

Managing Common Infections

Leg ulcer infection: antimicrobial prescribing

Stakeholder comments table

26/06/2019 – 23/07/2019

ID	Organisation	Document	Page No.	Line No.	Comments	Developer's response
1	University Hospitals Birmingham	Draft guideline	2	5	Dose advice for flucloxacillin. Patients over weight (i.e. BMI > 30) dose be given a dose of 1g QDS. Duration should range from 7 days upto 14 days.	Thank you for your comment. The recommended dose for oral flucloxacillin has been amended to 500 mg to 1 g, four times a day for all people. Based on the committee's experience of current practice, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed that a 7-day antibiotic course length will be appropriate for most people with infected leg ulcer. The committee agreed that extending the course of antibiotics should be an individualised decision based on clinical judgement at review. It noted evidence from the expert witness that people with an infected leg ulcer would be regularly reviewed, giving an opportunity for extending the antibiotic course length if appropriate.
2	University Hospitals Birmingham	Draft guideline	2	7-8	Clarithromycin and Erythromycin are poor choice for management for leg ulcer infection. Patients usually have poor vascular flow so high drug concentrations needed for treatment. Better to advise Clindamycin 450mg (or if BMI>> 30 = 600mg) qds for 7 to 14 days.	Thank you for your comment. The committee agreed that clarithromycin and erythromycin are suitable alternative antibiotics for people with penicillin allergy or in whom flucloxacillin is unsuitable because they have a similar spectrum of activity to flucloxacillin. They agreed that doses of erythromycin 500 mg four times a day and clarithromycin 500 mg twice a day were sufficient for leg ulcer infection, in line with other antimicrobial prescribing guidelines on cellulitis and diabetic foot infection. Clindamycin was not recommended as an alternative because of concerns over the risk of colitis and diarrhoea with this broad spectrum antibiotic and the need to reserve its use for more serious infections where broader cover may be needed.

3	University Hospitals Birmingham	Draft guideline	2	9	Doxycycline choice should be separate line related to patient previously identified as MRSA positive. Dose should be increased to 200mg STAT followed by 100mg BD as bacteriostatic and high dose required for effective treatment.	Thank you for your comment. The committee agreed that doxycycline is an appropriate antibiotic choice for people with an infected leg ulcer in whom flucloxacillin is not appropriate, regardless of their MRSA status. The committee agreed that the dose of doxycycline could be increased to 200 mg daily for the total course length, based on clinical judgement. This has been reflected in the antibiotic prescribing table.
4	University Hospitals Birmingham	Draft guideline	2	14	Dose of intravenous flucloxacillin should not be recommending 500mg QDS. This is sub-therapeutic. Change to 1000mg QDS minimum and if BMI > 30 give 2000mg QDS as a minimum.	Thank you for your comment. The recommended dose for intravenous flucloxacillin has been amended to 1 g to 2 g, four times a day.
5	University Hospitals Birmingham	Draft guideline	2	15, 18, 20	Gentamicin needs to also take into account patients who are overweight and using ideal body weight if BMI > 30. And adjusting for renal function. This also should apply to other lines with Gentamicin listed.	Thank you for your comment. The gentamicin dose is that given in the BNF, where adjusting doses according to serum-gentamicin concentration is advised. A footnote is also included in the antibiotic prescribing table, referring to the BNF for appropriate dosing in specific populations, including renal impairment. NICE is also aware that localities may follow local guidelines on gentamicin use.
6	British association of Dermatologists				Antiseptic soaks and dressings could be used instead of antibiotics where there is a clinical suspicion of infection in a wet leg ulcer but no identifiable pathogenic organism. There could be a little more comment on the lack of good evidence for topical iodine and silver in dressings.	Thank you for your comment. The committee discussed the use of antiseptic soaks and dressings, including iodine and silver dressings. The rationale section of the guideline explains the reasons the committee could not make any recommendations for antiseptic dressings, which includes the limitations of the evidence, the unclear benefit and the risks of adverse events, particularly with cadexomer-iodine.
7	British association of Dermatologists				As the guideline points out, there is no guidance on how to investigate e.g. how to take a wound swab, which might give useful information.	Thank you for your comment. The committee agreed that taking a sample should be considered at reassessment if symptoms or signs of the infection are worsening or have not improved as expected. The committee agreed that it was appropriate that the leg ulcer should be cleaned before sending a sample and included this within the recommendation. However, the committee was unable to make any further recommendations on how to take a swab because this was not within the scope of the guideline, and it agreed that there were other resources available to provide this guidance.

8	Scottish Antimicrobial Prescribing Group	Visual summary	1		<ul style="list-style-type: none"> • Signs of infection – enlarging ulcer, malodour and increased exudate. These are probably the commonest reason for antibiotics and I am not clear of the supporting evidence. I think if this is allowed through then the guidance will have minimal impact on improving clinical practice/stewardship. • Suggest amend to “worsening and /or new malodour” as some ulcers can have a faint smell but no signs of infection • Under microbiology sampling & prescribing considerations – add in “and review sensitivities” 	<p>Thank you for your comment. The committee agreed that not all the symptoms or signs listed in the draft guideline were necessarily stand-alone indicators for infection and this has been amended in the final recommendations and the visual summary. Based on the committee's experience, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed that the symptoms or signs of infection include redness or swelling spreading beyond the ulcer, localised warmth, increased pain or fever.</p> <p>A recommendation is included in the guideline and the visual summary stating that 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. The prescribing table in the guideline and visual summary also indicates that second choice antibiotics should be guided by microbiological results if available.</p>
9	Scottish Antimicrobial Prescribing Group	Visual summary	2		<ul style="list-style-type: none"> • Content with antibiotic choices but duration could be shorter (5 to 7 days) depending on the presentation. • Consider increasing 1st line flucloxacillin dose range to 500mg – 1g • 1st line IV indications where gent/met may be of benefit add in diabetic • 1st line IV flucloxacillin consider increasing minimum dosing to 1g • Penicillin allergy – consider moving doxycycline to first line? • Suggest adding in MRSA PO options - ?doxycycline • Gentamicin dosing – suggest removing dosing as does not state maximum daily dose nor account for reduced renal function dosing. Add in “follow local guidelines”. 	<p>Thank you for your comment. Based on the committee's experience of current practice, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed that a 7-day antibiotic course length will be appropriate for most people with infected leg ulcer. The committee discussed that there is an absence of evidence for optimum course length and based this recommendation on its experience and extrapolation of evidence from people with cellulitis and diabetic foot infection.</p> <p>The recommended dose for oral flucloxacillin has been amended to 500 mg to 1 g, four times a day.</p> <p>The committee agreed that the antibiotic prescribing table could not include choices for all possible indications and that the table should be used alongside clinical judgement when treating individuals, including people with diabetes.</p>

					<p>The recommended dose for intravenous flucloxacillin has been amended to 1 g to 2 g, four times a day.</p> <p>Doxycycline is recommended as an alternative first choice for people with penicillin allergy.</p> <p>The committee discussed that MRSA is rare in leg ulcer infection and the antibiotic choices of vancomycin, teicoplanin or (if these were not suitable) linezolid were appropriate to cover such an infection if it was suspected or confirmed.</p> <p>The committee agreed that it was appropriate to include the BNF dose for gentamicin, with footnotes, to refer to the BNF for information on therapeutic drug monitoring and monitoring of patient parameters. A footnote is also included which refers to the BNF for appropriate use and dosing in specific population, including renal impairment. NICE is also aware that localities may follow local guidelines on gentamicin use.</p>
10	Scottish Antimicrobial Prescribing Group	Guideline			<p>The inclusion of information on dressings and topical products is welcomed.</p> <p>Thank you for your comment.</p>
11	Scottish Antimicrobial Prescribing Group	Guideline			<p>Comments provided on visual summary above apply to guideline too.</p> <p>Thank you for your comment.</p>
12	Scottish Antimicrobial Prescribing Group	Guideline	20	<ul style="list-style-type: none"> Medicines safety – doxycycline add in photosensitivity Although BNF states use of urinalysis in glycopeptides therapy, this is not mentioned in any of the manufacturers SPCs. Patients will have regular renal function monitoring 	<p>Thank you for your comment. Information on avoiding exposure to sunlight or sun lamps for people given doxycycline (and other tetracyclines) has been added to the medicines safety section.</p> <p>A footnote is included in the prescribing table for the recommended glycopeptides, to refer to the BNF for information on therapeutic drug monitoring and monitoring of patient parameters, which includes urinalysis. The committee agreed this was appropriate for people who are given a glycopeptide. The committee also noted the SPC for vancomycin which specifies that 'all patients receiving vancomycin should have periodic</p>

						haematologic studies, urine analysis, liver and renal function tests’.
13	Scottish Antimicrobial Prescribing Group	Questions			In terms of choice of therapy the guideline is in line with current practice. Use of higher doses and shorter courses may be challenging to implement without awareness raising amongst clinical teams and changes to GP computer systems to make first line treatments (choice, dose and duration) the default.	Thank you for your comment. Please note implementation is for commissioners and providers to consider and determine locally.
14	Royal College of General Practitioners	Guideline	2	6	The committee should consider making it clearer that with colonisation of bacteria but no infection, antibiotics are not required. “Most leg ulcers are not clinically infected and so do not need antibiotics, but are likely to be colonised with bacteria”	Thank you for your comment. The committee agreed that recommendation 1.1.1 clearly states that people should be aware that most leg ulcers are not clinically infected but are likely to be colonised with bacteria and that antibiotics do not help to promote healing when a leg ulcer is not clinically infected. Recommendation 1.1.2 also states only offer an antibiotic for adults with a leg ulcer when there are symptoms or signs of infection. Therefore, no changes have been made to this recommendation regarding these points.
15	Royal College of General Practitioners	Guideline	2	Footnote 1	Cellulitis is a diagnosis not a symptom or a sign of infection whilst this is a direct quote from the SIGN guideline, the committee should reword to reflect this.	Thank you for your comment. The committee agreed that the symptoms or signs listed in the draft guideline were not necessarily stand-alone indicators for infection and this has been amended in the final recommendations, including deletion of this footnote.
16	Royal College of General Practitioners	Guideline	3	3	The committee should consider including adding details of systemic symptoms and significant increase in pain (see comment 6) to the list of “advice to patients on when to seek help”	Thank you for your comment. The committee discussed the symptoms or signs of infection and agreed that it was appropriate to give advice to seek medical help if these worsen rapidly or significantly at any time or do not start to improve within 2 to 3 days of starting treatment. The committee agreed the appropriate symptoms or signs of infection, and these include increased pain. The committee also noted that the recommendations state that adults with an infected leg ulcer should be reassessed if the person becomes systemically unwell or has severe pain out of proportion to the infection.
	Royal College of General Practitioners	Guideline	3	12	Necrotising fasciitis is rare and healthcare professionals may not know the signs and symptoms of this. It maybe beneficial to include further details as a footnote.	Thank you for your comment. Further details on necrotising fasciitis have been added as a ‘term’ in the terms used in the guideline section.

17	Royal College of General Practitioners	Guideline	3	10	Should we only review if the patient is “very systemically unwell?” Can the committee consider removing “very” so it reads “becomes systemically unwell or there are signs of sepsis?	Thank you for your comment. The committee agreed to remove the word “very” so that the recommendation states that adults with an infected leg ulcer should be reassessed if the person becomes “systemically unwell”. The recommendations on referral state that adults with an infected leg ulcer should be referred to hospital if they have any symptoms or signs suggesting a more serious illness or condition, such as sepsis, necrotising fasciitis or osteomyelitis.
18	Royal College of General Practitioners	Guideline	3	11	The committee should consider adding further detail here perhaps as a footnote. We assume stating review if the patient has severe pain that is out of proportion to the infection is due to an invasive group A strep infection. Consideration should be taken to adding this information to line 4, worsening symptoms advice for the patient.	Thank you for your comment. The recommendation on advice to give people with an infected leg ulcer includes information about seeking medical help if symptoms or signs of infection worsen rapidly or significantly at any time, which includes increased pain. The committee agreed that this was appropriate detail to include in the recommendation because the reassessment recommendation that follows states ‘Reassess adults with an infected leg ulcer 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.’
19	Royal College of General Practitioners	Guideline	3	12	<p>The committee should make it clearer what action to take if there are positive findings in relation to these points.</p> <p>Point 1: ‘any symptoms or signs suggesting a more serious illness or condition, such as sepsis, necrotising fasciitis, osteomyelitis or lymphangitis’ – these are later listed as reasons to refer. Could the committee consider adding “which will require referral”</p> <p>Point 2: ‘other comorbidities, such as diabetes or immunosuppression these are at higher risk of complications and therefore an indication for referral – as stated in the referral section (1.1.11. page 4, line 7) – it would be better to make that point explicitly and link the recommendation to refer.</p>	<p>Thank you for your comment. The committee agreed that for clarity, the recommendations for people with any symptoms or signs suggesting a more serious illness or condition such as sepsis, necrotising fasciitis, osteomyelitis or lymphangitis should only be referenced in recommendations on referral and seeking specialist advice. The guideline has been amended to remove reference to this population from the recommendations on reassessment.</p> <p>Similarly, reference to people with other co-morbidities, such as diabetes or immunosuppression has been removed from the recommendations on reassessment, and the recommendation on considering referral or specialist advice has been amended to refer to this population specifically.</p>

20	Royal College of General Practitioners	Guideline	3	17	<p>Can the committee be more explicit and state that on initial review of a leg ulcer swabbing is not indicated, but only after completion of the first course of antibiotics and worsening symptoms and explain it is to check for antibiotic resistance bacteria as detailed in the rationale.</p> <p>The committee should consider giving further guidance on taking the swab itself as detailed in the rationales line 25 e.g. e.g. after cleaning (removing contaminants, slough or necrotic tissue)</p>	<p>Thank you for your comment. The committee agreed to add a recommendation to the section on treatment to add clarity on this point: “Do not routinely take a sample for microbiological testing from people with a leg ulcer”</p> <p>The remit of the guideline does not cover the diagnosis of leg ulcer infection; therefore, recommendations cannot be made for detailed use of swabs. The committee agreed that there were other resources available to provide this guidance.</p>
21	Royal College of General Practitioners	Guideline	4	17	<p>The committee should provide further detail on the decision to recommend a 7 day course as detailed in the rationale based on consensus/ BNF as there is no trail to determine shortest effective length of treatment.</p>	<p>Thank you for your comment. Based on the committee's experience of current practice, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed that a 7-day antibiotic course length will be appropriate for most people with infected leg ulcer. The committee discussed that there is an absence of evidence for optimum course length and based this recommendation on its experience and extrapolation of evidence from people with cellulitis and diabetic foot infection. This detail has been included in the rationale section of the guideline.</p>
22	Royal College of General Practitioners	Guideline	4	17	<p>Can the committee consider adding a footnote stating explicitly that 250mg qds of flucloxacillin is not an appropriate dose for treatment as in the rationale?</p>	<p>Thank you for your comment. The recommended dose for oral flucloxacillin has been amended to 500 mg to 1 g, four times a day.</p>
23	Royal College of General Practitioners	Visual Summary			<p>In vertical box on left of page – prescribing considerations – 3 listed the relevance of the 3 points are not clear. How should ‘severity of symptoms’ or ‘risk of complications’ influence the choice of antibiotic? Can the committee consider adding more details to the visual summary perhaps in a footnote for those clinicians who only look at the visual summary?</p>	<p>Thank you for your comment. The visual summary includes key information from the guideline only. The detail has been included in the rationale section of the guideline where it states ‘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 co-morbidities, such as diabetes or immunosuppression), and any previous antibiotic use (which may have led to the development of antimicrobial resistance).</p>

24	Royal College of General Practitioners	Visual Summary			In the flow diagram on the right: the middle box of the top row that starts with 'Give advice about seeking medical help if:' Can the committee consider removing "very" so it reads "Reassess if symptoms worsen rapidly or significantly at any time, do not start to improve within 2-3 days, or if the person become systemically unwell....."	Thank you for your comment. The committee agreed to remove the word "very" so that the visual summary states that adults with an infected leg ulcer should be reassessed if the person becomes "systemically unwell".
25	Royal College of General Practitioners	Visual Summary			In the white box at the top of the page, consider adding systemic symptoms to the advice given to patients and add a list of systemic symptoms to consider.	Thank you for your comment. The committee discussed the symptoms or signs of infection and agreed that it was appropriate to give advice to seek medical help if these worsen rapidly or significantly at any time or do not start to improve within 2 to 3 days of starting treatment. The symptoms and signs of infection have been included in the grey box on page 1 of the visual summary and have been amended in line with the final guideline.
26	Royal College of General Practitioners	Visual Summary			Referral box. The committee should consider adding IM antibiotics to the options as many ambulatory care units and community services will use 1 dose if IV antibiotics and then IM community antibiotics.	Thank you for your comment. The committee agreed that the wording 'to explore possible options for intravenous antibiotics at home or in the community' would include switching intravenous antibiotics to intramuscular antibiotics.
27	Royal Pharmaceutical Society	Guideline	4	Table	First choice oral antibiotic - flucloxacillin 500mg four times a day: we suggest a dose range of 500mg-1g of flucloxacillin as first choice for oral treatment four times a day, when prescribing antibiotics for an infected leg ulcer in adults aged 18 years and over.	Thank you for your comment. The recommended dose for oral flucloxacillin has been amended to 500 mg to 1 g, four times a day.
28	Royal Pharmaceutical Society	Guideline	4	Table	Alternative first choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable: we suggest listing doxycycline ahead of macrolides due to their interactions and adverse effects when used in combination with medicines that prolong QTc interval.	Thank you for your comment. The antibiotic prescribing table has been amended, to list doxycycline above macrolides, although all antibiotics listed within a certain section of the table are equal options.
29	Royal Pharmaceutical Society	Guideline	5	Table	First choice intravenous antibiotics - flucloxacillin 500mg-2g four times a day: we suggest a dose range of 1g-2g of flucloxacillin for intravenous treatment four times a day, if unable to take oral antibiotics or severely unwell and guided by microbiological results.	Thank you for your comment. The recommended dose for intravenous flucloxacillin has been amended to 1 g to 2 g, four times a day.

30	British Infection Association	Draft visual summary and full guidance	1		<p>Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics if possible.</p> <p>This could be worded instead “Review intravenous antibiotics by 48 hours and switch to oral antibiotics.”</p> <p>It would be exceptional to require IV treatment beyond 48 hours so it is unclear this should be presumed in a guideline. Also more inclusion is needed of clarity as to when IV treatment can be avoided and if it is needed when OPAT might be appropriate.</p>	<p>Thank you for your comment. Please note that the prescribing table indicates when intravenous therapy is indicated (unable to take oral antibiotic or severely unwell) and recommendation 1.1.4 recommends reviewing IV antibiotics by 48 hours and switching to oral treatment if possible. We do not separate out community and hospital options as such and the decision about patient suitability for ambulatory care is a clinical one based upon individual patient factors. However, the committee have included suitable antibiotic options for ambulatory care in response to stakeholder comments.</p>
31	British Infection Association	Draft visual summary and full guidance	2		<p>We are concerned about the excessive use of gentamicin. These patients often have pre-existing nephropathy and are susceptible to further insults with nephrotoxic drugs and vestibular toxicity could be life-changing in these patients. Gentamicin monitoring is not always reliably performed. There is no clear evidence of this role for gentamicin use in the management of infected ulcers and it is likely the risks outweigh the benefits in this group of patients. A single dose of gentamicin for sepsis may be required but this would be as suggested in liaison with microbiology.</p>	<p>Thank you for your comment. The committee agreed that it was appropriate to include gentamicin as an option to add to flucloxacillin, co-amoxiclav or co-trimoxazole (with or without metronidazole) because broad antimicrobial cover may be necessary for some people. A footnote is included in the table to refer to the BNF for appropriate use in specific populations, including people with renal impairment and footnotes have been added to refer to the BNF for information on therapeutic drug monitoring and monitoring of patient parameters, specifically for gentamicin. The committee agreed that it may be appropriate to give a single dose of gentamicin in some people and therefore amended the antibiotic prescribing table to state that subsequent doses are ‘if required’. The committee discussed that it would not be appropriate to recommend seeking advice from a microbiologist for all people who are given gentamicin, particularly for a single dose.</p>
32	British Infection Association	Draft visual summary and full guidance	2		<p>Metronidazole- This is suggested as IV 500mg tds but has excellent oral bioavailability so more usual would be metronidazole po 400mg tds if required.</p>	<p>Thank you for your comment. Metronidazole is listed in the prescribing table under intravenous antibiotics for people who are unable to take oral antibiotics or are severely unwell and therefore require intravenous antibiotics. The rationale outlines the committee discussion that because metronidazole has good oral bioavailability, this could be given orally instead of intravenously if people were able to take oral antibiotics.</p>

33	British Infection Association	Draft visual summary and full guidance	2		Linezolid is only suggested IV but has excellent oral bioavailability so could be used orally with a reduction in expected side effects as no requirement for IV access.	Thank you for your comment. The antibiotic prescribing table has been amended to include the option for oral or intravenous route of administration for linezolid.
34	British Infection Association	Draft visual summary and full guidance	2		Erythromycin (in pregnancy) Does this mean rather than clarithromycin in pregnancy? It is not clear and could be misinterpreted to not give flucloxacillin.	Thank you for your comment. Please note that the heading for the table section is <i>Alternative first choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable</i> .
35	British Infection Association	Draft visual summary and full guidance	2		First choice intravenous antibiotic (if unable to take oral antibiotics or severely unwell): Flucloxacillin 500 mg to 2 g four times a day 500mg flucloxacillin is a sub-optimal dose for a severely unwell patient, 2g qds would be optimal (if normal renal function). It is not usual practice to use a lower dose than 2g qds unless patient has significant renal impairment.	Thank you for your comment. The recommended dose for intravenous flucloxacillin has been amended to 1 g to 2 g, four times a day.
36	British Infection Association	Draft visual summary and full guidance	2		Vancomycin -15 to 20 mg/kg two or three times a day)- this is not usually given three times a day. It is usually twice a day and usually a range of target levels is provided but not on this table. Also there is no mention of teicoplanin which is a commonly used alternative and allows OPD management.	Thank you for your comment. The committee agreed that it was appropriate to include the BNF dose which is two- or three-times daily administration of vancomycin. A footnote has been added to the antimicrobial prescribing table to refer to the BNF for therapeutic drug monitoring, where information can be found on the appropriate range of target levels. Teicoplanin has been added as an option for an antibiotic to be combined with another antibiotic if MRSA infection is suspected or confirmed.
37	British Infection Association	Draft visual summary and full guidance	2		Second choice oral antibiotics if symptoms or signs of infection worsening after 48 hours or no improvement after 7 days- this section needs to highlight the need to review the diagnosis and need for surgical intervention for example rather than a 'switch antibiotics' approach- it is more likely that a clinical review will alter an approach than that a failure would be due to resistance to flucloxacillin for example.	Thank you for your comment. The prescribing table in the choice of antibiotic section of the guideline just lists the antibiotic options. The reassessment and referral sections of the guideline cover requirements to review the diagnosis and possibly seek specialist advice which may other non-antimicrobial management strategies.

38	British Infection Association	Draft visual summary and full guidance	2		<p>'First choice oral antibiotic': Flucloxacillin 500 mg four times a day for 7 d Use of oral flucloxacillin doses up to 1g qds (although outside the licensed dose) is well established and is common practice in this country. This would provide optimal cover against both <i>Staph aureus</i> and group A Streptococci</p>	Thank you for your comment. The recommended dose for oral flucloxacillin has been amended to 500 mg to 1 g, four times a day.
39	All Wales Tissue Viability Nurse Forum	VS	2	10	<p>1.12- "Offer an antibiotic for adults with a leg ulcer only when there are symptoms or signs of infection" – do you need to be more specific here as many current guidelines recommend using topical antimicrobial dressings(AMD) for local infection for example Health Improvement Scotland (2015) , agreed that there was poor evidence to support topical AMD dressings , But they have produced a nationally agreed management algorithm which suggests that locally infected wounds should be treated with an AMD rather than antibiotics . This has also been reflected in the recent Evidence based procurement board advice statement from Wales in 2018 . Should this be considered for this guidance as this current statement may actually increase the use of antibiotics rather than decrease their use. It may be that if AMD dressings are not to be included in the guidance due to the lack of robust evidence then maybe the title of the document should be changed to leg ulcer infection - Antibiotic prescribing rather than antimicrobial prescribing .</p>	Thank you for your comment. The committee discussed topical antiseptics (including in dressings) and acknowledged that these are used in clinical practice to manage more minor, localised infections. However, the committee agreed that it could not make recommendations on the use of topical antiseptics for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline.
40	All Wales Tissue Viability Nurse Forum	VS	6	4	correct terminology should be " wound " rather than "sore" within the text	Thank you for your comment. The definition used is that used in the NHS .
41	All Wales Tissue Viability Nurse Forum	VS	6	6	leg ulcer infection Whilst it is accepted that many chronic leg ulcers will be colonized with bacteria that is not preventing healing , there is approximately 60% of chronic wounds that may	Thank you for your comment. The committee heard from an expert witness and discussed the presence of biofilms in infected leg ulcers. However, the committee agreed there was not sufficient evidence to make

					have a biofilm present and may present with clinical signs of infection , however this will not respond to antibiotic treatment and is best suited to regular debridement and topical AMD dressings (IWII 2015, Wounds UK BPS 2017).	recommendations concerning biofilms. The committee agreed that it could not make recommendations on the use of topical antiseptics (including in dressings) for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline.
42	All Wales Tissue Viability Nurse Forum	VS	7	15	As previously highlighted in clinical practice antibiotics are not always required if a patient has signs of local infection and often respond to AMD dressings – again there should be some deliberation/discussion on the difference between local infection and systemic infection .	Thank you for your comment. The committee discussed topical antiseptics and acknowledged that these are used in clinical practice to manage more minor, localised infections. However, the committee agreed that it could not make recommendations on the use of topical antiseptics for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline, where it states the inability to differentiate between a more localised or widespread infection in the evidence base or in clinical practice makes defining any place in therapy for topical antiseptics difficult.
43	All Wales Tissue Viability Nurse Forum	VS	8		Antiseptics – Whilst it is accepted that the evidence for AMDs is poor and the outcomes in many studies are healing rather than resolution in infection. It is felt that expert opinion was not given enough consideration – as stated before Scotland and Wales have produced some recommendations for topical antiseptics which should not be dismissed and may need to be considered when local infection may be present . There are also only silver and iodine included in the document when in fact there are several other AMDS such as PHMB/Honey Octeniline which are often used in clinical practice .	Thank you for your comment. The committee heard from an expert witness who discussed topical antiseptics. The committee acknowledged that these are used in clinical practice to manage more minor, localised infections. However, the committee agreed that it could not make recommendations on the use of topical antiseptics (including in dressings) for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline. Please note that the evidence review included honey but it was untested in people with an infected leg ulcer and found not to be effective in people with either an unclear leg ulcer infection status or in those with an uninfected leg ulcer. No evidence was found for the intervention of Octeniline / octenilin and infected leg ulcers and this was included within the search strategy. A study by Sibbald et al (2011) using polyhexamethylene biguanide dressing (PHMB) was excluded from the review by O'Meara due to incorrect study population.

44	All Wales Tissue Viability Nurse Forum	ER	6		In several places leg ulcers are referred to as a "sore" – consider changing the terminology to "Wound" rather than "Sore" as this is not a descriptor that is used commonly with Health Care Professionals (HCP).	Thank you for your comment. The definition used is that used in the NHS .
45	All Wales Tissue Viability Nurse Forum		6	7	Arterial ulcers also sometimes differ in appearance to venous leg ulcers as well as cause – e.g punched out in appearance etc 2nd paragraph – Guest et al 2015 (BMJ) has produced some more up to date prevalence figures on leg ulcer Etiology.	Thank you for your comment. The committee were aware that arterial leg ulcers can look different to venous leg ulcers when infection is not present, however we found no robust evidence on appearance, symptoms or signs of infected arterial ulcers. We have updated the text in the evidence review to include the Guest et al 2015 prevalence estimate data.
46	All Wales Tissue Viability Nurse Forum		6	17	It has been suggested that the terminology critical colonization not be used due to lack of specific definition and this has been replaced with " local infection" (International Wound Infection Institute (IWII) Wound infection in clinical practice. Wounds International 2016): There are also overt and covert signs of infection which are described as: Subtle signs of local infection: Hyper-granulation (excessive 'vascular' tissue) , Bleeding, friable granulation , Epithelial bridging and pocketing in granulation tissue , Wound breakdown and enlargement , Delayed wound healing beyond expectations , New or increasing pain , Increasing malodour Classic signs of local infection: Erythema , Local warmth , Swelling, Purulent discharge , Delayed wound healing beyond expectations , New or increasing pain , Increasing malodour	Thank you for your comment. The remit of this guidance does not cover the diagnosis of infected leg ulcer, the information given on appearance is general background only. Based on the committee's experience, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed to include possible symptoms and signs of an infected leg ulcer as redness or swelling spreading beyond the ulcer, localised warmth, increased pain or fever. <ul style="list-style-type: none"> The IWII (2016) wound-infection guidelines are not an eligible study type (Systematic review or RCT) for reference or inclusion in this guideline
47	British Geriatrics Society	Evidence review	4-5 table one	Table one	Question 1: This recommendation on duration of therapy is welcome however it will be a challenging change in practice because of the tendency of some prescribers to prescribe a 14 day course of treatment.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned
48	British Geriatrics Society	Evidence review	4-5 table one	Table one	Question 2: A national information campaign would be helpful	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned

49	British Geriatrics Society	Evidence review	4-5 table one	Table one	Question 3: The key issues for professionals are that a longer course is not superior to a shorter course and that re-evaluation of the wound is key.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned
50	British Geriatrics Society	Evidence review	9	21-24	Question 1: This recommendation on wound swabbing after cleaning the wound is welcome however it will be a challenging change in practice because of the tendency of some practitioners to swab before cleaning the wound.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned
51	British Geriatrics Society	Evidence review	9	21-24	Question 2: A national information campaign targeting nursing and medical staff would be helpful	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned
52	British Geriatrics Society	Evidence review	9	21-24	Question 3: The key issues for professionals are that wounds do become colonised and there is confusion regarding colonisation and critical colonisation.	Thank you for your response. Your comments will be considered by NICE where relevant support activity is being planned
53	British Geriatrics Society	Evidence review	12	1-2	Question 1: This recommendation on flucloxacillin dosage is welcome.	Thank you for your comment. The doses recommended for flucloxacillin have been amended in the final guideline based on the committee's discussion of stakeholder comments. The recommended doses of flucloxacillin are 500 mg to 1 g for oral administration and 1 g to 2 g for intravenous administration.
54	British Geriatrics Society	Evidence review	12	1-2	Question 2: It might be helpful to amend the BNF to ensure this information is provided.	Thank you for your comment.
55	British Geriatrics Society	Evidence review	19-20	13-26	Question 1: This information on adverse effects of antibiotics is welcome however clostridium risk is not covered. We recommend a section outlining C. difficile risk as older people are most likely to develop leg ulcers and are at greater risk of developing c. difficile	Thank you for your comment. The committee noted the risks with broad-spectrum antibiotics in particular, and therefore recommended the relatively narrow spectrum penicillin, flucloxacillin, first-line. There is detail in the rationale section of the guideline outlining that it is important to only use broad-spectrum antibiotics if first-choice antibiotics are not effective because, by disrupting normal flora, broad-spectrum antibiotics can leave people susceptible to harmful bacteria such as Clostridium difficile in community settings.
56	Royal College of Nursing	General			The Royal College of Nursing welcomes proposals to develop the guidelines on antimicrobial prescribing for leg ulcer infection.	Thank you for your comment.

					The RCN invited members who have experience and knowledge of this clinical area to review the draft guideline on its behalf. The comments below reflect the views of our reviewers.	
57	Royal College of Nursing	Guideline			The guidelines seem clear and well written. They are easy to follow.	Thank you for your comment.
58	Royal College of Nursing	Questions		1	Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why: Our reviewers are not aware of any particular challenges for the implementation of these guidelines.	Thank you for your comment on our question asked at consultation.
59	Royal College of Nursing	Questions		3	For the guideline: <ul style="list-style-type: none"> • Are there any recommendations that will be a significant change to practice or will be difficult to implement? If so, please give reasons why. • What are the key issues or learning points for professional groups? Key learning points for staff are the timing and choice of antibiotics and that there is insufficient evidence for the use of antiseptics in treatment of infected leg ulcers.	Thank you for your comment on our question asked at consultation.
60	Smith & Nephew UK Limited	Draft guidance visual summary	1	Left hand information box: Background	Please add a bullet highlighting that a minimum of 78% non-healing chronic wounds contain a biofilm Malone, M. <i>et al.</i> The prevalence of biofilms in chronic wounds: a systematic review and meta-analysis of published data. <i>J. Wound Care</i> 26 , 20–25 (2017).	Thank you for your comment. The visual summary includes key information from the guideline only. The committee heard from an expert witness and discussed the presence of biofilms in infected leg ulcers. However, the committee agreed there was not sufficient evidence to make recommendations concerning biofilms, therefore this information has not been included on the visual summary. <ul style="list-style-type: none"> • Malone et al 2017 – did not meet the criteria for inclusion based on population (chronic wounds, where it was unclear if the wound was infected) and intervention (this was an epidemiological study).

61	Smith & Nephew UK Limited	Draft guidance visual summary	1	Left hand information box: Signs and symptoms of infection	Can the committee please clarify if there is a threshold number of signs and symptoms of infection the clinician should observe to diagnose infection – i.e. is it >3 of these criteria or just one.	Thank you for your comment. The remit of this guidance does not cover the diagnosis of leg ulcer infection therefore the committee could not specify the number of signs or symptoms which indicate an infection, nor could it provide an exhaustive list. Based on the committee's experience, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed to include possible symptoms and signs of an infected leg ulcer as redness or swelling spreading beyond the ulcer, localised warmth, increased pain or fever.
62	Smith & Nephew UK Limited	Draft guidance visual summary	1	1 st Dark Grey box from left	<p>Please add a bullet here regarding the use of antimicrobial dressings such as “Consider a local antimicrobial (antiseptic) dressing to manage bioburden at the site of infection (as per guidance documents guidelines - Ayello 2012, Gottrup 2013, Cooper 2018, Lipsky 2016)”</p> <p>Ayello, E. A. <i>et al.</i> International consensus. Appropriate use of silver dressings in wounds. An expert working group consensus. <i>Wounds Int.</i> 1–24 (2012).</p> <p>Gottrup, F. <i>et al.</i> EWMA document: Antimicrobials and non-healing wounds. Evidence, controversies and suggestions. <i>J. Wound Care</i> 22, S1-89 (2013).</p> <p>Cooper, R. & Kirketerp-Møller, K. Non-antibiotic antimicrobial interventions and antimicrobial stewardship in wound care. <i>J. Wound Care</i> 27, 355–377 (2018).</p> <p>Lipsky, B. A. <i>et al.</i> Antimicrobial stewardship in wound care: a Position Paper from the British Society for Antimicrobial Chemotherapy and European Wound Management Association. <i>J. Antimicrob.</i></p>	<p>Thank you for your comment. The committee discussed topical antiseptics (including in dressings) and acknowledged that these are used in clinical practice to manage more minor, localised infections. However, the committee agreed that it could not make recommendations on the use of topical antiseptics for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline.</p> <ul style="list-style-type: none"> • Ayello et al 2012 - did not meet the criteria for inclusion based on study type • Gottrup et al 2013 – did not meet the criteria for inclusion based on study type • Cooper et al 2018 – did not meet the criteria for inclusion based on study type. • Lipsky et al 2016 – did not meet the criteria for inclusion based on study type

					<i>Chemother.</i> 71 , 3026–3035 (2016).	
63	Smith & Nephew UK Limited	Draft guidance visual summary	1	2 nd Dark Grey box from left	<p>Antibiotic failure may also be as a result of biofilm presence (Schultz 2017) – therefore please add additional bullet to reflect this. “Also consider biofilm presence and treatment interventions” Schultz 2017”</p> <p>Schultz, G. <i>et al.</i> Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds. <i>Wound Repair Regen.</i> 25, 744–757 (2017).</p>	<p>Thank you for your comment. The visual summary includes key information from the guideline only. The committee heard from an expert witness and discussed the presence of biofilms in infected leg ulcers. However, the committee agreed there was not sufficient evidence to make recommendations concerning biofilms, therefore this information has not been included on the visual summary.</p> <ul style="list-style-type: none"> • Schulz et al 2017 - did not meet the criteria for inclusion based on study type.
64	Smith & Nephew UK Limited	Draft guidance visual summary	1	2 nd white box from top	<p>If infection not resolving or symptoms worsening/ recurrent infections this may be due to ineffective treatment as a result of biofilm presence. Antibiotics do not work against bacteria in this state therefore alternative multifunctional topical treatments should be considered such as Debridement and Topical antiseptics effective against biofilms (Schultz 2017, Malone 2017)</p> <p>Please add an additional bullet to this box stating “If recurrent infections consider biofilm and adjust therapy to follow biofilm based wound care including debridement and antiseptic dressings effective against biofilms” (Schultz 2017, Malone 2017)</p> <p>Schultz, G. <i>et al.</i> Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds. <i>Wound Repair Regen.</i> 25, 744–757 (2017).</p> <p>Malone, M. <i>et al.</i> Effect of cadexomer iodine on the microbial load and diversity of chronic non-healing diabetic foot ulcers complicated by biofilm in vivo. <i>J. Antimicrob. Chemother.</i> 72, 2093–2101 (2017).</p>	<p>Thank you for your comment. The visual summary includes key information from the guideline only. The committee heard from an expert witness and discussed the presence of biofilms in infected leg ulcers. However, the committee agreed there was not sufficient evidence to make recommendations concerning biofilms, therefore this information has not been included on the visual summary.</p> <ul style="list-style-type: none"> • Schulz et al 2017 - did not meet the criteria for inclusion based on study type. • Malone et al 2017 – did not meet the criteria for inclusion based on study type and study population.

65	Smith & Nephew UK Limited	Draft guidance visual summary	2		<p>The committee have omitted to include topical non-antibiotic antimicrobial therapies (such as antimicrobial dressings) for use in managing bioburden/ local infection in VLU's, even though their use is standard practice where appropriate with wound care professionals. The evidence review performed by NICE as part of this guideline development also highlights there are some products such as Cadexomer iodine with clear evidence to support faster healing rates in VLU including a positive Cochrane review (O'Meara 2014) which as a result have been incorporated into VLU treatment guidelines in the Netherlands (Maessen Visch 2014) .</p> <p>We feel strongly that non-antibiotic antimicrobials (such as antiseptic dressings) are an essential part of VLU treatment and should be included in the guidelines including the addition of a table reflecting antimicrobial dressings supported by evidence in the review to guide wound care clinicians appropriately.</p> <p>O'Meara, S. <i>et al.</i> Antibiotics and antiseptics for venous leg ulcers. <i>Cochrane database Syst. Rev.</i> 1, CD003557 (2014).</p> <p>Maessen-Visch, M. B. & de Roos, K.-P. Dutch Venous Ulcer guideline update. <i>Phlebology</i> 29, 153–156 (2014).</p>	<p>Thank you for your comment. The committee discussed topical antiseptics (including in dressings) and acknowledged that these are used in clinical practice to manage more minor, localised infections of leg ulcers. However, the committee agreed that it could not make recommendations on the use of topical antiseptics for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline.</p> <ul style="list-style-type: none"> • O'Meara et al 2014 – is included in the evidence review for this guideline. • Maessen-Visch et al 2014 – did not meet the criteria for inclusion based on study type
66	Smith & Nephew UK Limited	Draft guideline full document	2	10/11	<p>The recommendation in 1.1.2 states “Offer an antibiotic for adults with a leg ulcer only when there are symptoms or signs of infection.” Can the panel clarify the specific number of signs and symptoms required to be present to determine a clinical infection (i.e. >3 criteria) as this is debated amongst wound care experts in the published literature (Sibbald 2007, Gago 2008, Woo 2009, Bui 2019)</p>	<p>Thank you for your comment. The remit of this guidance does not cover the diagnosis of leg ulcer infection therefore the committee could not specify the number of signs or symptoms which indicate an infection, nor could it provide an exhaustive list. Based on the committee's experience, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed to include possible symptoms and signs of an infected leg ulcer as redness or swelling spreading</p>

				<p>Sibbald, R. G. et al. Bacteriology, Inflammation, and Healing. <i>Adv. Skin Wound Care</i> 20, 549–558 (2007).</p> <p>Gago, M. et al. A Comparison of Three Silver-containing Dressings in the Treatment of Infected, Chronic Wounds. <i>Wounds</i> 20, 2–7 (2008).</p> <p>Woo, K. Y. & Sibbald, R. G. A cross-sectional validation study of using NERDS and STONEES to assess bacterial burden. <i>Ostomy. Wound. Manage.</i> 55, 40–8 (2009)</p> <p>Bui, U. T., Finlayson, K. & Edwards, H. The diagnosis of infection in chronic leg ulcers: A narrative review on clinical practice. <i>Int. Wound J.</i> 1–20 (2019).</p>	<p>beyond the ulcer, localised warmth, increased pain or fever.</p> <ul style="list-style-type: none"> • Sibbald et al 2007 – did not meet the criteria for inclusion based on study type and intervention. • Gago et al 2007 - did not meet the criteria for inclusion based on study type and intervention. • Woo et al 2009 – did not meet the criteria for inclusion based on study type, intervention and study population. • Bui et al 2019 – did not meet the criteria for inclusion based on intervention.
67	Smith & Nephew UK Limited	Draft guideline full document	2	15/16 <p>The document refers only to antibiotic treatment recommendations. Multiple consensus documents highlight the role for non-antibiotic antimicrobials against high bioburden and localised infection in chronic wounds (Ayello 2012, Gottrup 2013, Lipsky 2016, Cooper 2018). Please consider inclusion of these interventions in the treatment recommendations.</p> <p>Ayello, E. A. <i>et al.</i> International consensus. Appropriate use of silver dressings in wounds. An expert working group consensus. <i>Wounds Int.</i> 1–24 (2012).</p> <p>Gottrup, F. <i>et al.</i> EWMA document: Antimicrobials and non-healing wounds. Evidence, controversies and suggestions. <i>J. Wound Care</i> 22, S1-89 (2013).</p> <p>Cooper, R. & Kirketerp-Møller, K. Non-antibiotic antimicrobial interventions and antimicrobial stewardship in wound care. <i>J. Wound Care</i> 27,</p>	<p>Thank you for your comment. The committee discussed topical antiseptics and acknowledged that these are used in clinical practice to manage more minor, localised infections. However, the committee agreed that it could not make recommendations on the use of topical antiseptics for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline.</p> <ul style="list-style-type: none"> • Ayello et al 2012 - did not meet the criteria for inclusion based on study type. • Gottrup et al 2013 – did not meet the criteria for inclusion based on study type. • Cooper et al 2018 – did not meet the criteria for inclusion based on study type. • Lipsky et al 2016 – did not meet the criteria for inclusion based on study type.

					355–377 (2018). Lipsky, B. A. <i>et al.</i> Antimicrobial stewardship in wound care: a Position Paper from the British Society for Antimicrobial Chemotherapy and European Wound Management Association. <i>J. Antimicrob. Chemother.</i> 71 , 3026–3035 (2016).	
68	Smith & Nephew UK Limited		2	15/16	The treatment section 1.1, does not detail any additional protocol areas such as cleansing and/ or debridement to remove necrotic or sloughy tissue, a nidus for bacteria in chronic wounds – this should be clearly part of the treatment plan providing effective wound bed preparation (Schultz 2003, Moore 2019) Schultz, G. S. <i>et al.</i> Wound bed preparation: a systematic approach to wound management. <i>Wound Repair Regen.</i> 11 Suppl 1, S1-28 (2003). Moore, Z. <i>et al.</i> TIME CDST: an updated tool to address the current challenges in wound care. <i>J. Wound Care</i> 28, 154–161 (2019)	Thank you for your comment. Please note that the guideline only covers the antimicrobial management of people with infected leg ulcers; it does not cover the general management of leg ulcers. <ul style="list-style-type: none"> • Schulz et al 2003 - did not meet the criteria for inclusion based on study type and intervention. • Moore et al 2019 - did not meet the criteria for inclusion based on study type and intervention.
69	Smith & Nephew UK Limited	Draft guideline full document	3	6	After the section stating “If symptoms of infection worsen or do not improve over 2-3 days” an additional bullet point should be added to raise the important issue of potential biofilm Please add an additional bullet to this box stating “If recurrent infections consider biofilm and adjust therapy to follow biofilm based wound care including debridement and antiseptic dressings effective against biofilms” (Schultz 2017, Malone 2017) Schultz, G. <i>et al.</i> Consensus guidelines for the identification and treatment of biofilms in chronic nonhealing wounds. <i>Wound</i>	Thank you for your comment. The committee heard from an expert witness and discussed the presence of biofilms in infected leg ulcers. However, the committee agreed there was not sufficient evidence to make recommendations concerning biofilms. <ul style="list-style-type: none"> • Schulz et al 2017 - did not meet the criteria for inclusion based on study type. • Malone et al 2017 – did not meet the criteria for inclusion based on study type and study population.

					<p><i>Repair Regen.</i> 25, 744–757 (2017).</p> <p>Malone, M. <i>et al.</i> Effect of cadexomer iodine on the microbial load and diversity of chronic non-healing diabetic foot ulcers complicated by biofilm in vivo. <i>J. Antimicrob. Chemother.</i> 72, 2093–2101 (2017).</p>	
70	Smith & Nephew UK Limited	Draft guideline full document	6	1	<p>After table 1 Antibiotics for adults over 18 years old, an additional table should be added for topical antiseptic dressings.</p> <p>The document refers only to antibiotic treatment recommendations. Multiple consensus documents highlight the role for non-antibiotic antimicrobials against high bioburden and localised infection in chronic wounds (Ayello 2012, Gottrup 2013, Lipsky 2016, Cooper 2018)</p> <p>Ayello, E. A. <i>et al.</i> International consensus. Appropriate use of silver dressings in wounds. An expert working group consensus. <i>Wounds Int.</i> 1–24 (2012).</p> <p>Gottrup, F. <i>et al.</i> EWMA document: Antimicrobials and non-healing wounds. Evidence, controversies and suggestions. <i>J. Wound Care</i> 22, S1-89 (2013).</p> <p>Cooper, R. & Kirketerp-Møller, K. Non-antibiotic antimicrobial interventions and antimicrobial stewardship in wound care. <i>J. Wound Care</i> 27, 355–377 (2018).</p> <p>Lipsky, B. A. <i>et al.</i> Antimicrobial stewardship in wound care: a Position Paper from the British Society for Antimicrobial Chemotherapy and European Wound Management Association. <i>J. Antimicrob. Chemother.</i> 71, 3026–3035 (2016).</p>	<p>Thank you for your comment. The committee discussed topical antiseptics (including in dressings) and acknowledged that these are used in clinical practice to manage more minor, localised infections. However, the committee agreed that it could not make recommendations on the use of topical antiseptics for treating leg ulcers because of the limitations of the evidence and the unclear benefit. This discussion is included in the rationale section of the guideline.</p> <ul style="list-style-type: none"> • Ayello et al 2012 - did not meet the criteria for inclusion based on study type. • Gottrup et al 2013 – did not meet the criteria for inclusion based on study type. • Cooper et al 2018 – did not meet the criteria for inclusion based on study type. • Lipsky et al 2016 – did not meet the criteria for inclusion based on study type.

71	Smith & Nephew UK Limited	Draft guideline full document	8	7/8	In the rationale section, the committee state that 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' (one being reliant on laboratory growth and the other stating that inflammation was the only symptom required). However earlier in the document the committee recommendations do not state the number of clinical signs of infection to present to diagnose infection either. Please review this statement a) in light of this discrepancy between the number of criteria required to diagnose infection and b) clarify if the evidence pertains to reduction of infection/specific bacteria or faster healing rates with cadexomer iodine.	Thank you for your comment. We do not consider this information about the limitations of individual studies to be a discrepancy. It would be inappropriate not to report study limitations in relation to defining characteristics of the population of interest (people with an infected leg ulcer). a) One RCT used criteria for infection that could also be associated with wound colonisation rather than wound infection, and the second RCT only reported a broad term of inflammation (undefined) rather than specifying the presence of the cardinal signs of inflammation (dolor, calor, rubor, tumor, functio laesa); or further symptoms or signs of infection. Please note the remit of the guideline does not cover the diagnosis of leg ulcer infection. b) The evidence review document clearly sets out the outcomes and effects for cadexomer iodine in people with infected leg ulcer (see the evidence review)
72	Smith & Nephew UK Limited	Draft guideline full document Evidence review	8	18-20	Please re-evaluate the statement about adverse events during cadexomer iodine use. This statement is based on X studies only (as highlighted in the evidence review pX LXX), when literature searches clearly report over 25 RCT's highlighting effective use of Cadexomer iodine in VLU's. In addition We would like to draw the committee to the in-market post market surveillance data for Cadexomer iodine products which highlight a 1:169,477 chance of a sensitisation reaction from data analysed from 2006-2019.* The statement around AI's suggest they consisted of minor local skin irritation, rash and pain, in addition this adverse event data is highlighted in the evidence review (page 13/ detailed in comment 14 below) as low or very low quality.	Thank you for your comment. The evidence review identified only 1 RCT which examined the use of cadexomer iodine in the population of interest (people with an infected leg ulcer) extrapolating adverse effect data from other populations may not be appropriate due to changes in infected leg ulcer tissue, although this is uncertain. It is unclear if the post market surveillance data referred to is in the correct population of interest (people with an infected leg ulcer). It is incorrect that based on the strength of GRADE evidence alone one outcome should take priority over another or be judged as more important than another. GRADE is designed to facilitate assessment of the strength of evidence for each individual outcome only. In this case both adverse effects and clinical effectiveness outcomes were judged by the committee to be of equal critical importance (see GRADE table 4 in the evidence review).

					<p>In contrast the statement around the benefits of Cadexomer iodine in relation to faster wound healing highlight the benefits over the risks of using antimicrobials appropriately, helping to remove the barriers to healing in these wounds. Furthermore this data was classified as moderate level of evidence suggesting this should be valued and iterated more strongly than the adverse events statement. The possible side effects of antibiotics listed (p19-20) can be quite severe, however these treatments are still included.</p> <p>*PMS data 2006-2012 calculated from available sales figures 2012-2019 therefore is worst case scenario.</p>	<p>The reporting of the evidence is complete in relation to what information was available for each intervention. There was no information presented in the included studies for adverse effects of antibiotics, whereas there was information for adverse effects presented for cadexomer iodine (please see the GRADE tables in the evidence review for specific details). As no such information was available for antibiotics we have included in the medicines safety section of the guideline (see page 19 of the guideline) additional published information on the adverse effects of antibiotics recommended in the guideline.</p>
73	Smith & Nephew UK Limited	Draft guideline full document	8	23	<p>The committee state they cannot make any recommendations for treatment of infected leg ulcers with antiseptics due to the limited evidence. We would like to draw the committee's attention to the systematic review and meta-analysis performed by O'Meara 2014 which highlights the evidence for faster rates of healing in VLU's using the topical cadexomer iodine antiseptic dressing. In contrast this document also reviewed the evidence for antibiotic use in VLU's and suggests no between-group differences were detected in terms of complete healing for the following comparisons: antibiotics given according to antibiogram versus usual care; ciprofloxacin versus standard care/placebo; trimethoprim versus placebo; ciprofloxacin versus trimethoprim; and amoxicillin versus topical povidone-iodine. This evidence as to the limitations of antibiotics is not discussed in the review.</p> <p>There have been a plethora of recent publications and guidance for the use of</p>	<p>Thank you for your comment. The evidence review, which included the O'Meara et al 2014 study, identified only 1 RCT which examined the use of cadexomer iodine in the population of interest (people with an infected leg ulcer). Extrapolating effectiveness data from other populations (people in whom leg ulcer infection status was uncertain or those who were uninfected) may not be appropriate due to changes in infected leg ulcer tissue, although this is uncertain. The antibiotic studies were limited by similar issues - only 1 RCT was conducted in the population of interest, this is noted in the guideline by the committee. As no safety information was available for antibiotics we have included in the medicines safety section of the guideline additional published information on the side effects and adverse effects of antibiotics recommended in the guideline.</p>

					antimicrobials in wound care which should be considered (see comment 2, 7 and 10) by the panel and the bias in this document towards antibiotics re-addressed particularly in light of the current national campaign to reduce antibiotic use.	
74	Smith & Nephew UK Limited	Evidence review	13	3-6 37-43	The minor adverse effects detailed in p 13 (page numbers opposite) were either found to be non-significant and of very low quality evidence across the 3 studies detailed. As detailed in comment 12 above, the beneficial effects of interventions such as Cadexomer iodine in infected VLU's far outweigh these minor issues. The severity of this data has been mis-represented – please re-address these statements.	Thank you for your comment. Please note that in the population of interest (people with an infected leg ulcer) 1 RCT was identified and the outcomes did not include resolution of infection which is the purpose of this guideline. The main outcomes reported for this study (see evidence review) were pain and mean percentage change in ulcer area. The study is confounded for the outcome of resolution of infection as, as stated in footnotes to GRADE table 4, other treatments including antibiotics were allowed.
75	Smith & Nephew UK Limited	Committee members			The reviewer has noted the lack of any wound care specialists or consultation with wound care bodies such as EWMA or TVS on the panel of experts forming these guidelines. This poses a potential mismatch between actual and recommended practice and should be addressed in second round reviews.	Thank you for your comment. Five expert reviewers with experience in wound management reviewed the draft guideline and provided comments which were considered by the committee. The committee also heard evidence from an expert witness, with experience as a nurse consultant in tissue viability who is co-lead of the limb ulcer pathway within the national wound care strategy programme. Details of the evidence heard from the expert witness can be found in the project documents tab of the guideline documents.
76	Smith & Nephew UK Limited	Guidelines Evidence review Visual Summary			There is limited information provided to assess whether or not a leg ulcer is infected, particularly as this is the criteria on which these guidelines are based. Indeed, the evidence review states on page 6 lines 27 and 28 the difficulty of diagnosing infection due to the high prevalence of colonization and the potential lack of classical signs and symptoms of infection. However, it does not provide any substantial guidance on this exact issue. While it does mention proposed signs and symptoms of critical colonization as described in O'Meara et al 2014 (based on Gardner SE <i>et al</i> 2001 and Cutting K <i>et al</i> 2004) on page 6 lines 17-	Thank you for your comment. The guideline states that it does not cover the diagnosis of infected leg ulcers. Please note that no recommendation has been made by the committee on the diagnosis of infected leg ulcer as diagnosis and assessment are out-of-scope for this guideline. The information given on page 2 of the evidence review is as part of the background information to the evidence review only. Based on the committee's experience, stakeholder comments, and the experience of expert reviewers and an expert witness, the committee agreed that the symptoms and signs of infection may include redness or swelling spreading beyond the ulcer, localised warmth,

				<p>21, the guidelines fall short of making a recommendation on how these wounds should be assessed. Furthermore, despite this inclusion in the evidence review, the signs and symptoms listed in the guidelines (page 2 lines 10-11) and visual summary come from a third source, the 2010 SIGN guidelines on management of chronic venous leg ulcers, with minimal reference material to support this list of signs and symptoms. A rationale as to why these signs and symptoms were chosen would also be of interest. We propose the addition of a section on diagnostics to improve wound assessment.</p> <p>O'Meara and others have consistently acknowledged that clinical signs and symptoms of infection can underestimate the presence of significant bacterial load (Reddy M <i>et al</i> JAMA 2012). Indeed, a meta-analysis of 1056 chronic wounds, including leg ulcers, indicated that, of the clinical signs and symptoms of infection, only pain was an accurate indicator of infection; all other classic signs and symptoms had no predictive value (Reddy M <i>et al</i> JAMA 2012). Similarly, Denis et al reported that a clinician's subjective judgement of infection alone was not predictive of bacterial load, in a study of 200 leg ulcers (Denis LA <i>et al</i> BJS 2010). In a recently published cohort study of chronic wounds (89% of which were venous leg ulcers), clinical signs and symptoms alone had an accuracy of only 26% in detecting wounds containing greater than 10⁴ CFU/g of bacteria (Serena T <i>et al</i> J Wound Care 2019). This study suggests fluorescence imaging as a potential addition to clinical signs and symptoms in assessing wounds for the presence of these concerning bacterial loads. Combined with clinical signs and symptoms, fluorescence imaging increased the accuracy</p>	<p>increased pain or fever. This has been reflected in the final guidance.</p> <ul style="list-style-type: none"> • O'Meara et al 2014 – is included in the evidence review for this guideline. • Reddy et al 2012 – did not meet the criteria for inclusion based on intervention. • Denis et al 2010 – did not meet the criteria for inclusion based on intervention and study type. • Serena et al 2019 – did not meet the criteria for inclusion based on intervention, study type and population. • Hurley et al 2019 - did not meet the criteria for inclusion based on intervention, study type and population.
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				<p>of assessment for bacterial presence ($>10^4$ CFU/g) to 74% (Serena et al J Wound Care 2019), a 3-fold increase over clinical signs and symptoms alone. A separate, independent cohort study of chronic wounds examined correlation between bacterial fluorescence and bacterial load (Hurley <i>et al</i> J Wound Care 2019). The authors reported similar diagnostic measures for fluorescence imaging correlating with bacterial loads greater than 10^4 CFU/g, including an accuracy of 96% and sensitivity of 100% (Hurley <i>et al</i> J Wound Care 2019). While these authors did not report accuracy measures for clinical signs and symptoms alone, they reported that 95.4% of swabs were positive for bacteria, while only 21% of patients displayed overt clinical signs and symptoms of infection (Hurley <i>et al</i> J Wound Care 2019). Serena et al also investigated the change in standard of care following the additional information gained from the fluorescence imaging and found that in 73% of study wounds fluorescence imaging changed the clinician's treatment plan for the patient including changes to the prescription of antibiotics and/or antimicrobial dressings (Serena <i>et al</i> J Wound Care 2019).</p> <p>Together, these studies position fluorescence imaging as a useful tool to assess leg ulcers for the presence of bacteria at moderate to heavy loads. We would note that these studies were published in June/July 2019, after initial draft of these NICE guidelines was formulated, however their evidence highlighting the benefits of fluorescence imaging information should not be overlooked in wound assessment. We suggest that in the guidelines, evidence review and visual summary, additional information on the assessment of wound infection is needed, potentially by</p>	
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					including the option of fluorescence imaging to the listed symptoms of infection.	
77	Smith & Nephew UK Limited	Guidelines Visual Summary	9	21-24	It is concerning that the guidelines appear to only suggest microbiological testing if there is a worsening infection or no improvement after antibiotics. As clearly described on page 7, lines 20-27 of the evidence review, narrow spectrum antibiotics should be considered the first-choice intervention followed by more broad-spectrum antibiotics only as a second choice. By appearing to limit microbiological testing to only after the initial prescribed antibiotic is found to be ineffective, the result would be a delay in the identification of the bacterial species and the prescription of more targeted therapies. This may also result in an increase in potentially unnecessary or ineffective use of first line antibiotics. We recommend that both the guidelines and visual representation is altered to include microbiological testing at an earlier stage or include a rationale for its inclusion only at this later stage.	Thank you for your comment. The committee discussed microbiological testing and agreed to amend the guideline to be clearer that microbiological testing should not be routinely performed for people with a leg ulcer. This is because bacterial growth from a sample is likely regardless of infection status which could lead to inappropriate antibiotic prescribing. The committee agreed that if the leg ulcer is clinical infected, the most likely causative organism is <i>Staphylococcus aureus</i> which would be covered by empirical treatment with flucloxacillin. They went on to agree that although microbiological sampling is not required at initial presentation, it is appropriate to consider microbiological sampling for an infected leg ulcer that is worsening or not improved following a completed course of antibiotics. This discussion is included in the rationale section of the guideline.
78	Smith & Nephew UK Limited				While the Levine technique of swabbing continues to be the most common method of sampling a wound for microbiology, evidence suggests that this method of sampling can result in less accurate culture results compared to tissue samples (Gardner SE et al 2006 Wound Repair Regen). Recently, fluorescence imaging has emerged as a diagnostic tool to guide sampling to areas of moderate to heavy loads of bacteria (Rennie MY et al J Wound Care 2017). In this cohort study, 60 wounds, including 14 venous leg ulcers, were sampled in areas of red fluorescence found under fluorescence imaging. The authors reported a 100% positive predicted value for bacterial loads above 104 CFU/g or moderate to heavy, essentially eliminating false negative	Thank you for your comment. The guideline states that it does not cover the diagnosis of infected leg ulcers, and therefore recommendations for specific sampling techniques have not been made. The reference to the Levine technique has been removed from the committee discussion on reassessment. The committee agreed that national guidance, such as 'Public Health England guidance on venous leg ulcers: infection diagnosis and microbiological investigation guide for primary care' should be referred to when performing microbiological sampling and this has been reflected in the committee discussion. <ul style="list-style-type: none"> • Gardener et al 2006 – did not meet the criteria for inclusion based on study type and intervention. • Rennie et al 2017 – did not meet the criteria for inclusion based on study type and intervention.

microbiological swabs (Rennie MY et al J Wound Care 2017). This 100% positive predictive value was recently confirmed by Serena T et al (2019) in a 19-patient cohort study of predominately (89%) venous leg ulcers. Similarly, Hurley et al reported that swab sampling in areas of bacterial fluorescence had a positive predictive value of 95.4% for detecting bacterial load (Hurley CM et al JWC 2019). Furthermore, Hurley et al highlights the use of fluorescence imaging in guiding the location of the swab and suggests the swab may have been a false negative using standard swabbing techniques. A further, albeit limited, study compared Levine technique swabbing to fluorescence guided swabbing of chronic wounds and reported that fluorescence guided swabbing was 50% more accurate than Levine technique in detecting moderate to heavy loads of bacteria (Ottolino-Perry K et al IWJ 2017).

Superior to the Levine technique, the use of biopsy or tissue sampling has been shown to improve the accuracy of culture results. In a study of 395 diabetic foot ulcers, a comparison of the Levine technique compared to tissue samples obtained by curettage or scalpel found that in 58% of wounds there was a difference in pathogens between these two sampling methods, and that the tissue sample detected more pathogens with few contaminants (Nelson A et al BMJ 2018). While this study examines a different wound population, the idea of tissue sampling may well to applied to leg ulcers as well and may further be enhanced by guiding fluorescence sampling.

As the Levine technique is listed as an alternative method of swabbing in the guidelines, we suggest adding fluorescence guided swabbing or tissue sampling as an

- [Serena et al 2019](#) – did not meet the criteria for inclusion based on intervention, study type and population.
- [Hurley et al 2019](#) - did not meet the criteria for inclusion based on intervention, study type and population.
- [Ottolino-Perry et al 2017](#) – did not meet the criteria for inclusion based on study type, intervention and population.
- [Nelson et al 2018](#) - did not meet the criteria for inclusion based on study type, intervention and population.

					equally alternative method of sampling the wound. We also suggest implementing this recommendation on the visual representation in the microbiological sampling section by suggesting fluorescence guidance in addition to taking the sample deep within the wound.	
79	NHS England				Thanks for the opportunity to comment on this. While there is a cross-reference to management of chronic venous leg ulcers guidance at the end of the document I think it would also be worth stating near the beginning that many people who have chronic leg ulcers above the inside of the ankle may be suitable for curative treatment of their ulcers by surgical treatment of their underlying varicose veins.	Thank you for your comment. A link to the SIGN guideline on chronic venous leg ulcers is included upfront in the guideline, in the overview page, directing readers to further information. This is intended to be a clear link to information such as surgical treatment for varicose veins.
80	NHS England	Guideline			We welcome this guideline as an attempt to improve antibiotic stewardship. In primary care, a lot of unnecessary swabs are taken which then show "mixed growth". There is then a dilemma as to whether to treat with antibiotics. This guideline is very useful in addressing this. There may be some resistance/need for changing current practice, but appears a pragmatic approach.	Thank you for your comment on our question asked at consultation.
81	NHS England	Guideline	5	Table	In primary care, we generally discourage the prescribing of co-amoxiclav and co-trimoxazole that are recommended for second line use. You may need to insert a qualifier to seek local microbiology laboratory advice as there are some joint formularies that no longer contain either of these two antibiotics.	Thank you for your comment. The committee discussed your comment, however no changes were made to recommendations for co-amoxiclav or co-trimoxazole (in penicillin allergy) as second choice oral antibiotics. The committee agreed that the presence of gram-negative organisms may be a reason why an infected leg ulcer is not healing and that these antibiotics are active against gram-negative organisms and therefore are appropriate second-choice antibiotics.
82	NHS England	Guideline	1	10	Advises to offer antibiotics when there are symptoms or signs of infection. It would be helpful to list the symptoms and signs.	Thank you for your comment. The committee agreed, based on their experience, stakeholder comments, and the experience of expert reviewers and an expert witness that symptoms and signs of infection may include redness or swelling spreading beyond the ulcer, localised warmth, increased pain or fever, which is included in the

						recommendations. However, the committee agreed that this wasn't an exhaustive list and that identifying symptoms and signs of a leg ulcer would also rely on clinical judgement.
83	NHS England	Guideline	4	17 onwards	When the guidance says "and/or" gentamicin, or "with or without" is there any guidance as to when a combination should be used and when not? This does not seem to be explained on P11 line 27 to page 12 line 27 line 8.	Thank you for your comment. The required combination of antibiotics would be an individualised decision based on clinical judgement.