer to 40 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up unclear; assessed with honey impregnated dressing versus standard care)											
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[9]	none	111/187 (59.4%)[5]	84/181 (46.4%)[6]	RR 1.28 (1.05 to 1.56)	130 more per 1000 (from 23 more to 260 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; MRSA, Meticillin resistant *Staphylococcus Aureus*; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias
[3] Downgraded 1 level - the infection status of the participants leg ulcers at baseline was unclear
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with honey
[5] Intervention was calcium alginate dressing impregnated with manuka honey plus compression
[6] Control was dressing choice of district nurse from alginate, hydrofibre, hydrocolloid, foam, hydrogel, nonadherent, iodine or silver dressing plus compression
[7] Please note that the O'Meara et al 2014 Cochrane review contains 2 RCTs for this outcome, however the Gethin et al 2008 paper on efficacy and healing outcomes has been subsequently retracted see https://onlinelibrary.wiley.com/doi/abs/10.1111/jocn.12652
[8] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with honey impregnated dressing
[9] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with honey impregnated dressing.

Table 13: GRADE profile – honey versus standard care for adults with uninfected leg ulcer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Honey**	**standard care**	**Relative (95% CI)**	**Absolute**		
Participants with MRSA eradication (follow-up 4 weeks; assessed with topical manuka honey versus hydrogel)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	7/10 (70%)[4]	1/6 (16.7%)[5]	RR 4.20 (0.67 to 26.3)[6]	533 more per 1000 (from 55 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; MRSA, Meticillin resistant *Staphylococcus Aureus*; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with honey, and no meaningful difference or appreciable harm with hydrogel
[4] Intervention was manuka honey (topical) 5 g/20 cm2 applied weekly plus foam dressing and compression
[5] Control was hydrogel 3 g/20 cm2 applied weekly plus foam dressing and compression
[6] This RCT (Gethin et al 2008) is separate to the withdrawn paper by the same authors for effectiveness.

H.1.4 Silver in adults with leg ulcer

Table 14: GRADE profile – silver sulfadiazine versus non adherent dressing for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Silver sulfadiazine	Placebo or other intervention	Relative (95% CI)	Absolute		
Complete healing (follow-up 12 weeks; assessed with silver sulfadiazine versus non-adherent dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	19/30 (63.3%)[5]	24/30 (80%)[6]	RR 0.79 (0.57 to 1.1)	168 fewer per 1000 (from 344 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane authors as at risk of bias.
[3] Downgraded 1 level - all ulcers initially contaminated (not further defined) infection status unclear. 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).
[4] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with silver sulfadiazine.
[5] Intervention was silver sulfadiazine cream, ulcers were cleaned with saline, had compression and weekly dressing changes.
[6] Control was nonadherent dressing, ulcers were cleaned with saline, had compression and weekly dressing changes.

Table 15: GRADE profile – silver sulfadiazine versus placebo or standard care for adults with uninfected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Silver sulfadiazine	Placebo or other intervention	Relative (95% CI)	Absolute		
Complete healing (follow-up 4 weeks; assessed with silver sulfadiazine cream versus placebo cream)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	6/31 (19.4%)[5]	1/30 (3.3%)[6]	RR 5.81 (0.74 to 45.4)	160 more per 1000 (from 9 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Median time to healing (treatment was for 6 weeks; assessed with silver sulfadiazine cream versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	serious[7]	very serious[8]	none	n=17[9, 10]	n=17[9, 11]	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[8].		⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias.
[3] Downgraded 1 level - patients with leg ulcer culture >10^5 bacteria/gram ulcer tissue (tissue biopsy) were excluded as were those with systemic sepsis or bone infection.
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with 1% silver sulfadiazine, and no meaningful difference or appreciable harm with placebo.
[5] Intervention was topical silver sulfadiazine cream (1%) plus nonadherent dressing and elastic support, ulcer cleaned with normal saline and all participants had compression and elevation at rest.
[6] Control was placebo cream plus nonadherent dressing and elastic support, ulcer cleaned with normal saline and all participants had compression and elevation at rest.
[7] Downgraded 1 level – Participants were described as infection free at baseline.
[8] Downgraded 2 levels – insufficient data to recalculate, p value not presented.
[9] N=17 each participant had 2 ulcers and acted as their own control.
[10] Intervention was application of 1% silver sulphadiazine cream in addition to usual care (hydrocolloid dressing and a 'compressive bandage'-no further details were provided).
[11] Control was usual care alone.

Table 16: GRADE profile – silver impregnated dressing versus non-adhesive dressing for adults with infected leg ulcer

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Silver impregnated dressing	Silver impregnated or other dressing	Relative (95% CI)	Absolute		
Complete healing (follow-up 9 weeks; assessed with silver dressing plus compression versus non-adhesive dressing)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	17/21 (81%)[4]	10/21 (47.6%)[5]	RR 1.70 (1.04 to 2.79)	333 more per 1000 (from 19 more to 852 more)	⊕⊕OO LOW	CRITICAL
Pain free at end of study (follow-up unclear[6]; assessed with silver dressing versus non-adhesive dressing)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	21/21 (100%)[4]	13/21 (61.9%)[5]	RR 1.59 (1.14 to 2.23)	365 more per 1000 (from 87 more to 761 more)	⊕⊕OO LOW	CRITICAL
Adverse effects (follow-up unclear; assessed with silver dressing versus non-adhesive dressing)												
2[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[7]	none	26/239 (10.9%)[8]	27/218 (12.4%)[9]	RR 0.87 (0.53 to 1.44)	16 fewer per 1000 (from 58 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors to be at low risk of bias
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with silver dressing
[4] Intervention was non-adhesive silver releasing foam (Dimakakos 2009) plus compression, ulcers cleaned with sterile water and a 10% povidone-iodine solution in twice weekly changes and antibiotics if wound cultures were positive
[5] Control was non-adhesive foam dressing plus standard care (Dimakakos 2009)
[6] Follow-up reported as end of study for control group and at 8 weeks for intervention group (treatment duration was 9 weeks)
[7] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with silver dressing, and no meaningful difference or appreciable harm with non-antimicrobial dressings.
[8] Interventions were non-adhesive silver releasing foam (Dimakakos 2009) plus compression, ulcers cleaned with sterile water and a 10% povidone-iodine solution in twice weekly changes and antibiotics if wound cultures were positive; silver-donating foam dressing (Contreet Ag). Both adhesive and non-adhesive versions of the dressing were used (Munter 2006).
[9] Controls were non-adhesive foam dressing plus standard care (Dimakakos 2009); local best practice (Munter 2006), including the following dressings-foams/alginates (53%), hydrocolloids (12%), gauze (3%), silver dressings (17%), other antimicrobial dressings (9%), other active dressings (6%).

Table 17: GRADE profile – silver impregnated dressing versus silver impregnated or other dressing for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Silver impregnated dressing	Silver impregnated or other dressing	Relative (95% CI)	Absolute		
Complete healing (follow-up 12 weeks; assessed with silver dressing versus 5-layer silver dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	10/20 (50%)[5]	7/20 (35%)[6]	RR 1.43 (0.68 to 3)	150 more per 1000 (from 112 fewer to 700 more)	⊕OOO VERY LOW	CRITICAL
Complete healing (follow-up 4 to 12 weeks; assessed with silver dressing versus non-antimicrobial dressing)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[7]	very serious[8]	none	11/85 (12.9%)[9]	7/84 (8.3%)[10]	RR 1.56 (0.64 to 3.8)	47 more per 1000 (from 30 fewer to 233 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up time point not reported; assessed with silver dressing versus non-antimicrobial dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[11]	very serious[8]	none	4/65 (6.1%)[12]	3/64 (4.7%)[13]	RR 1.31 (0.31 to 5.63)	15 more per 1000 (from 32 fewer to 217 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors to be at low risk of bias.
[3] Downgraded 1 level - it was unclear if the participants had a clinical infection, although all had bacterial colonisation at baseline.
[4] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with Avance, and no meaningful difference or appreciable harm with Acticoat 7.
[5] Intervention was a silver-impregnated polyurethane foam dressing plus compression.
[6] Control was 5-layer silver impregnated dressing comprising 2 absorbent layers sandwiched with 3 layers of silver-coated, low adherent polyethylene net plus compression.
[7] Downgraded 1 level – In 1 RCT (Jorgensen 2005) infection in the leg ulcer was a reason for exclusion but the ulcer needed to display critical colonisation, in the 2nd RCT (Wunderlich 1991) no information was reported about leg ulcer infection status.
[8] Downgraded 2 levels – at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with silver dressing, and no meaningful difference or appreciable harm with non-antimicrobial dressings.
[9] Interventions were non-adhesive silver releasing foam (Jorgensen 2005) secured with gauze or tape changed weekly, ulcers cleaned with saline or tap water, zinc cream if peri-ulcer skin and compression according to treating centre practise; silver impregnated activated charcoal dressing (Wunderlich 1991) plus initial debridement (mechanical or enzymatic) with daily dressing changes.
[10] Controls were hydrocellular foam dressing plus standard care (Jorgensen 2005); various topical agents (mineral oil, sea salt, povidone-iodine paste, paraffin gauze, oil-and-water emulsion) plus standard care (Wunderlich 1991).
[11] Downgraded 1 level – In 1 RCT (Jorgensen 2005) infection in the leg ulcer was a reason for exclusion but the ulcer needed to display critical colonisation.
[12] Interventions were non-adhesive silver releasing foam (Jorgensen 2005) secured with gauze or tape changed weekly, ulcers cleaned with saline or tap water, zinc cream if peri-ulcer skin and compression according to treating centre practise.
[13] Controls were hydrocellular foam dressing plus standard care (Jorgensen 2005).

Table 18: GRADE profile – silver impregnated dressing versus silver impregnated or other dressing for adults with uninfected leg ulcer

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Silver impregnated dressing	Silver impregnated or other dressing	Relative (95% CI)	Absolute		
Complete healing (follow-up 4 to 12 weeks; assessed with silver dressing plus compression versus non-antimicrobial dressing)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	62/107 (57.9%)[5]	59/106 (55.6%)[6]	RR 1.04 (0.82 to 1.32)	22 more per 1000 (from 100 fewer to 178 more)	⊕OOO VERY LOW	CRITICAL
Complete healing (follow-up 6 months; assessed with silver dressing versus non-antimicrobial dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	87/107 (81.3%)[5]	78/106 (73.6%)[6]	RR 1.10 (0.96 to 1.28)	74 more per 1000 (from 29 fewer to 206 more)	⊕OOO VERY LOW	CRITICAL
Complete healing (follow-up 12 months; assessed with silver dressing versus non-adhesive dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	95/107 (88.8%)[5]	90/106 (84.9%)[6]	RR 1.05 (0.94 to 1.16)	42 more per 1000 (from 51 fewer to 136 more)	⊕⊕OO LOW	CRITICAL
Ulcer recurrence within 1 year (follow-up 12 months; assessed with silver dressing versus non-adhesive dressing)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[7]	none	11/95 (11.6%)[5]	13/90 (14.4%)[6]	RR 0.80 (0.38 to 1.7)	29 fewer per 1000 (from 90 fewer to 101 more)	⊕OOO VERY LOW	IMPORTANT
Change in ulcer surface area (cm squared) (follow-up 4 weeks; measured with silver dressing versus non-antimicrobial dressing; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	very serious[8]	serious[21]	none	n=89[10]	n=81[11]	-	MD 4.70 lower (8.46 to 0.94 lower)	⊕OOO VERY LOW	CRITICAL
Change in ulcer surface area (%) (follow-up 4 weeks; measured with silver dressing versus non-antimicrobial dressing; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	very serious[12]	very serious[8]	serious[9]	none	n=89[10]	n=81[11]	-	MD 6.13 lower (32.59 lower to 20.32 higher)	⊕OOO VERY LOW	CRITICAL
Healing rate (cm squared per day) (follow-up unclear[13]; measured with silver dressing versus non-antimicrobial dressing; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	very serious[8]	serious[9]	none	n=89[10]	n=81[11]	-	MD 0.12 lower (0.28 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects (follow-up unclear; assessed with silver dressing versus non-antimicrobial dressing)												
2[1]	randomised trials	serious[2]	serious[12]	serious[14]	very serious[15]	none	16/82 (19.5%)[29]	31/82 (37.8%)[30]	RR 0.50 (0.13 to 1.87)	189 fewer per 1000 (from 329 fewer to 329 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; MD, Mean difference; UTD, Unable to determine; RCT, Randomised controlled trial.

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors to be at low risk of bias.
[3] Downgraded 1 level - 1 RCT (Michaels 2009) withdrew participants needing antibiotics, no other information on participants leg ulcer infection status provided.
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with silver dressing.
[5] Intervention was any UK approved silver dressing plus compression changed weekly (Michaels 2009).
[6] Control was non-antimicrobial low-adherent dressing plus standard care (Michaels 2009).

[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with silver dressings, and no meaningful difference or appreciable harm with non-adhesive dressings.
[8] Downgraded 2 levels - both RCTs excluded or withdrew participants requiring antibiotic treatment or with signs of clinical infection.
[9] Downgraded 1 level - at a default minimal important difference of 0.5 of the standard deviation of the control arm data is consistent with no meaningful difference or appreciable benefit with silver dressing
[10] Interventions were contact layer silver dressing (non-adhesive), non-occlusive polyester mesh impregnated with hydrocolloid particles and vaseline. Standard care was wound cleansing with normal saline, mechanical debridement to remove slough or necrotic tissue, secondary dressings and compression, dressings changed every other day or less frequently, local antiseptics were allowed (Lazareth 2008); Silver releasing hydro alginate dressing, plus standard care of cleansing with sterile saline, debridement as necessary using surgical or mechanical methods, sterile pad as secondary dressings, systemic antibiotics if indicated, dressings changed 5X in first fortnight and every 2 to 3 days thereafter, compression was used (Meaume 2005).
[11] Controls were contact layer dressing without silver plus standard care (Lazareth 2008); calcium alginate dressing plus standard care (Meaume 2005).
[12] Downgraded 2 levels - NICE meta-analysis, I^2>50%, random effects model used.
[13] The number of days over which the healing rate was calculated was not reported.
[14] Downgraded 1 level - both RCTs excluded or withdrew participants requiring antibiotic treatment or with signs of clinical infection.
[15] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with silver dressings, and no meaningful difference or appreciable harm with non-antimicrobial dressings.
[16] Interventions were contact layer silver dressing (non-adhesive), non-occlusive polyester mesh impregnated with hydrocolloid particles and vaseline. Standard care was wound cleansing with normal saline, mechanical debridement to remove slough or necrotic tissue, secondary dressings and compression, dressings changed every other day or less frequently, local antiseptics were allowed (Lazareth 2008); charcoal dressing impregnated with silver plus standard care of sharp debridement of necrotic tissue, wound cleansing with sterile saline, dressings changed 2 to 3 times per week plus compression (Kerihuel 2010).
[17] Controls were contact layer dressing without silver plus standard care (Lazareth 2008); hydrocolloid dressing plus standard care (Kerihuel 2010).

H.2 Antibiotic prescribing strategies in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.3 Antibiotics in adults with leg ulcers

H.3.1 Efficacy of antibiotics

Table 19: GRADE profile – systemic antibiotics versus standard care for adults with leg ulcer infection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Systemic antibiotics	Standard care	Relative (95% CI)	Absolute		
Frequency of complete healing (follow-up at 3 months; assessed with ciprofloxacin versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	3/18 (16.6%)[5]	0/8 (0%)[6]	RR 3.32 (0.19 to 57.61)	-	⊕OOO VERY LOW	CRITICAL
Emergence of antibiotic-resistant strains (follow-up at 3 months; assessed with ciprofloxacin versus standard care)												

1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[7]	none	12/18 (66.7%)[5]	0/8 (0%)[6]	RR 11.84 (0.79 to 178.54)	-	⊕OOO VERY LOW	IMPORTANT
Bacterial eradication (follow-up 3 months; assessed with ciprofloxacin versus standard care)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[8]	none	6/18 (33.3%)[5]	1/8 (12.5%)[6]	RR 2.67 (0.38 to 18.67)	209 more per 1000 (from 78 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT assessed by the Cochrane reviewers was found to be at low risk of bias.
[3] Downgraded 1 level – in the RCT (Valtonen 1989) adults had infected leg ulcer with *Pseudomonas aeruginosa* or other Gram-negative rod present but it was unclear if this was at baseline only or if infection occurred at other time points.
[4] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with ciprofloxacin, and no meaningful difference or appreciable harm with standard care.
[5] Intervention in 1 RCT (Valtonen 1989) the intervention was oral ciprofloxacin 750 mg twice daily for 3 months plus standard care (NB some participants received lower dose as the study progressed (250 mg or 500 mg twice daily) to achieve desired therapeutic levels (standard care was daily ulcer cleansing with warm water and disinfectants [chlorhexidine or potassium permanganate]; mechanical or enzymatic debridement; coverage with dextranomer paste or hydrocolloid dressing).
[6] Control in 1 RCT (Valtonen 1989) was standard care.
[7] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm, with very wide 95% confidence intervals RR 11.84 (95%CI 0.79 to 178.54).
[8] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with ciprofloxacin, and no meaningful difference or appreciable harm with standard care; very wide 95% confidence intervals RR 2.67 (95%CI 0.38 to 18.67).

Table 20: GRADE profile – systemic antibiotics versus placebo for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Systemic antibiotics**	**Standard care or placebo**	**Relative (95% CI)**	**Absolute**		
Frequency of complete healing (follow-up time point unclear[1]; assessed with ciprofloxacin versus placebo)												
1[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	very serious[5]	none	5/13 (38.4%)[6]	3/11 (27.3%)[7]	RR 1.41 (0.43 to 4.61)	112 more per 1000 (from 155 fewer to 985 more)	⊕OOO VERY LOW	CRITICAL
Frequency of complete healing (follow-up time point unclear[1]; assessed with trimethoprim versus placebo)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[8]	none	3/12 (25%)[6]	3/11 (27.3%)[7]	RR 0.92 (0.23 to 3.63)	22 fewer per 1000 (from 210 fewer to 717 more)	⊕OOO VERY LOW	CRITICAL
Emergence of antibiotic-resistant strains (follow-up time point unclear[1]; assessed with ciprofloxacin versus placebo)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	serious[9]	none	8/12 (66.7%)[6]	1/10 (10%)[7]	RR 6.67 (1.0 to 44.66)	567 more per 1000 (from 0 more to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Emergence of antibiotic-resistant strains (follow-up time point unclear[8]; assessed with trimethoprim versus placebo)												

1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[10]	none	6/9 (66.7%)[6]	1/10 (10%)[7]	RR 6.67 (0.98 to 45.29)	567 more per 1000 (from 2 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] Treatment duration was 12 weeks in 1 RCT (unclear).
[2] O'Meara et al 2014.
[3] Downgraded 1 level - no RCT assessed by the Cochrane reviewers was found to be at low risk of bias.
[4] Downgraded 1 level - it was unclear if the participants in 1 RCT (Huovinen 1994) had colonised or infected leg ulcers (84% of ulcers had *Staphylococcus aureus* at baseline), the other RCT (Valtonen 1989) had adults with infected leg ulcer with *Pseudomonas aeruginosa* or other Gram-negative rod present at baseline but it was unclear if this was at baseline only or if infection occurred at other time points.
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with ciprofloxacin, and no meaningful difference or appreciable harm with placebo with local care or standard care.
[6] Intervention in 1 RCT (Huovinen 1994) was trimethoprim 160 mg twice daily plus local treatment (0.2 g zinc in 1 g petroleum-paraffin ointment and elastic bandage).
[7] Control in 1 RCT (Huovinen 1994) was placebo (tablet) plus local treatment.
[8] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with trimethoprim, and no meaningful difference or appreciable benefit with placebo.
[9] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm, very wide 95% confidence intervals RR 8.65 (95%CI 1.76 to 42.60).
[10] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with trimethoprim, very wide 95% confidence interval.

Table 21: GRADE profile – systemic antibiotics versus standard care for adults with uninfected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Systemic antibiotics**	**Standard care or placebo**	**Relative (95% CI)**	**Absolute**		
Complete healing at 3 weeks (follow-up 3 weeks; assessed with antibiotics given according to sensitivities)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	very serious[4]	none	5/30 (16.7%)[5]	7/26 (26.9%)[6]	RR 0.62 (0.22 to 1.72)	102 fewer per 1000 (from 210 fewer to 194 more)	⊕OOO VERY LOW	CRITICAL
Complete healing-eventual (follow-up time point unclear; assessed with antibiotics given according to sensitivities)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	very serious[4]	none	21/30 (70%)[5]	20/26 (76.9%)[6]	RR 0.91 (0.66 to 1.25)	69 fewer per 1000 (from 262 fewer to 192 more)	⊕OOO VERY LOW	CRITICAL
Bacterial eradication (follow-up time point unclear; assessed with antibiotics given according to sensitivities)												
1[1]	randomised trials	serious[2]	not applicable	very serious[3]	very serious[7]	none	8/24 (33.3%)[5]	5/24 (20.8%)[6]	RR 1.60 (0.61 to 4.19)	125 more per 1000 (from 81 fewer to 665 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - no RCT assessed by the Cochrane reviewers was found to be at low risk of bias.
[3] Downgraded 2 levels - adults with clinically infected ulcers were excluded from the trial (all had a positive bacterial wound culture *Staphylococcus aureus*: 25.4%; *Pseudomonas aeruginosa*: 18.2%; *β-haemolytic strep*: 14.5%).
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with systemic

antibiotics, and no meaningful difference or appreciable benefit with standard care.
[5] Bed rest with standard treatment plus a 10-day course of systemic antibiotics (co-trimoxazole, gentamicin or amikacin according to sensitivity). No dosing information or route of administration reported. Results for, or numbers given each, individual antibiotic not reported.
[6] Standard care was bed rest, merbromin 2% solution applied to ulcer surface. Betamethasone dipriorionate 0.05% cream applied to rest of leg, zinc oxide and icthamol-impregnated gauze bandage wrapped around the leg and elastic support bandage from applied from toes to knees. Bandages in place for 20 days.
[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with systemic antibiotics, and no meaningful difference or appreciable harm with standard care.

Table 22: GRADE profile – topical mupirocin dressing versus paraffin gauze for adults with uninfected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mupirocin dressing	Paraffin gauze	Relative (95% CI)	Absolute		
Frequency of complete healing (follow-up 12 weeks; assessed with mupirocin dressing versus paraffin dressing)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	8/15 (53.3%)[5]	7/15 (46.7%)[6]	RR 1.14 (0.56 to 2.35)	65 more per 1000 (from 205 fewer to 630 more)	⊕OOO VERY LOW	CRITICAL
Eradication of gram-positive bacteria (follow-up unclear; assessed with mupirocin dressing versus paraffin dressing)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	5/5 (100%)[5]	0/5 (0%)[6]	RR 11.00 (0.77 to 158.01)	-	⊕OOO VERY LOW	IMPORTANT
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk.												

[1] O'Meara et al 2014
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias
[3] Downgraded 1 level - there were no reports of symptoms or signs of clinical infection, although 5 participants in each group had a gram positive bacteria present in their wound at baseline, no further details reported.
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with mupirocin dressing, and no meaningful difference or appreciable harm with paraffin gauze dressing
[5] Intervention was mupirocin impregnated dressing plus compression
[6] Control was white soft paraffin dressing plus compression

H.3.2 Antibiotics versus povidone-iodine

Table 23: GRADE profile – amoxicillin with compression versus povidone-iodine alone or with compression for adults with infected leg ulcers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Systemic antibiotics with compression	Povidone-iodine alone or with compression	Relative (95% CI)	Absolute		

Frequency of complete healing (follow-up 12 weeks; assessed with amoxicillin plus compression versus povidone-iodine alone)											
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	18/21 (85.7%)[5]	13/21 (61.9%)[6]	RR 1.38 (0.95 to 2.02)	235 more per 1000 (from 31 fewer to 631 more)	⊕OOO VERY LOW	CRITICAL
Frequency of complete healing (follow-up 12 weeks; assessed with amoxicillin plus compression versus povidone-iodine plus compression)											
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	18/21 (85.7%)[5]	17/21 (81%)[6]	RR 1.06 (0.81 to 1.39)	49 more per 1000 (from 154 fewer to 316 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] O'Meara et al 2014.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at unclear risk of bias.
[3] Downgraded 1 level - participants ulcers were described as infected but no further details are provided, unclear if this relates to baseline status or incidence during the trial.
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with amoxicillin plus compression.
[5] Intervention was amoxicillin the dose, route and frequency of administration was not reported.
[6] Comparator dose or frequency not reported.

H.3.3 Choice of antibiotics

Table 24: GRADE profile – ciprofloxacin versus trimethoprim for adults with unclear leg ulcer infection status

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Systemic antibiotics**	**Other systemic antibiotics**	**Relative (95% CI)**	**Absolute**		
Frequency of complete healing (follow-up unclear [1]; assessed with ciprofloxacin versus trimethoprim)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[5]	none	5/13 (38.5%)[6]	3/12 (25%)[7]	RR 1.54 (0.46 to 5.09)	135 more per 1000 (from 135 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Emergence of antibiotic-resistant strains (follow-up unclear[1]; assessed with ciprofloxacin versus trimethoprim)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[5]	none	8/12 (66.7%)[6]	6/9 (66.7%)[7]	RR 1.00 (0.54 to 1.84)	0 fewer per 1000 (from 307 fewer to 560 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] Treatment duration was 12 weeks.
[2] O'Meara et al 2014.
[3] Downgraded 1 level - this RCT was assessed by the Cochrane authors as not low risk of bias.
[4] Downgraded 1 level - it was unclear if the participants in the RCT (Huovinen 1994) had colonised or infected leg ulcers (84% of ulcers had *Staphylococcus aureus* at baseline).
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with ciprofloxacin, and no meaningful difference or appreciable harm with trimethoprim.
[6] Intervention in 1 RCT (Huovinen 1994) was ciprofloxacin 750 mg twice daily plus local treatment (0.2 g zinc in 1 g petroleum-paraffin ointment and elastic bandage).
[7] Control in 1 RCT (Huovinen 1994) was trimethoprim 160 mg twice daily plus local treatment.

H.4 Antibiotic dose in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.5 Antibiotic dose frequency in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.6 Antibiotic course length in adults with leg ulcer

No systematic reviews or randomised controlled trials met the inclusion criteria.

Appendix I: **Studies not prioritised**

Gethin G (2009) Manuka honey versus hydrogel - a prospective, open label, multicentre, randomised controlled trial to compare desloughing efficacy and healing outcomes in venous ulcers.

Appendix J: **Excluded studies**

Study reference	Reason for exclusion
Anonymous (2001) Australian honey-based product is effective against resistant bacteria. *Manufacturing Chemist* 72(5), 11.	Excluded on study type. Not a systematic review or RCT.
Anonymous (2014) Topical therapy for venous ulcers. *International Angiology* 33(2), 140-143.	Excluded on study type. Not a systematic review or RCT.
Armstrong DG (2009) Manuka honey improved wound healing in patients with sloughy venous leg ulcers. *Evidence-Based Medicine* 14(5), 148.	Excluded on study type. Not a systematic review or RCT.
Bianchi T, Wolcott RD, Peghetti A et al. (2016) Recommendations for the management of biofilm: a consensus document. *Journal of wound care* 25(6), 305-17.	Excluded on outcomes. No clinical outcomes reported.
BlueCross BlueShield, and Association (2001) Graftskin for the treatment of skin ulcers. 23.	Excluded on study type. Not a systematic review or RCT.
Bogner JR, Kutaiman A, Esguerra-Alcalen M et al. (2013) Moxifloxacin in complicated skin and skin structure infections (cSSSIs): A prospective, international, non-interventional, observational study. *Advances in therapy* 30(6), 630-43.	Excluded on outcomes (no effect sizes presented).
Bouza C, Munoz A, Amate J M (2005) Efficacy of modern dressings in the treatment of leg ulcers: a systematic review. *Wound Repair and Regeneration* 13(3), 218-229.	Excluded on population (not infected leg ulcer population).
Briggs M, Nelson EA, Martyn-St J (2012) Topical agents or dressings for pain in venous leg ulcers. *The Cochrane database of systematic reviews* 11, CD001177.	Excluded on intervention (not an antimicrobial intervention).
Brolmann FE, Ubbink DT, Nelson EA et al. (2012) Evidence-based decisions for local and systemic wound care. *The British journal of surgery* 99(9), 1172-83.	Excluded on outcomes (no effect sizes presented).
Cadth (2011) Non-adherent versus traditional dressings for wound care: comparative effectiveness, safety, and guidelines.	Excluded on population (not infected leg ulcer population).
Cadth (2012) Negative pressure wound therapy for patients with diabetic foot ulcers and pressure ulcers: a review of the clinical effectiveness.	Excluded on population (not infected leg ulcer population).
Cadth (2012) Topical oxygen treatment for wound healing: a review of clinical and cost-effectiveness.	Excluded on intervention (not an antimicrobial intervention).
Cadth (2013) Optimal care of chronic, non-healing, lower extremity wounds: a review of clinical evidence and guidelines.	Excluded on intervention (not antimicrobial interventions).
Cadth (2014) Foot care for seniors in the community setting: clinical effectiveness and guidelines.	Excluded on relevance (foot care is out-of-scope).
Canadian Coordinating Office for Health Technology, and Assessment (2002) Topical ozone therapy for the treatment of diabetic leg ulcers.	Excluded on intervention (not an antimicrobial intervention).

Study reference	Reason for exclusion
Carter MJ, Tingley-Kelley K, Warriner RA (2010) Silver treatments and silver-impregnated dressings for the healing of leg wounds and ulcers: a systematic review and meta-analysis. *Journal of the American Academy of Dermatology* VOL 63 PT 4 PP 668-79	More recent (up-to-date) O'Meara et al 2014 systematic review included
Chakraborti C, Le C, Yanofsky A (2010) Sensitivity of superficial cultures in lower extremity wounds. *Journal of hospital medicine* 5(7), 415-20.	Excluded on intervention (diagnostics are out-of-scope).
Chambers H, Dumville JC, Cullum N (2007) Silver treatments for leg ulcers: a systematic review. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society* VOL 15 PT 2 PP 165-73	More recent (up-to-date) O'Meara et al 2014 systematic review included
Charles H (2002) Venous leg ulcer pain and its characteristics. *Journal of tissue viability* 12(4), 154-8.	Excluded on outcomes (no infected leg ulcer outcomes).
Chen W, Zhang Y, Li X et al. (2013) Chinese herbal medicine for diabetic peripheral neuropathy. *Cochrane Database of Systematic Reviews* (10).	Excluded on population (not infected leg ulcer population).
Chrisman CA (2010) Care of chronic wounds in palliative care and end-of-life patients. *International wound journal* 7(4), 214-35.	Excluded on study type. Not a systematic review or RCT.
Close-Tweedie J (2001) The role of povidone-iodine in podiatric chronic wound care. *Journal of wound care* 10(8), 339-42.	Excluded on study type. Not a systematic review or RCT.
Coleridge-Smith P, Lok C, Ramelet AA (2005) Venous leg ulcer: a meta-analysis of adjunctive therapy with micronized purified flavonoid fraction. *European journal of vascular and endovascular surgery: the official journal of the European Society for Vascular Surgery* 30(2), 198-208.	Excluded on intervention (not an antimicrobial intervention).
Cullum N, Buckley H, Dumville J et al. (2016) Wounds research for patient benefit: a 5-year programme of research.	More relevant population in the included O'Meara et al 2014 systematic review
Daroczy J (2006) Quality control in chronic wound management: the role of local povidone-iodine (Betadine) therapy *Dermatology* (Basel, and Switzerland) VOL 212 Suppl 1 PP 82-7	RCT included in O'Meara et al 2014 systematic review
Davies P, McCarty S, Hamberg K (2017) Silver-containing foam dressings with Safetac: a review of the scientific and clinical data. *Journal of wound care* 26(Sup6a), S1-S32.	Excluded on study type. Not a systematic review or RCT.
Dissemond J, Bottrich JG, Braunwarth H et al. (2017) Evidence for silver in wound care - meta-analysis of clinical studies from 2000-2015 *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG* VOL 15 PT 5 PP 524-535	Excluded on population (not infected leg ulcer population)
Forster R, Pagnamenta F (2015) Dressings and topical agents for arterial leg ulcers. *The Cochrane database of systematic reviews* (6), CD001836.	Excluded on intervention (not antimicrobial interventions).

Study reference	Reason for exclusion
Frank C, Bayoumi I, Westendorp C (2005) Approach to infected skin ulcers. *Canadian family physician Medecin de famille canadien* 51, 1352-9.	Excluded on outcomes (no effect sizes presented).
Fuentes SL, Briseno RG, Hernandez A (2001) An open, comparative, randomized study about oral ambulatory therapy with levofloxacine vs ciprofloxacine in complicated infections of skin and soft tissues. *Investigacion medica internacional* 28(1), 21-27.	Excluded on language (not English language).
Grey JE, Enoch S, Harding KG (2006) Venous and arterial leg ulcers. *British Medical Journal* 332(7537), 347-350.	Excluded on outcomes (no effect sizes presented).
Gurusamy KS, Koti R, Toon CD et al. (2013) Antibiotic therapy for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) in non-surgical wounds. *The Cochrane database of systematic reviews* (11), CD010427.	Excluded on population (not infected leg ulcer population).
Holland LC, Norris JM (2015) Medical grade honey in the management of chronic venous leg ulcers *International journal of surgery* (London, and England) VOL 20 PP 17-20	Includes the same studies as the included O'Meara et al 2014 systematic review
Jull A (2007) Honey and venous leg ulceration: a systematic review and randomised controlled trial. *Unpublished PHD thesis, and University of Auckland*.	RCT included in O'Meara et al 2014 systematic review
Jull AB, Cullum N, Dumville JC et al. (2015) Honey as a topical treatment for wounds *The Cochrane database of systematic reviews* PT 3 PP CD005083	More relevant population in the included O'Meara et al 2014 systematic review
Klebes M, Ulrich C, Kluschke F et al (2015) Combined antibacterial effects of tissue-tolerable plasma and a modern conventional liquid antiseptic on chronic wound treatment. *Journal of biophotonics* 8(5), 382-91.	Excluded on study type. Not a systematic review or RCT.
Krasowski G, Jawien A, Tukiendorf A et al. (2015) A comparison of an antibacterial sandwich dressing vs dressing containing silver. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society* VOL 23 PT 4 PP 525-30	Excluded on intervention (Intervention not available in the form used in the study in the UK)..
Launois R (2015) Health-related quality-of-life scales specific for chronic venous disorders of the lower limbs. Journal of vascular surgery. *Venous and lymphatic disorders* 3(2), 219-3.	Excluded on outcomes (not antimicrobial outcomes).
Leaper D, Munter C, Meaume S et al. (2013) The use of biatain Ag in hard-to-heal venous leg ulcers: meta-analysis of randomised controlled trials *PloS one* VOL 8 PT 7 PP e67083	More recent (up-to-date) O'Meara et al 2014 systematic review included
Lipsky BA, Itani KM, Weigelt JA et al. (2011) The role of diabetes mellitus in the treatment of skin and skin structure infections caused by methicillin-resistant Staphylococcus aureus: results from three randomized controlled trials. *International journal of infectious diseases: IJID: official*	Excluded on population (not infected leg ulcer population).

Study reference	Reason for exclusion
publication of the International Society for Infectious Diseases 15(2), e140-6.	
Lo SF, Chang CJ, Hu WY et al. (2009) The effectiveness of silver-releasing dressings in the management of non-healing chronic wounds: a meta-analysis *Journal of Clinical Nursing* VOL 18(5) PP 716-728	More recent (up-to-date) O'Meara et al 2014 systematic review included
Lo SF, Hayter M, Chang CJ et al. (2008) A systematic review of silver-releasing dressings in the management of infected chronic wounds *Journal of Clinical Nursing* VOL 17(15) PP 1973-1985	More recent (up-to-date) O'Meara et al 2014 systematic review included
Maessen-Visch M Birgitte, de Roos, Kees-P (2014) Dutch Venous Ulcer guideline update. *Phlebology* 29(1 suppl), 153-156.	Excluded on outcomes (no clinical outcomes reported).
Marston W, Tang J, Kirsner RS et al. (2016) Wound Healing Society 2015 update on guidelines for venous ulcers. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society* 24(1), 136-44.	Excluded on study type. Not a systematic review or RCT.
MeReC Bulletin (2010) Evidence-based prescribing of advanced wound dressings for chronic wounds in primary care *MEREC* VOL 21 PT 1 PP 1-7	Excluded on study type. Not a systematic review or RCT.
Michaels JA, Campbell WB, King BM et al. (2009) A prospective randomised controlled trial and economic modelling of antimicrobial silver dressings versus non-adherent control dressings for venous leg ulcers: The VULCAN trial	RCT included in O'Meara et al 2014 systematic review
Miller CN, Newall N, Kapp SE et al. (2010) A randomized-controlled trial comparing cadexomer iodine and nanocrystalline silver on the healing of leg ulcers. *Wound repair and regeneration: official publication of the Wound Healing Society [and] the European Tissue Repair Society* VOL 18 PT 4 PP 359-67	RCT included in O'Meara et al 2014 systematic review
Miller CN, Carville K, Newall N et al. (2011) Assessing bacterial burden in wounds: comparing clinical observation and wound swabs. *International wound journal* VOL 8 PT 1 PP 45-55	More relevant population in the included O'Meara et al 2014 systematic review
Mosti G, Magliaro A, Mattaliano V et al. (2015) Comparative study of two antimicrobial dressings in infected leg ulcers: a pilot study *Journal of wound care* VOL 24 PT 3 PP 121-7	Excluded on outcomes. Does not report infection or wound healing.
Mwipatayi BP, Angel D, Norrish J et al. (2004) The use of honey in chronic leg ulcers: a literature review *Primary Intention* VOL 12(3) PP 107-108, 110-112	More recent (up-to-date) O'Meara et al 2014 systematic review included
Nazarko L (2012) An evidence-based approach to diagnosis and management of cellulitis. *British journal of community nursing* 17(1), 6-2.	Excluded on population (not infected leg ulcer population).

Study reference	Reason for exclusion
Nelson EA (2011) Venous leg ulcers. *BMJ clinical evidence* 2011.	Excluded on population (not infected leg ulcer population).
Nherera LM, Woodmansey E, Trueman P et al (2016) Estimating the Clinical Outcomes and Cost Differences Between Standard Care With and Without Cadexomer Iodine in the Management of Chronic Venous Leg Ulcers Using a Markov Model. *Ostomy/wound management* 62(6), 26-40.	Excluded on study type. Not a systematic review or RCT.
Norman G, Westby MJ, Rithalia AD et al. (2018) Dressings and topical agents for treating venous leg ulcers. *Cochrane Database of Systematic Reviews* 2018(6), CD012583.	Excluded on population (not infected leg ulcer population).
O'Meara S, Cullum N, Majid M et al (2000) Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration., 1-237	Excluded on study type. Not a systematic review or RCT.
O'Meara SM, Cullum NA, Majid M et al. (2001) Systematic review of antimicrobial agents used for chronic wounds *The British journal of surgery* VOL 88 PT 1 PP 4-21	More recent (up-to-date) O'Meara et al 2014 systematic review included
O'Meara S, Richardson R, Lipsky BA (2014) Topical and systemic antimicrobial therapy for venous leg ulcers JAMA - *Journal of the American Medical Association* VOL 311 PT 24 PP 2534-2535	Summarises the included Cochrane systematic review (O'Meara et al. 2014)
Oryan A, Alemzadeh E, Moshiri A (2016) Biological properties and therapeutic activities of honey in wound healing: A narrative review and meta-analysis *Journal of Tissue Viability* VOL 25 PT 2 PP 98-118	More relevant population in the included O'Meara et al 2014 systematic review
Palfreyman S, Nelson EA, Michaels JA (2007) Dressings for venous leg ulcers: systematic review and meta-analysis. *BMJ* 335, 244.	Excluded on intervention (not infected leg ulcer population).
Pavlova L, Nikolovska S, Matevska-Cifrevska V (2000) Evaluation of healing rate and predicting of healing of venous leg ulcers. *Acta Dermatovenerologica Croatica* 8(2), 73-76.	Excluded on outcomes (not antimicrobial outcomes).
Poku E, Aber A, Phillips P et al (2017) Systematic review assessing the measurement properties of patient-reported outcomes for venous leg ulcers. *BJS open* 1(5), 138-147.	Excluded on relevance (not antimicrobial interventions).
Puzniak LA, Quintana A, Wible M et al (2014) Methicillin-resistant Staphylococcus aureus infection epidemiology and clinical response from tigecycline soft tissue infection trials. *Diagnostic microbiology and infectious disease* 79(2), 261-5.	Excluded on relevance (not antimicrobial interventions).
Sasseville D (2010) Neomycin. *Dermatitis* 21(1), 3-7.	Excluded on study type. Not a systematic review or RCT.
Scheinfeld NS (2007) Skin disorders in elderly persons: Part 3, bacterial diseases. *Consultant* 47(2), 177-186.	Excluded on study type. Not a systematic review or RCT.

Study reference	Reason for exclusion
Serra R, Butrico L, Ruggiero M et al (2015) Epidemiology, diagnosis and treatment of chronic leg ulcers: A systematic review. *Acta Phlebologica* 16(1), 9-18.	Excluded on outcomes (not antimicrobial outcomes).
Sharpe JN (2004) Antibiotics as an adjunct to surgical management of lower extremity ulcerations. *Microsurgery* 24(1), 8-17.	Excluded on study type. Not a systematic review or RCT.
Singer AJ, Tassiopoulos A, Kirsner RS (2017) Evaluation and management of lower-extremity ulcers. *New England Journal of Medicine* 377(16), 1559-1567.	Excluded on study type. Not a systematic review or RCT.
Sumpio BE (2000) Foot ulcers. *The New England journal of medicine* 343(11), 787-93.	Excluded on study type. Not a systematic review or RCT.
Tricco AC, Cogo E, Isaranuwatchai W et al. (2015) A systematic review of cost-effectiveness analyses of complex wound interventions reveals optimal treatments for specific wound types. *BMC Medicine* 13(1), 90.	Excluded on population (not infected leg ulcer population).
Ubbink DT, Santema TB, Stoekenbroek RM (2014) Systemic wound care: a meta-review of cochrane systematic reviews *Surgical technology international* VOL 24 PP 99-111	More recent (up-to-date) O'Meara et al 2014 systematic review included
Ulrich C, Kluschke F, Patzelt A et al. (2015) Clinical use of cold atmospheric pressure argon plasma in chronic leg ulcers: A pilot study. *Journal of wound care* 24(5), 196-3.	Excluded on population (not infected leg ulcer population).
Vandamme L, Heyneman A, Hoeksema H et al. (2013) Honey in modern wound care: A systematic review *Burns* VOL 39 PT 8 PP 1514-1525	More relevant population in the included O'Meara et al 2014 systematic review
Vermeulen H, Van Hattem JM, Storm-Versloot MN et al. (2009) Topical silver for treating infected wounds *Cochrane Database of Systematic Reviews* PT 4 PP CD005486	More recent (up-to-date) O'Meara et al 2014 systematic review included
Wilkinson E, Hawke C (1999) Zinc and chronic leg ulcers: a systematic review of oral zinc in the treatment of chronic leg ulcers. *Journal of Tissue Viability* 9(1), 21.	Excluded on study type. Not a systematic review or RCT.
Witkowski JA, Parish LC (2000) Wound healing and leg ulcers: Unapproved treatments or indications. *Clinics in Dermatology* 18(2), 211-217.	Excluded on study type. Not a systematic review or RCT.
Yaghoobi R, Kazerouni A, Kazerouni O (2013) Evidence for Clinical Use of Honey in Wound Healing as an Anti-bacterial, Anti-inflammatory Anti-oxidant and Anti-viral Agent: A Review. *Jundishapur journal of natural pharmaceutical products* 8(3), 100-4.	Excluded on outcomes (no clinical outcomes reported).
Zenilman J, Valle MF, Malas MB et al. (2013) Chronic venous ulcers: a comparative effectiveness review of treatment modalities.	Excluded on study type. Not a systematic review or RCT.

Appendix K: **Research recommendations**

1. What is the clinical effectiveness of topical treatments (antibiotics and antiseptics) compared with oral antibiotics for the treatment of infected leg ulcer?

The current recommendations for people with symptoms or signs of an infected leg ulcer are to offer oral antibiotics (if able to take oral medicines and not severely unwell). The committee based this recommendation on its experience that untreated infection causes delay in ulcer healing which affects quality of life and can result in hospital admission. There was no evidence identified that compared topical treatments (antibiotics or antiseptics) with oral antibiotics in a relevant population, as most of the evidence was in a population either without an infection or with unclear infection status.

Further research is needed to evaluate if antibiotic sparing interventions such as antiseptics are effective compared with antibiotics, and to assess whether topical application of antibiotics or antiseptics is more effective than oral administration. If topical antiseptics are effective, they would be antibiotic sparing, and therefore could help reduce levels of antimicrobial resistance and adverse events associated with antibiotic use.

There were only 2 RCTs in O'Meara et al. (2014) of antiseptics in people with infected leg ulcer. The committee noted that the 2 RCTs were of low quality, had small sample sizes and the definition of 'infection' in each study had limitations (one being reliant on laboratory growth and the other stating that inflammation was the only symptom required). There was no evidence comparing topical versus oral antibiotics in the evidence review. The committee concluded that further RCTs with the power to detect a statistically significant difference in a well-defined infected leg ulcer population were needed.

PICO	**Population:** People with infected leg ulcer **Interventions:** Standard care for ulcer management plus topical antiseptics or antibiotics (excluding any oral antibiotic use) **Comparator:** Standard care for ulcer management plus oral antibiotic **Outcomes:** Infection cure rate Time to clinical cure Time to ulcer healing Reduction in symptoms of infection Adverse events
Current evidence base	1 RCT (n=42)
Study design	Randomised controlled trial
Other comments	Studies should be adequately powered