

1 **Leg ulcer infection: antimicrobial prescribing**

2 **NICE guideline**

3 **Draft for consultation, June 2019**

This guideline sets out an antimicrobial prescribing strategy for leg ulcer infection in adults. It aims to optimise antibiotic use and reduce antibiotic resistance.

The recommendations in this guideline are for the use of antibiotics to manage leg ulcer infection in adults. It does not cover diagnosis or the general management of leg ulcers. See the SIGN guideline on [chronic venous leg ulcers](#) for more information.

For managing other skin infections, see our web page on [skin conditions](#).

See a 2-page visual summary of the recommendations, including tables to support prescribing decisions.

Who is it for?

- Healthcare professionals; commissioners and providers
- Adults with leg ulcer infection, their families and carers

The guideline contains:

- the draft recommendations
- the rationales
- summary of the evidence.

Information about how the guideline was developed is on the [guideline's page](#) on the NICE website. This includes the full evidence review, details of the committee and any declarations of interest.

1 Recommendations

2 **1.1** *Managing leg ulcer infection in adults*

3 **Treatment**

4 1.1.1 Be aware that:

- 5 • there are many causes of leg ulcers
- 6 • most leg ulcers are not clinically infected but are likely to be colonised
7 with bacteria
- 8 • antibiotics do not help to promote healing when a leg ulcer is not
9 clinically infected.

10 1.1.2 Offer an antibiotic for adults with a leg ulcer only when there are
11 symptoms or signs of infection¹. When choosing an antibiotic (see the
12 recommendations on choice of antibiotic) take account of:

- 13 • the severity of symptoms
- 14 • the risk of developing complications
- 15 • previous antibiotic use.

16 1.1.3 Give oral antibiotics first-line if the person can take oral medicines, and
17 the severity of their condition does not require intravenous antibiotics.

18 1.1.4 If intravenous antibiotics are given, review by 48 hours and consider
19 switching to oral antibiotics if possible.

To find out why the committee made the recommendations on treatment for adults with an infected leg ulcer, see the [rationales](#).

¹ Clinical symptoms and signs of infection include cellulitis, pyrexia, increased pain, rapid extension of area of ulceration, malodour and increased exudate ([SIGN guideline on management of chronic venous leg ulcers](#) [2010])

1 **Advice**

- 2 1.1.5 When prescribing antibiotics for an infected leg ulcer, give advice about
3 seeking medical help if symptoms of the infection (enlarging ulcer, pain,
4 heat, swelling or redness) worsen rapidly or significantly at any time, or do
5 not start to improve within 2 to 3 days.

To find out why the committee made the recommendation on advice for adults having antibiotics for an infected leg ulcer, see the [rationales](#).

6 **Reassessment**

- 7 1.1.6 Reassess adults with an infected leg ulcer if symptoms or signs of the
8 infection worsen rapidly or significantly at any time, do not start to improve
9 within 2 to 3 days, or the person:
- 10 • becomes systemically very unwell, **or**
 - 11 • has severe pain out of proportion to the infection.
- 12 1.1.7 When reassessing adults with an infected leg ulcer, take account of:
- 13 • any symptoms or signs suggesting a more serious illness or condition,
14 such as sepsis, necrotising fasciitis, osteomyelitis or lymphangitis
 - 15 • other co-morbidities, such as diabetes or immunosuppression
 - 16 • previous antibiotic use, which may have led to resistant bacteria.
- 17 1.1.8 Consider sending a sample (from deep within the leg ulcer after cleaning)
18 for microbiological testing if symptoms or signs of the infection are
19 worsening or have not improved following a completed course of
20 antibiotics.
- 21 1.1.9 When microbiological results are available:
- 22 • review the choice of antibiotic(s), **and**
 - 23 • change the antibiotic(s) according to results if symptoms or signs of the
24 infection are not improving, using a narrow spectrum antibiotic if
25 possible.

To find out why the committee made the recommendations on reassessment for adults with an infected leg ulcer, see the [rationales](#).

1 Referral or seeking specialist advice

2 1.1.10 Refer adults with an infected leg ulcer to hospital if they have any
3 symptoms or signs suggesting a more serious illness or condition, such as
4 sepsis, necrotising fasciitis or osteomyelitis.

5 1.1.11 Consider referring or seeking specialist advice for adults with an infected
6 leg ulcer if they:

- 7 • have a higher risk of complications, **or**
- 8 • have lymphangitis, **or**
- 9 • have spreading infection that is not responding to oral antibiotics, **or**
- 10 • cannot take oral antibiotics (exploring locally available options for giving
11 intravenous antibiotics at home or in the community, rather than in
12 hospital, where appropriate).

To find out why the committee made the recommendations on referral and specialist advice for adults with an infected leg ulcer, see the [rationales](#).

13

14 1.2 Choice of antibiotic

15 1.2.1 When prescribing antibiotics for an infected leg ulcer in adults aged
16 18 years and over, follow the recommendations in table 1.

17 **Table 1. Antibiotics for adults aged 18 years and over**

Antibiotic ¹	Dosage and course length ²
First choice oral antibiotic	
Flucloxacillin	500 mg four times a day for 7 days
Alternative first choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable	
Clarithromycin	500 mg twice a day for 7 days
Erythromycin (in pregnancy)	500 mg four times a day for 7 days
Doxycycline	200 mg on first day, then 100 mg once a day for 6 days (7-day course in total)

Second choice oral antibiotics if symptoms or signs of infection worsening after 48 hours or no improvement after 7 days (guided by microbiological results when available)	
Co-amoxiclav	500/125 mg three times a day for 7 days
Co-trimoxazole (in penicillin allergy)	960 mg twice a day for 7 days
First choice intravenous antibiotics (if unable to take oral antibiotics or severely unwell; guided by microbiological results when available)^{3,4}	
Flucloxacillin <i>with or without</i>	500 mg to 2 g four times a day
Gentamicin <i>and/or</i>	Initially 5 to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration ⁵
Metronidazole	500 mg three times a day
Co-amoxiclav <i>with or without</i>	1.2 g three times a day
Gentamicin	Initially 5 to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration ⁵
Co-trimoxazole (in penicillin allergy) <i>with or without</i>	960 mg twice a day (increased to 1.44 g twice a day if severe infection)
Gentamicin <i>and/or</i>	Initially 5 to 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration ⁵
Metronidazole	500 mg three times a day
Second choice intravenous antibiotics (guided by microbiological results when available or following specialist advice)^{3,4}	
Piperacillin with tazobactam	4.5 g three times a day (increased to 4.5 g four times a day if severe infection)
Ceftriaxone <i>with or without</i>	2 g once a day
Metronidazole	500 mg three times a day
Intravenous antibiotics to be added if MRSA infection (combination therapy with intravenous antibiotics listed above)⁴	
Vancomycin	15 to 20 mg/kg two or three times a day (maximum 2 g per dose), adjusted according to serum-vancomycin concentration ⁶
Linezolid (if vancomycin cannot be used; specialist advice only)	600 mg twice a day
<p>¹ See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.</p> <p>² Oral doses are for immediate-release medicines.</p> <p>³ Give oral antibiotics first line if the person can take oral medicines, and the severity of their symptoms does not require intravenous antibiotics.</p> <p>⁴ Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics if possible.</p> <p>⁵ Therapeutic drug monitoring and assessment of renal function is required (BNF May 2019).</p> <p>⁶ Therapeutic drug monitoring and assessment of renal function is required. A loading dose can be used (see BNF, May 2019 for full dosage information).</p>	

Abbreviations: MRSA, Meticillin-resistant *Staphylococcus aureus*

1

To find out why the committee made the recommendations see the rationales on [choice of antibiotic](#).

2 **Terms used in the guideline**

3 **Leg ulcer**

4 A leg ulcer is a long-lasting (chronic) sore that takes more than 4 to 6 weeks to heal.

5 Leg ulcers usually develop on the inside of the leg, just above the ankle.

6 **Leg ulcer infection**

7 Clinical symptoms and signs of leg ulcer infection include cellulitis, fever, increased

8 pain, rapid extension of the area of ulceration, malodour and increased exudate

9 ([SIGN guideline on management of chronic venous leg ulcers](#)).

10 **Rationales**

11 The recommendations in this guideline are for adults and are based on the evidence

12 identified and the experience of the committee. No evidence was found for children

13 with leg ulcers. This group are likely to have underlying conditions that need highly

14 specialist and different treatment. For this reason, the committee agreed that it was

15 not appropriate to extrapolate evidence for adults to children and so made

16 recommendations for adults only.

17 ***Treatment***

18 **Why the committee made the recommendations**

19 [Recommendations 1.1.1 to 1.1.4](#)

20 The committee agreed that health professionals should be aware that there are

21 many causes of leg ulcers, and that although most leg ulcers are colonised by

22 bacteria, few are infected. Skin or general wound swabs are therefore likely to be of

23 limited use when there are no other symptoms or signs of infection, as bacterial

24 growth is likely regardless of infection status.

1 The committee discussed whether a recommendation could be made not to offer
2 antibiotics to people who had a leg ulcer that was not infected. The committee felt
3 that although there was no difference between antibiotics and standard care in
4 people with uninfected leg ulcers, the evidence was not sufficient to make such a
5 strong recommendation (a small, very low quality study with no dosage or route of
6 administration details reported).

7 Evidence showed no difference in complete healing of the leg ulcer with antibiotics
8 compared with standard care or placebo. However, in all but one study, the ulcer
9 was either uninfected or the infection status was unclear. No study stated that
10 children and young people (under 18 years) were included. The committee agreed
11 that this age group are very unlikely to develop a leg ulcer and if they do the cause is
12 likely to be from a condition that needs specialist management. Therefore, it was not
13 appropriate to extrapolate evidence for adults to children and young people and so
14 the committee made recommendations for adults only.

15 The committee agreed that antibiotic treatment should be offered to all adults with a
16 leg ulcer if there are symptoms or signs of an infection, because from its experience
17 untreated infection causes delays in ulcer healing, affecting quality of life and
18 resulting in possible hospital admission.

19 Based on its experience, the committee agreed that antibiotic choice will depend on
20 the severity of symptoms or signs of infection (for example, how rapidly the infection
21 is progressing or expanding), the person's risk of complications, and any previous
22 antibiotic use (which may have led to the development of antimicrobial resistance).

23 In line with the NICE guideline on [antimicrobial stewardship](#) and [Start smart – then
24 focus](#), oral antibiotics should be given first line if the person can take them, and if the
25 severity of their infection does not require intravenous antibiotics. The use of
26 intravenous antibiotics should be reviewed by 48 hours (taking into account the
27 person's response to treatment and any microbiological results) and switched to oral
28 treatment where possible.

1 ***Antiseptics***

2 Evidence comparing antibiotics with povidone-iodine (an antiseptic) for leg ulcer
3 infection was limited by small sample size. The majority of evidence was in adults
4 with unclear infection status or uninfected leg ulcer.

5 There was some evidence of effect for cadexomer-iodine and silver dressings in
6 people with infected leg ulcer (compared with standard care and non-adherent foam
7 dressing respectively), but there were severe limitations, including: an unclear
8 definition of 'infection' (one being reliant on laboratory growth and the other stating
9 that inflammation was the only symptom required). For the comparison of silver
10 dressings compared to foam dressings, the only sign of infection required was
11 inflammation, there were very wide confidence intervals and both study arms had the
12 option to use antibiotics (and the number of people taking systemic antibiotics was
13 not reported). The committee discussed that silver dressings can be expensive and
14 could have considerable resource impact. Therefore, due to the inadequate definition
15 of infection, the confounding issue of use of antibiotics in the trial, the uncertainty of
16 the effect estimate and the potential cost of making the recommendation, the
17 committee chose not to recommend silver dressings based on the evidence.

18 The committee also raised concerns about the rate of adverse effects with
19 cadexomer-iodine. These were mainly local skin irritation, rash and pain, all of which
20 may make leg ulcers worse. No adverse effects were reported for silver dressings
21 but this may have been due to the small sample size.

22 Additionally, the committee was aware of issues with the availability of iodine-based
23 preparations, particularly in community settings. The committee agreed that it could
24 not make any recommendations on the use of any antiseptics for treating infected
25 leg ulcers due to the limitations of the evidence.

26 For more details, see the summary of the evidence on [antibiotics](#) and [topical](#)
27 [antiseptics](#).

28 [Return to the recommendations](#).

1 **Advice**

2 **Why the committee made the recommendations**

3 [Recommendation 1.1.5](#)

4 In line with the NICE guideline on [antimicrobial stewardship](#) the committee agreed
5 that adults with leg ulcer infection should be advised about the possible adverse
6 effects of the antibiotic and when to seek medical help. In its experience, some
7 improvement in infection symptoms or signs would be expected within 2 to 3 days. If
8 symptoms of the infection worsen rapidly or significantly, this may indicate that the
9 person has a more serious illness or condition.

10 [Return to the recommendations.](#)

11 **Reassessment**

12 **Why the committee made the recommendations**

13 [Recommendations 1.1.6 to 1.1.9](#)

14 Based on its experience, the committee agreed when adults with an infected leg
15 ulcer should be reassessed. This should take account of reassessment of symptoms
16 or signs that may indicate the person has a more serious illness or condition, any
17 co-morbidities that may affect their treatment, and any previous antibiotic use as this
18 may have led to resistant bacteria. If symptoms of the infection worsen rapidly or
19 significantly, or the person does not improve as expected, this may indicate that the
20 person has a more serious illness or a resistant infection.

21 The committee agreed that an appropriate microbiological sample should be
22 considered for adults with an infected leg ulcer if symptoms or signs of the infection
23 are worsening or have not improved following a completed course of antibiotics, in
24 order to guide future antibiotic choice if the person has a resistant infection. The
25 committee agreed that this can be taken after cleaning the wound (removing surface
26 contaminants, slough or necrotic tissue), swabbing viable tissue with visible infection
27 and using a swab with a charcoal transport medium. Alternatively, the committee
28 agreed that the Levine technique (pressing the swab into the ulcer bed displacing

1 deeper organisms) could be used. This is because inappropriate skin or wound
2 surface swabbing may identify an organism which is not the infective organism.

3 The committee agreed that when microbiological results are available, the choice of
4 antibiotic should be reviewed and changed according to results if symptoms or signs
5 of the infection are not improving, using a narrow spectrum antibiotic to minimise the
6 risk of antimicrobial resistance if appropriate.

7 [Return to the recommendations.](#)

8 ***Referral or seeking specialist advice***

9 **Why the committee made the recommendations**

10 [Recommendations 1.1.10 and 1.1.11](#)

11 Based on its experience, the committee agreed that adults with symptoms or signs
12 suggesting a more serious illness or condition should be referred to hospital, to
13 ensure that they receive appropriate treatment. Some people may have an infected
14 leg ulcer that is more difficult to treat, for example due to their higher risk of
15 complications or other underlying conditions or because they may have a resistant
16 infection, and referral or specialist advice should be considered (which may include
17 giving intravenous antibiotics).

18 [Return to the recommendations.](#)

19 ***Choice of antibiotic***

20 [Recommendation 1.2.1](#)

21 **Why the committee made the recommendations**

22 The committee noted the very limited evidence on the choice of antibiotics in adults
23 with an infected leg ulcer.

24 Based on its experience, current practice and resistance data, the committee agreed
25 that the **first-choice oral antibiotic** in adults with an infected leg ulcer should be
26 **flucloxacillin** (a penicillin). This is a relatively narrow spectrum penicillin which has
27 good penetration for skin and soft tissue infections and is effective against

1 gram-positive organisms, including the most common causative organism
2 *Staphylococcus aureus*.

3 The **alternative first-choice antibiotics** in adults with penicillin allergy or in whom
4 flucloxacillin is unsuitable should be **clarithromycin**, or **erythromycin** (in
5 pregnancy; macrolides) or **doxycycline** (a tetracycline) because they all have a
6 similar spectrum of activity to flucloxacillin.

7 If symptoms or signs of infection were worsening after 48 hours, or not improving
8 after 7 days, this would be a reason to change the antibiotic.

9 The committee agreed that the **second-choice oral antibiotics** (guided by
10 microbiological results if an appropriate sample has been taken) would be the
11 broader spectrum antibiotics **co-amoxiclav** (a penicillin with a beta-lactamase
12 inhibitor), or **co-trimoxazole** (in penicillin allergy) which are more active against
13 gram-negative organisms. The committee discussed that the presence of
14 gram-negative organisms may be a reason why an infected leg ulcer is not healing;
15 these antibiotics are active against gram-negative organisms and therefore are
16 appropriate second choice antibiotics..

17 Oral antibiotics should be given first-line if possible. But based on its experience and
18 resistance data, the committee agreed that several **intravenous antibiotics** (or
19 combinations of antibiotics) are recommended for adults with an infected leg ulcer
20 who are severely unwell or who are unable to take oral antibiotics. This enables
21 antibiotics to be selected based on a person's individual preferences, likely
22 pathogens, and antibiotic susceptibilities from microbiological results (if relevant).

23 In people who are severely unwell, broader antimicrobial cover is needed because
24 both anaerobes and gram-negative bacteria may be present. However, in line with
25 antimicrobial stewardship principles, narrower spectrum antibiotics should be used
26 where possible.

27 For adults with an infected leg ulcer who require intravenous antibiotics the
28 committee agreed that **flucloxacillin** was the most appropriate first choice, with or
29 without the addition of **gentamicin** (a broad-spectrum aminoglycoside) and/or
30 **metronidazole**.

1 The committee agreed that additional choices would be:

- 2 • **co-amoxiclav** with or without **gentamicin**
- 3 • **co-trimoxazole** with or without **gentamicin** and/or **metronidazole** (if penicillin
- 4 allergy).

5 The committee discussed that **metronidazole** (which is used to cover anaerobic
6 bacteria) may be useful in people with leg ulcers related to arterial disease or
7 diabetes, who may have a reduced blood supply that can encourage anaerobic
8 bacterial growth.

9 **Second choice intravenous antibiotics** (guided by microbiological results if an
10 appropriate sample has been taken, or following specialist advice) are:

- 11 • **piperacillin with tazobactam** (a penicillin with a beta-lactamase inhibitor), or
- 12 • **ceftriaxone** (a third-generation cephalosporin) with **metronidazole**.

13 The committee discussed that intravenous **ceftriaxone** may be administered to a
14 person as an outpatient without the need for hospital admission.

15 Meticillin-resistant *Staphylococcus aureus* (MRSA) may be found on swabbing, but
16 the current likelihood of MRSA infection is very low. The committee agreed that for
17 these people one of the following intravenous antibiotics with activity against MRSA
18 should be added to the treatment regimen:

- 19 • **vancomycin** (a glycopeptide) or
- 20 • **linezolid** (an oxazolidinone; if **vancomycin** cannot be used, following specialist
- 21 advice only).

22 ***Course length and dosage and route of administration***

23 There was very little evidence on antibiotic dosage, course length and route of
24 administration. Therefore, recommendations were based on the committee's
25 experience of current practice and the [British National Formulary](#) (BNF).

26 The committee agreed that usual BNF doses for skin and soft tissue infections
27 should be used. However, it was aware that there is a dose range for flucloxacillin

1 (250 to 500 mg four times a day), and it agreed that the lower dose was not
2 appropriate for treating an infected leg ulcer in adults.

3 The committee agreed that the shortest course that is likely to be effective should be
4 prescribed to minimise adverse effects from broader spectrum antibiotics and reduce
5 the risk of antimicrobial resistance, and that this should be balanced against the
6 need for a course length that provides effective treatment for the infection. In the
7 absence of evidence for optimum course length, based on its experience and
8 extrapolation of evidence for people with cellulitis and diabetic foot infection, the
9 committee agreed a total course of 7 days of antibiotics.

10 In line with the NICE guideline on [antimicrobial stewardship](#) and [Start smart – then](#)
11 [focus](#), oral antibiotics should be given first line if the person can take them, and the
12 severity of their condition does not require intravenous antibiotics. The use of
13 intravenous antibiotics should be reviewed by 48 hours (taking into account the
14 person’s response to treatment and any microbiological results) and switched to oral
15 treatment where possible.

16 For more detail see the summary of the evidence on choice of antibiotic.

17 [Return to the recommendations.](#)

18 **Context**

19 A leg ulcer is a long-lasting (chronic) sore that takes more than 4 to 6 weeks to heal.
20 Leg ulcers usually develop on the inside of the leg, just above the ankle.

21 Studies suggest that 80% to 100% of leg ulcers may have bacteria (usually
22 *Staphylococcus aureus* or *Pseudomonas aeruginosa*) present in the wound, but this
23 does not necessarily mean the wound is infected.

24 **Summary of the evidence**

25 This is a summary of the evidence, for full details see the [evidence review](#).

26 The review protocol included a population of adults, young people and children with
27 infected leg ulcers. There was minimal evidence for this population (2 small studies),

1 therefore the population was expanded to people with leg ulcers that had an unclear
2 infection status or were not infected. For antiseptic and antibiotics, the results have
3 been presented separately for people with:

- 4 • an infected leg ulcer
- 5 • a leg ulcer with unclear infection status
- 6 • an uninfected leg ulcer.

7 All the evidence is based on 1 systematic review of antibiotics and antiseptics for
8 venous leg ulcers ([O'Meara et al. 2014](#)), which included 45 randomised controlled
9 trials (RCTs). Nine of these were not included in the review because 8 contained
10 ineligible interventions and 1 study was withdrawn. Seven RCTs included people
11 exclusively with leg ulcer infection (however 5 of these RCTs had an uncertain
12 definition of infection); 14 RCTs included people with unclear leg ulcer infection
13 status and 15 studies included people with leg ulcers that were not infected.

14 No studies included in the review stated that they included children. The committee
15 discussed that leg ulcer infection in children and young people is extremely rare, and
16 usually a result of an underlying illness that requires specialist management.
17 Therefore, the committee considered that the evidence presented here applied only
18 to an adult population and the evidence was not extrapolated to a population of
19 children and young people.

20 Standard care is the care given in addition to the intervention and/or the control. The
21 included studies were limited as the definition of standard care for each study varied
22 widely, full details of what composed standard care is noted in the GRADE tables
23 (appendix H of the evidence review).

24 ***Topical antiseptics***

25 **Iodine-based preparations**

26 ***Infected leg ulcer***

27 In a single RCT, cadexomer-iodine was significantly better than standard care at
28 reducing the average size of the ulcers, the amount of pain experienced from the

1 ulcers and reducing or eliminating the presence of *Staphylococcus aureus* at 6
2 weeks.

3 There was no significant difference for:

- 4 • cadexomer-iodine compared with silver dressing for the frequency of complete
5 healing at 12 weeks and for participant satisfaction. Neither group reported any
6 adverse effects
- 7 • povidone-iodine plus compression compared to moist or foam dressings plus
8 compression for complete healing at 4 months.

9 ***Unclear leg ulcer infection status***

10 Cadexomer-iodine (topical application) was significantly better compared with
11 standard care (varied by RCT) for the frequency of complete healing at 4 to 12
12 weeks, mean percentage change ulcer area and mean rate of ulcer healing.
13 However, adverse events were significantly more common in the cadexomer-iodine
14 group.

15 ***Uninfected leg ulcer***

16 Cadexomer-iodine was not significantly different compared with hydrocolloid
17 dressing or paraffin gauze for the frequency of complete healing at 12 weeks, neither
18 group reported any adverse effects.

19 Povidone-iodine plus compression was not significantly different to hydrocolloid plus
20 compression for the frequency of complete healing at 4 months.

21 Povidone-iodine 10% solution plus compression was significantly better for time to
22 healing compared with hydrocolloid plus compression.

23 **Peroxide-based preparations**

24 ***Unclear leg ulcer infection status***

25 Benzoyl peroxide (10% and 20%) was significantly better than a saline dressing for
26 reducing average ulcer size at 42 days. Data on adverse effects were limited and
27 poorly reported.

1 ***Uninfected leg ulcer***

2 Hydrogen peroxide 1% cream was significantly better for median decrease in ulcer
3 area compared with [placebo](#) cream at 10 days follow-up. Data on adverse effects
4 were limited and poorly reported.

5 **Honey-based preparations**

6 ***Unclear leg ulcer infection status***

7 Honey (calcium alginate dressing impregnated with Manuka honey) was not
8 significantly different compared with standard care for:

- 9 • complete healing at 12 weeks
10 • incidence of ulcer infection during treatment for 12 weeks.

11

12 There were significantly more adverse effects in the honey group than the standard
13 care group.

14 ***Uninfected leg ulcer***

15 Honey (topical Manuka honey) was not significantly different to hydrogel (3 g/20 cm²
16 applied weekly) for the eradication of meticillin-resistant *Staphylococcus aureus*
17 (MRSA) at 4 weeks.

18 **Silver-based preparations**

19 ***Infected leg ulcer***

20 Silver dressing plus compression was significantly better compared with
21 non-adhesive plus compression dressing for:

- 22 • complete healing at 9 weeks
23 • proportion of adults who were pain free at the of the trial.

24 Silver dressings were not significantly different to non-adhesive dressings for
25 adverse effects.

1 ***Unclear leg ulcer infection status***

2 There was no significant difference between the following comparisons for complete
3 healing (4–12 weeks):

- 4 • silver sulfadiazine (1% cream) plus compression compared to non-adherent
5 dressing plus compression
- 6 • silver impregnated dressings (with or without compression) compared to non-
7 antimicrobial dressings (with or without compression)
- 8 • silver-impregnated polyurethane foam dressing plus compression compared with
9 5-layer silver impregnated dressing plus compression.

10 Silver dressings were not significantly different to non-antimicrobial dressings for
11 adverse effects.

12 ***Uninfected leg ulcer***

13 There was no significant difference for:

- 14 • silver sulfadiazine (1% cream) with non-adhesive foam dressing and compression
15 compared to placebo cream with non-adherent dressing and compression for
16 complete healing at 4 weeks
- 17 • silver sulfadiazine (1% cream) compared to standard care for median [range] time
18 to healing
- 19 • silver dressing plus compression compared with low adherent dressing for
20 complete healing at 4 to 12 weeks; 6 months or 12 months, or for the outcome of
21 ulcer recurrence within 12 months
- 22 • silver dressings compared with non-antimicrobial dressings for adverse effects.

23 Silver dressing plus compression was significantly better than non-antimicrobial
24 dressings plus compression for reducing ulcer surface area when measured using
25 cm² at 4 weeks but was not significantly different when measured as a percentage
26 change. The healing rate (cm² per day) in these 2 RCTs was not significantly
27 different.

1 ***Antibiotics***

2 **Antibiotics compared with standard care or placebo**

3 ***Infected leg ulcer***

4 Ciprofloxacin was not significantly different to standard care for the frequency of
5 complete healing, emergence of antibiotic resistant strains or bacterial eradication at
6 3 months

7 ***Unclear leg ulcer infection status***

8 For the frequency of complete healing (unclear follow-up time), there was no
9 significant difference between:

- 10 • ciprofloxacin and placebo, or
- 11 • trimethoprim and placebo.

12 Emergence of resistance was significantly higher with ciprofloxacin compared with
13 placebo, but there was no significant difference in the emergence of resistance with
14 trimethoprim compared with placebo.

15 ***Uninfected leg ulcer***

16 There was no significant difference between:

- 17 • systemic antibiotics (co-trimoxazole, gentamicin or amikacin according to
18 sensitivities) compared with standard care for the outcomes of complete healing at
19 3 weeks, complete eventual healing or bacterial eradication
- 20 • topical mupirocin compared to standard care for frequency of complete healing at
21 12 weeks or for the outcome of eradication of gram-positive bacteria.

22 Data on adverse effects were limited and poorly reported.

23 **Antibiotics compared with antiseptics**

24 ***Infected leg ulcer***

25 Amoxicillin with compression was not significantly different to povidone-iodine alone
26 or with compression for complete healing at 12 weeks in people with an infected leg
27 ulcer.

1 No data on adverse effects were reported.

2 ***Choice of antibiotic***

3 ***Unclear leg ulcer infection status***

4 Ciprofloxacin was not significantly different to trimethoprim for the frequency of
5 complete healing.

6 Limited data on adverse effects were reported. However, it was reported that
7 ciprofloxacin and trimethoprim increased the emergence of antimicrobial resistance
8 compared with standard care or placebo. This finding was statistically significant for
9 ciprofloxacin, but did not reach significance for trimethoprim.

10 ***Antibiotic course length, dosage and route of administration***

11 No evidence from systematic reviews or RCTs was identified.

12 **Other considerations**

13 ***Medicines safety***

14 Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking
15 antibiotics, depending on the antibiotic used ([NICE Clinical Knowledge Summary](#)
16 [\[CKS\]: diarrhoea – antibiotic associated](#)).

17 About 10% of the general population claim to have a penicillin allergy; this is often
18 because of a skin rash that occurred while taking a course of penicillin as a child.
19 Fewer than 10% of people who think they are allergic to penicillin are truly allergic.
20 See the NICE guideline on [drug allergy: diagnosis and management](#) for more
21 information.

22 Cholestatic jaundice and hepatitis can occur with flucloxacillin up to 2 months after
23 stopping treatment, with risk factors being increasing age and use for more than
24 14 days ([BNF, May 2019](#)). Cholestatic jaundice can also occur with co-amoxiclav,
25 and is more common in people over 65 years and in men; treatment should not
26 usually exceed 14 days ([BNF, May 2019](#)).

- 1 People with a history of immediate hypersensitivity to penicillin's may also react to
2 cephalosporins and other beta lactam antibiotics ([BNF, May 2019](#)).
- 3 Macrolides (for example clarithromycin) should be used with caution in people with a
4 predisposition to QT interval prolongation ([BNF, May 2019](#)).
- 5 Tetracyclines (for example doxycycline), can deposit in growing bone and teeth (by
6 binding to calcium) causing staining and occasionally dental hypoplasia. They should
7 not be given to pregnant or breast-feeding women, and use in children under
8 12 years is either contraindicated or cautioned for use in severe or life-threatening
9 infections where there are no alternatives ([BNF, May 2019](#)).
- 10 Co-trimoxazole is associated with rare but serious side effects including blood
11 disorders and Stevens-Johnson syndrome. It is cautioned for use in older people
12 because there is an increased risk of serious side effects, and in those with a
13 predisposition to hyperkalaemia. Monitoring of blood counts is recommended with
14 prolonged treatment ([BNF, May 2019](#)).
- 15 Aminoglycoside (for example gentamicin) doses are based on body weight and renal
16 function. Ototoxicity and nephrotoxicity are important side effects to consider, and
17 whenever possible treatment should not exceed 7 days ([BNF, May 2019](#)).
- 18 Glycopeptide (for example vancomycin) doses are based on body weight.
19 Therapeutic drug monitoring and monitoring of various patient parameters including
20 blood count, urinalysis, auditory function, hepatic function and renal function is
21 recommended depending on the particular glycopeptide ([BNF, May 2019](#)).
- 22 Severe optic neuropathy can occur with linezolid, particularly if used for longer than
23 28 days. Blood disorders have also been reported and weekly full blood counts are
24 recommended ([BNF, May 2019](#)).
- 25 See the [summaries of product characteristics](#) for information on contraindications,
26 cautions and adverse effects of individual medicines.

1 ***Medicines adherence***

2 Medicines adherence may be a problem for some people taking antibiotics that need
3 frequent dosing or longer treatment duration (see the NICE guideline on [medicines](#)
4 [adherence](#)).

5 ***Resource implications***

6 Recommended antibiotics are available as generic formulations. See [Drug Tariff](#)
7 and [BNF](#) for costs.

8 See the [evidence review](#) for more information.

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