

# Leg ulcer infection: antimicrobial prescribing

NICE guideline

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[www.nice.org.uk/guidance/ng152](https://www.nice.org.uk/guidance/ng152)

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should [assess and reduce the environmental impact of implementing NICE recommendations](#) wherever possible.

# Contents

Overview .....	4
Who is it for? .....	4
Recommendations.....	5
1.1 Managing leg ulcer infection in adults.....	5
1.2 Choice of antibiotic .....	7
Terms used in the guideline .....	11
Recommendation for research.....	12
1 Topical treatments for infected leg ulcer .....	12
Rationales.....	13
Treatment.....	13
Reassessment .....	15
Referral or seeking specialist advice.....	16
Choice of antibiotic .....	17
Context.....	21
Summary of the evidence.....	22
Topical antiseptics .....	23
Antibiotics .....	26
Choice of antibiotic .....	27
Antibiotic course length, dosage and route of administration .....	27
Other considerations.....	28
Medicines safety .....	28
Medicines adherence.....	29
Resource implications.....	29
Finding more information and committee details.....	30
Update information .....	31

## Overview

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

See a [2-page visual summary](#) of the recommendations, including a table to support prescribing decisions.

We have also produced [guidelines on cellulitis and erysipelas](#) and [antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#).

The recommendations in this guideline were developed before the COVID-19 pandemic.

## Who is it for?

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

# Recommendations

## 1.1 Managing leg ulcer infection in adults

### Treatment

#### 1.1.1 Be aware that:

- there are many causes of leg ulcers: underlying conditions, such as venous insufficiency and oedema, should be managed to promote healing
- most leg ulcers are not clinically infected but are likely to be colonised with bacteria
- antibiotics do not help to promote healing when a leg ulcer is not clinically infected.

#### 1.1.2 Do not take a sample for microbiological testing from a leg ulcer at initial presentation, even if it might be infected.

#### 1.1.3 Only offer an antibiotic for adults with a leg ulcer when there are symptoms or signs of infection (for example, redness or swelling spreading beyond the ulcer, localised warmth, increased pain or fever). When choosing an antibiotic (see the recommendations on choice of antibiotic) take account of:

- the severity of symptoms or signs
- the risk of developing complications
- previous antibiotic use.

#### 1.1.4 Give oral antibiotics if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.

#### 1.1.5 If intravenous antibiotics are given, review by 48 hours and consider switching to oral antibiotics if possible.

For a short explanation of why the committee made these recommendations, see the [rationale section on treatment](#).

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

## Advice

- 1.1.6 When prescribing antibiotics for an infected leg ulcer in adults, give advice to seek medical help if symptoms or signs of the infection worsen rapidly or significantly at any time, or do not start to improve within 2 to 3 days of starting treatment.

## Reassessment

- 1.1.7 Reassess an infected leg ulcer in adults if:
- symptoms or signs of the infection worsen rapidly or significantly at any time, or do not start to improve within 2 to 3 days
  - the person becomes systemically unwell or has severe pain out of proportion to the infection.
- 1.1.8 When reassessing an infected leg ulcer in adults, take account of previous antibiotic use, which may have led to resistant bacteria.
- 1.1.9 Be aware that it will take some time for a leg ulcer infection to resolve, with full resolution not expected until after the antibiotic course is completed.
- 1.1.10 Consider sending a sample from the leg ulcer (after cleaning) for microbiological testing if symptoms or signs of the infection are worsening or have not improved as expected.
- 1.1.11 When microbiological results are available:

- review the choice of antibiotic(s) **and**
- change the antibiotic(s) according to results if symptoms or signs of the infection are not improving, using a narrow-spectrum antibiotic if possible.

For a short explanation of why the committee made these recommendations, see the [rationale section on reassessment](#).

## Referral or seeking specialist advice

- 1.1.12 Refer adults with an infected leg ulcer to hospital if they have any symptoms or signs suggesting a more serious illness or condition, such as sepsis, [necrotising fasciitis](#) or [osteomyelitis](#).
- 1.1.13 Consider referring or seeking specialist advice for adults with an infected leg ulcer if they:
- have a higher risk of complications because of comorbidities, such as diabetes or immunosuppression
  - have lymphangitis
  - have spreading infection that is not responding to oral antibiotics
  - cannot take oral antibiotics (exploring locally available options for giving intravenous or intramuscular antibiotics at home or in the community, rather than in hospital, where appropriate).

For a short explanation of why the committee made these recommendations, see the [rationale section on referral or seeking specialist advice](#).

## 1.2 Choice of antibiotic

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

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

Treatment	Antibiotic, dosage and course length
<b>First-choice oral antibiotic</b>	<p><b>Flucloxacillin:</b> 500 mg to 1 g four times a day for 7 days (In February 2020, 1 g four times a day was off label. See <a href="#">NICE's information on prescribing medicines.</a>)</p>
<b>Alternative first-choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable</b>	<p><b>Doxycycline:</b> 200 mg on the first day, then 100 mg once a day (can be increased to 200 mg daily) for 7 days in total</p> <p><b>Clarithromycin:</b> 500 mg twice a day for 7 days</p> <p><b>Erythromycin (in pregnancy):</b> 500 mg four times a day for 7 days</p>
<b>Second-choice oral antibiotics</b> (guided by microbiological results when available)	<p><b>Co-amoxiclav:</b> 500/125 mg three times a day for 7 days</p> <p><b>Co-trimoxazole (in penicillin allergy):</b> 960 mg twice a day for 7 days (In February 2020, co-trimoxazole was off label for leg ulcer infection. See <a href="#">NICE's information on prescribing medicines.</a> See the <a href="#">BNF</a> for information on monitoring.)</p>



Treatment	Antibiotic, dosage and course length
<p><b>First-choice antibiotics if severely unwell</b> (guided by microbiological results if available)</p>	<p><b>Flucloxacillin:</b> 1 g to 2 g four times a day intravenously <b>with or without</b></p> <p><b>Gentamicin:</b> Initially, 5 mg/kg to 7 mg/kg once daily intravenously, subsequent doses if needed according to serum gentamicin concentration (see the <a href="#">BNF</a> for information on monitoring) <b>and/or</b></p> <p><b>Metronidazole:</b> 400 mg three times a day orally or 500 mg three times a day intravenously</p> <p><b>Co-amoxiclav:</b> 1.2 g three times a day intravenously <b>with or without</b></p> <p><b>Gentamicin:</b> Initially, 5 mg/kg to 7 mg/kg once daily intravenously, subsequent doses if needed according to serum gentamicin concentration (see the <a href="#">BNF</a> for information on monitoring)</p> <p><b>Co-trimoxazole</b> (in penicillin allergy): 960 mg twice a day intravenously (increased to 1.44 g twice a day if severe infection) (In February 2020, co-trimoxazole was off label for leg ulcer infection. See <a href="#">NICE's information on prescribing medicines</a>. See the <a href="#">BNF</a> for information on monitoring.) <b>with or without</b></p> <p><b>Gentamicin:</b> Initially, 5 mg/kg to 7 mg/kg once daily intravenously, subsequent doses if needed according to serum gentamicin concentration (see the <a href="#">BNF</a> for information on monitoring)</p>

Treatment	Antibiotic, dosage and course length
	<p><b>and/or</b></p> <p><b>Metronidazole:</b> 400 mg three times a day orally or 500 mg three times a day intravenously</p>
<p><b>Second-choice antibiotics if severely unwell</b> (guided by microbiological results when available or following specialist advice)</p>	<p><b>Piperacillin with tazobactam:</b> 4.5 g three times a day intravenously (increased to 4.5 g four times a day if severe infection)</p> <p><b>Ceftriaxone:</b> 2 g once a day intravenously</p> <p><b>with or without</b></p> <p><b>Metronidazole:</b> 400 mg three times a day orally or 500 mg three times a day intravenously</p>
<p><b>Antibiotics to be added if meticillin-resistant <i>Staphylococcus aureus</i> infection is suspected or confirmed</b> (combination therapy with antibiotics listed above)</p>	<p><b>Vancomycin:</b> 15 mg/kg to 20 mg/kg two or three times a day intravenously (maximum 2 g per dose), adjusted according to serum vancomycin concentration (see the <a href="#">BNF</a> for information on monitoring)</p> <p><b>Teicoplanin:</b> Initially 6 mg/kg every 12 hours for three doses, then 6 mg/kg once a day intravenously (see the <a href="#">BNF</a> for information on monitoring)</p> <p><b>Linezolid</b> (if vancomycin or teicoplanin cannot be used; specialist advice only): 600 mg twice a day orally or intravenously (see the <a href="#">BNF</a> for information on monitoring)</p>

See the [BNF](#) for appropriate use and dosing in specific populations, for example, people with hepatic or renal impairment, in pregnancy and breastfeeding, and when administering intravenous (or, where appropriate, intramuscular) antibiotics.

Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics if possible.

Erythromycin is preferred if a macrolide is needed in pregnancy, for example, if there is true penicillin allergy and the benefits of antibiotic treatment outweigh the harms. See the [Medicines and Healthcare products Regulatory Agency \(MHRA\) Public Assessment Report on the safety of macrolide antibiotics in pregnancy](#).

For a short explanation of why the committee made the recommendation, see the [rationale section on choice of antibiotic](#).

For more detail, see the [summary of the evidence on choice of antibiotic](#).

## Terms used in the guideline

### Leg ulcer

A leg ulcer is a long-lasting (chronic) open wound that takes more than 4 to 6 weeks to heal. Leg ulcers usually develop on the lower leg, between the shin and the ankle.

### Necrotising fasciitis

This is a rare but serious bacterial infection that affects the tissue beneath the skin and surrounding muscles and organs (fascia). Early symptoms can include intense pain that is out of proportion to any damage to the skin, and fever. The most common cause is group A streptococcus.

### Osteomyelitis

This is an infection of the bone. It can be very painful and most commonly occurs in the long bones of the leg. It can also occur in other bones, such as those in the back or arms. Anyone can develop osteomyelitis, but certain people are more at risk, including people with diabetes and those with a weakened immune system.

## Recommendation for research

The guideline committee has made the following recommendation for research.

### 1 Topical treatments for infected leg ulcer

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

For a short explanation of why the committee made the recommendation for research, see the [rationale on treatment](#).

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

# Rationales

The recommendations in this guideline are for adults and are based on the evidence identified and the experience of the committee. No evidence was found for children with leg ulcers and recommendations were made for adults only.

## Treatment

### Why the committee made the recommendations

#### Recommendations 1.1.1 to 1.1.5

The committee agreed that health professionals should be aware that there are many causes of leg ulcers and that, although most leg ulcers are colonised by bacteria, few are infected. They discussed that it is important to ensure that underlying conditions, such as venous insufficiency and oedema, are managed appropriately.

The committee discussed that antibiotics should only be offered for adults with a leg ulcer when there are symptoms or signs of infection. They agreed that there was no difference in outcomes between treatment with antibiotics and standard care in people with uninfected leg ulcers (although this was from a small, very low-quality study with no details reported on dosage or route of administration).

Evidence showed no difference in complete healing of the leg ulcer with antibiotics compared with standard care or placebo. However, in all but 1 study, the ulcer was either uninfected or the infection status was unclear. No study stated that children and young people (under 18 years) were included. The committee agreed that this age group are very unlikely to develop a leg ulcer and if they do the cause is likely to be from a condition that needs specialist management. Therefore, it was not appropriate to extrapolate evidence for adults to children and young people and so the committee made recommendations for adults only.

The committee agreed that antibiotics should be offered to all adults with a leg ulcer if there are symptoms or signs of an infection, because untreated infection causes delays in ulcer healing, affecting quality of life and sometimes resulting in hospital admission. The committee discussed that studies did not use consistent criteria for identifying infection in

ulcers, and some signs of infection (such as localised redness, discharge and unpleasant smell) could be present in all leg ulcers, regardless of infection status, especially once compression is removed. Therefore, they agreed that the symptoms or signs to use to determine if the ulcer is infected may include redness or swelling spreading beyond the ulcer, localised warmth, increased pain or fever. The committee noted that healthcare professionals should be aware that redness, 1 of the signs of infection, may be less visible on darker skin tones.

Based on experience, the committee agreed that antibiotic choice will depend on the severity of symptoms or signs of infection (for example, how rapidly the infection is progressing or expanding), the person's risk of complications (possibly because of comorbidities, such as diabetes or immunosuppression) and any previous antibiotic use (which may have led to antimicrobial resistance).

In line with the [NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#) and [Public Health England's antimicrobial stewardship: start smart – then focus toolkit](#), oral antibiotics should be given first if the person can take them, and if the severity of their infection does not require intravenous antibiotics. The use of intravenous antibiotics should be reviewed by 48 hours (taking into account the person's response to treatment and any microbiological results) and switched to oral treatment where possible.

The committee discussed and agreed that samples for microbiological testing should not routinely be taken from a leg ulcer at initial presentation, whether it is thought to be infected or not. Most leg ulcers are colonised by bacteria, and bacterial growth from a sample is likely regardless of infection status. Universal sampling could lead to inappropriate antibiotic prescribing. If the leg ulcer is clinically infected, the most likely causative organism is *Staphylococcus aureus*, which would be covered by empirical treatment with flucloxacillin.

## Topical antiseptics

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

There was some evidence of effect for cadexomer-iodine and silver dressings in people with infected leg ulcer (compared with standard care and non-adherent foam dressing

respectively). But there were severe limitations, including an unclear definition of 'infection' (1 being reliant on laboratory growth and the other stating that inflammation was the only symptom required). For the comparison of silver dressings and foam dressings, the only sign of infection required was inflammation, there were very wide confidence intervals, and both study arms had the option to use antibiotics (and the number of people taking systemic antibiotics was not reported). Silver dressings can be expensive and could have considerable resource impact. Therefore, because of the inadequate definition of infection, the confounding issue of antibiotic use, the uncertainty of the effect estimate and the potential cost, the committee agreed not to recommend silver dressings.

The committee were also concerned about the adverse effects with cadexomer-iodine. These were mainly local skin irritation, rash and pain, all of which can make leg ulcers worse. No adverse effects were reported for silver dressings, but this may have been because of the small sample size. The committee were also aware of issues with the availability of iodine-based preparations, particularly in community settings.

In clinical practice, topical antiseptics are used for leg ulcers, often to manage minor, localised infections. However, the committee agreed that they could not make any recommendations on the use of topical antiseptics for treating infected leg ulcers because of the limitations of the evidence and the unclear benefit. The inability to differentiate between a more localised or widespread infection both in the evidence and in clinical practice makes it difficult to define any place in therapy for topical antiseptics. The committee decided that it was appropriate to make a recommendation for research on the effectiveness of topical treatments (antiseptics and antibiotics) compared with oral antibiotics.

[Return to recommendations](#)

## Reassessment

### Why the committee made the recommendations

#### Recommendations 1.1.7 to 1.1.11

Based on experience, the committee agreed when adults with an infected leg ulcer should be reassessed. If symptoms of the infection worsen rapidly or significantly at any time, or do not start to improve within 2 to 3 days, this may indicate that the person has a more

serious illness requiring referral, or a resistant infection (possibly because of previous antibiotic use). People with leg ulcers have routine reviews, often by nurses. However, this review and any decision on the need for further antibiotics should take into account the fact that a leg ulcer infection will take some time to resolve even after a course of effective antibiotics.

The committee agreed that adults should be reassessed if they have severe pain out of proportion to the infection because this can be a symptom of necrotising fasciitis, which is a rare but serious bacterial infection.

Although microbiological sampling is not required at initial presentation, the committee agreed that it is appropriate to consider this if symptoms or signs of the infection are worsening or have not improved as expected. This will guide future antibiotic choice if the person has a resistant infection. The committee agreed that before microbiological sampling the wound should be cleaned to remove surface contaminants, slough or necrotic tissue, in line with [Public Health England's guidance on venous leg ulcers: infection diagnosis and microbiological investigation guide for primary care](#).

When microbiological results are available, the choice of antibiotic should be reviewed and changed according to results if symptoms or signs of the infection are not improving, using a narrow-spectrum antibiotic if appropriate to minimise the risk of antimicrobial resistance.

[Return to recommendations](#)

## Referral or seeking specialist advice

### Why the committee made the recommendations

[Recommendations 1.1.12 and 1.1.13](#)

Based on experience, the committee agreed that adults with symptoms or signs suggesting a more serious illness or condition should be referred to hospital. Some people may have an infected leg ulcer that is more difficult to treat, for example, because they have a higher risk of complications or other underlying conditions, or they have a resistant infection. In these cases, referral or specialist advice should be considered (which may include giving intravenous antibiotics or adopting other non-antimicrobial management strategies).



[Return to recommendations](#)

## Choice of antibiotic

### [Recommendation 1.2.1](#)

### Why the committee made the recommendations

There was very limited evidence on the choice of antibiotics in adults with an infected leg ulcer. Only 1 study compared antibiotics with standard care, and this was limited by the criteria for diagnosing infection. It was unclear whether wounds had symptoms and signs of clinical infection at baseline or whether they were just colonised with bacteria.

Based on experience, current practice and resistance data, the committee agreed that the first-choice oral antibiotic in adults with an infected leg ulcer is flucloxacillin (a penicillin). This is a relatively narrow-spectrum penicillin, which has good penetration for skin and soft tissue infections and is effective against gram-positive organisms, including the most common causative organism *Staphylococcus aureus*.

The alternative first-choice antibiotics in adults with penicillin allergy or in whom flucloxacillin is unsuitable are doxycycline (a tetracycline), or clarithromycin or erythromycin (in pregnancy), which are macrolides. These all have a similar spectrum of activity to flucloxacillin. The committee agreed that the doses provided in the prescribing table were suitable for people with poor vascular flow.

The committee discussed the [MHRA Public Assessment Report on the safety of macrolide antibiotics in pregnancy](#). This found that the available evidence is insufficient to confirm with certainty whether there is a small increased risk of birth defects or miscarriage when macrolides are taken in early pregnancy. They agreed with the [UK Teratology Information Service monograph on the use of macrolides in pregnancy](#). They decided that there should be an informed discussion of the potential benefits and harms of treatment. Then, after such a discussion, macrolides can be used if there is a compelling clinical need and there are no suitable alternatives with adequate pregnancy safety data. Erythromycin is the preferred choice if a macrolide is needed during pregnancy, for example, if there is true penicillin allergy and the benefits of antibiotic treatment outweigh the harms. This is because there is more documented experience of its use than for other macrolides.

The committee agreed that the second-choice oral antibiotics if the first-choice oral

antibiotics are not effective (guided by microbiological results when available) are the broader-spectrum antibiotics co-amoxiclav (a penicillin with a beta-lactamase inhibitor) or co-trimoxazole (in penicillin allergy). These are more active against gram-negative organisms. The presence of gram-negative organisms may be a reason why an infected leg ulcer is not healing; these antibiotics are therefore appropriate second-choice antibiotics. However, the committee noted that it is important to only use broad-spectrum antibiotics if first-choice antibiotics are not effective. Broad-spectrum antibiotics can create a selective advantage for bacteria resistant to these agents, allowing such strains to proliferate and spread. By disrupting normal flora, broad-spectrum antibiotics can also leave people susceptible to harmful bacteria such as *Clostridium difficile* in community settings. The committee discussed that cephalosporins are not an appropriate option as a second-choice oral antibiotic because they do not provide adequate cover for anaerobes.

Oral antibiotics should be given first line if possible. But based on experience and resistance data, the committee agreed that several intravenous antibiotics (or combinations of antibiotics) can be used for adults who are severely unwell or unable to take oral antibiotics. This enables antibiotics to be selected based on individual patient factors, likely pathogens, and antibiotic susceptibilities from microbiological results (if known).

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

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

The committee agreed that additional choices would be:

- co-amoxiclav with or without gentamicin
- co-trimoxazole with or without gentamicin and/or metronidazole (if penicillin allergy).

The committee discussed that metronidazole (which is used for anaerobic bacteria) may be useful for people with leg ulcers related to arterial disease or diabetes. These people may have a reduced blood supply that can encourage anaerobic bacterial growth. Because metronidazole has good oral bioavailability, this could be given orally instead of

intravenously if people were able to take oral antibiotics.

Second choice intravenous antibiotics (guided by microbiological results when available or following specialist advice) are:

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

The committee discussed that intravenous ceftriaxone may be given as an outpatient without the need for hospital admission.

Meticillin-resistant *Staphylococcus aureus* (MRSA) may be found on swabbing, but the current likelihood of MRSA infection is very low. The committee agreed that if MRSA infection is suspected or confirmed, 1 of the following intravenous antibiotics with activity against MRSA should be added to the treatment regimen:

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

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

There was very little evidence on antibiotic dosage, course length and route of administration. Therefore, recommendations were based on the committee's experience of current practice. Flucloxacillin has poor oral bioavailability and in people with an infected leg ulcer who could have impaired circulation, a higher (off-label dose) of up to 1 g, 4 times a day orally, may be needed to adequately treat the infection.

The committee agreed that the shortest course that is likely to be effective should be prescribed to minimise adverse effects and reduce the risk of antimicrobial resistance, but that this should be balanced against the need for a course length that provides effective treatment.

In the absence of evidence for optimum course length, the committee agreed, based on experience and extrapolation of evidence from people with cellulitis and diabetic foot infection, that a course of 7 days is appropriate for most people with an infected leg ulcer.

They discussed that a decision for a longer course of antibiotics may be made on review if the infection is not improving, particularly for people with poor healing and a higher risk of complications because of comorbidities. However, 7 days should be adequate for most people if their wound and any underlying condition is being managed appropriately. Any decision on the need for further antibiotics should take into account the fact that a leg ulcer infection will take some time to resolve, even after a course of effective antibiotics.

The committee also discussed safety concerns around longer courses of flucloxacillin or co-amoxiclav, particularly in older people, because of the risk of cholestatic jaundice or hepatitis.

In line with the [NICE guideline on antimicrobial stewardship](#) and [Public Health England's antimicrobial stewardship: start smart – then focus toolkit](#), oral antibiotics should be given first line if the person can take them, and the severity of their condition does not require intravenous antibiotics. The use of intravenous antibiotics should be reviewed by 48 hours (taking into account the person's response to treatment and any microbiological results) and switched to oral treatment where possible.

[Return to recommendation](#)

## Context

A leg ulcer is a long-lasting (chronic) open wound that takes more than 4 to 6 weeks to heal. Leg ulcers usually develop on the lower leg, between the shin and the ankle.

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

## Summary of the evidence

This is a summary of the evidence. For full details see the [evidence review](#) and [expert testimony](#).

The review protocol included a population of adults, young people and children with infected leg ulcers. There was minimal evidence for this population (2 small studies), therefore the population was expanded to people with leg ulcers that had an unclear infection status or were not infected. For antiseptic and antibiotics, the results have been presented separately for people with:

- an infected leg ulcer
- a leg ulcer with unclear infection status
- an uninfected leg ulcer.

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

No studies included in the review stated that they included children. 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, they agreed not to extrapolate the evidence to children and young people.

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

## Topical antiseptics

### Iodine-based preparations

#### Infected leg ulcer

In a single RCT, cadexomer-iodine was significantly better than standard care at reducing the average size of the ulcers, the amount of pain experienced from the ulcers and reducing or eliminating the presence of *Staphylococcus aureus* at 6 weeks.

There was no significant difference for:

- cadexomer-iodine compared with silver dressing for the frequency of complete healing at 12 weeks and for participant satisfaction (neither group reported any adverse effects)
- povidone-iodine plus compression compared with moist or foam dressings plus compression for complete healing at 4 months.

#### Unclear leg ulcer infection status

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

#### Uninfected leg ulcer

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

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

Povidone-iodine 10% solution plus compression was significantly better for time to healing than hydrocolloid plus compression.

## Peroxide-based preparations

### Unclear leg ulcer infection status

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

### Uninfected leg ulcer

Hydrogen peroxide 1% cream was significantly better for median decrease in ulcer area compared with placebo cream at 10-day follow up. Data on adverse effects were limited and poorly reported.

## Honey-based preparations

### Unclear leg ulcer infection status

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

- complete healing at 12 weeks
- incidence of ulcer infection during 12 weeks of treatment.

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

### Uninfected leg ulcer

Honey (topical Manuka honey) was not significantly different from hydrogel (3 g/20 cm<sup>2</sup> applied weekly) for the eradication of meticillin-resistant *Staphylococcus aureus* (MRSA) at 4 weeks.



## Silver-based preparations

### Infected leg ulcer

Silver dressing plus compression was significantly better than non-adhesive plus compression dressing for:

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

Silver dressings were not significantly different from non-adhesive dressings for adverse effects.

### Unclear leg ulcer infection status

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

- silver sulfadiazine (1% cream) plus compression compared with non-adherent dressing plus compression
- silver impregnated dressings (with or without compression) compared with non-antimicrobial dressings (with or without compression)
- silver-impregnated polyurethane foam dressing plus compression compared with 5-layer silver impregnated dressing plus compression.

Silver dressings were not significantly different from non-antimicrobial dressings for adverse effects.

### Uninfected leg ulcer

There was no significant difference for:

- silver sulfadiazine (1% cream) with non-adhesive foam dressing and compression compared with placebo cream with non-adherent dressing and compression for complete healing at 4 weeks
- silver sulfadiazine (1% cream) compared with standard care for median time to healing

- silver dressing plus compression compared with low-adherent dressing for complete healing at 4 to 12 weeks, 6 months or 12 months, or for ulcer recurrence within 12 months
- silver dressings compared with non-antimicrobial dressings for adverse effects.

Silver dressing plus compression was significantly better than non-antimicrobial dressings plus compression for reducing ulcer surface area when measured using square centimetres at 4 weeks, but was not significantly different when measured as a percentage change. The healing rate (cm<sup>2</sup> per day) in these 2 RCTs was not significantly different.

## Antibiotics

### Antibiotics compared with standard care or placebo

#### Infected leg ulcer

Ciprofloxacin was not significantly different from standard care for the frequency of complete healing, emergence of antibiotic-resistant strains or bacterial eradication at 3 months.

#### Unclear leg ulcer infection status

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

- ciprofloxacin and placebo **or**
- trimethoprim and placebo.

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

#### Uninfected leg ulcer

There was no significant difference between:

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

Data on adverse effects were limited and poorly reported.

## **Antibiotics compared with antiseptics**

### **Infected leg ulcer**

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

No data on adverse effects were reported.

## **Choice of antibiotic**

### **Unclear leg ulcer infection status**

Ciprofloxacin was not significantly different from trimethoprim for the frequency of complete healing.

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

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

No evidence from systematic reviews or RCTs was identified.

## Other considerations

### Medicines safety

Antibiotic-associated diarrhoea is estimated to occur in 2% to 25% of people taking antibiotics, depending on the antibiotic used ([NICE clinical knowledge summary on diarrhoea – antibiotic associated](#)).

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

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

People with a history of immediate hypersensitivity to penicillin may also react to cephalosporins and other beta-lactam antibiotics ([BNF phenoxymethylpenicillin](#)).

Macrolides (for example, clarithromycin) should be used with caution in people with a predisposition to QT interval prolongation. Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side effects of macrolides. These are less frequent with clarithromycin than with erythromycin ([BNF erythromycin](#)).

Tetracyclines (for example, doxycycline) can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to pregnant women or women who are breastfeeding, and use in children under 12 years is either contraindicated or cautioned for use in severe or life-threatening infections where there are no alternatives. People should be advised to avoid exposure to sunlight or sun lamps because of photosensitivity reactions ([BNF doxycycline](#)).

Co-trimoxazole is associated with rare but serious side effects, including blood disorders and Stevens–Johnson syndrome. It is cautioned for use in older people because there is

an increased risk of serious side effects, and in those with a predisposition to hyperkalaemia. Monitoring of blood counts is recommended with prolonged treatment ([BNF co-trimoxazole](#)).

Aminoglycoside (for example, gentamicin) doses are based on body weight and renal function. Ototoxicity and nephrotoxicity are important side effects to consider, and whenever possible treatment should not exceed 7 days ([BNF gentamicin](#)).

Glycopeptide (for example, vancomycin and teicoplanin) doses are based on body weight. Therapeutic drug monitoring and monitoring of various patient parameters, including blood count, urinalysis, auditory function, hepatic function and renal function, is recommended, depending on the particular glycopeptide ([BNF vancomycin](#)).

Severe optic neuropathy can occur with linezolid, particularly if used for longer than 28 days. Blood disorders have also been reported, and weekly full blood counts are recommended ([BNF linezolid](#)).

See the [electronic medicines compendium's summaries of product characteristics](#) for information on contraindications, cautions and adverse effects of individual medicines.

## Medicines adherence

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

## Resource implications

Recommended antibiotics are available as generic formulations. See [NHS Drug tariff](#) and [BNF](#) for costs.

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

## Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the [NICE topic pages on injuries, accidents and wounds](#) and [antimicrobial stewardship](#).

For full details of the evidence and the guideline committee's discussions, see the [evidence review](#). You can also find information about [how the guideline was developed](#), including [details of the committee](#).

NICE has produced [tools and resources to help you put this guideline into practice](#). For general help and advice on putting our guidelines into practice, see [resources to help you put NICE guidance into practice](#).

# Update information

## Minor changes since publication

**January 2022:** We made minor wording changes to reflect updated advice on the use of macrolides in pregnancy.

November 2020: We amended table 1 to clarify that the gentamicin dosage is once daily.

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