Managing Common Infections

Cellulitis and erysipelas: antimicrobial prescribing

Stakeholder comments table

17/04/2019 – 10/05/2019

ID	Organisation	Document	Page No.	Line No.	Comments	Developers Response
1	Association of British Clinical Diabetologists				There needs to be more clarity that cellulitis & erysipelas are often harbingers of diabetes, so a high clinical level of suspicion should be maintained to look for un diagnosed pre or overt diabetes	Thank you for your comment. It is outside the scope of the guideline to make a recommendation about diagnosing the presence of specific comorbid conditions. We have added a new recommendation about managing any underlying conditions, including diabetes, that may predispose people to cellulitis or erysipelas, see recommendation 1.1.7
2	Association of British Clinical Diabetologists				If there is pre existing diabetes then glycaemic control should be optimized concurrently with anti microbial therapy	Thank you for your comment. The committee have added a new recommendation about managing any underlying conditions, including diabetes, that may predispose people to cellulitis or erysipelas, see recommendation 1.1.7
3	Association of British Clinical Diabetologists				Consider compartment syndrome if increasing pain and or failure to improve	Thank you for your comment. The evidence review found no outcomes reported for compartment syndrome as a serious sequalae of cellulitis, the committee agreed this would be a rare occurrence and did not wish to add compartment syndrome to the recommendation.
4	Association of British Clinical Diabetologists				Withhold proton pump inhibitor whilst on antibiotics and substitute with ranitidine if necessary	Thank you for your comment. The committee noted that this may be appropriate for those in whom *Clostridium difficile* may be a concern. However this is likely to be only a very small part of the guideline population of all people with cellulitis. Please note there will be a separate antimicrobial prescribing guideline on the management of *Clostridium difficile* infection.
5	Association of British Clinical Diabetologists				Ensure good skin hygiene both peri and post resolution of cellulitis (clean, moisturized skin)	Thank you for your comment. The evidence review did not include looking for evidence for skin hygiene interventions for cellulitis and erysipelas. Therefore, the

						committee could not make a recommendation on these interventions.
6	Association of British Clinical Diabetologists				Avoid quinolones in those with pre existing diabetes as increased risk of tendon rupture	Thank you for your comment. Please note that the guideline does not recommend the use of quinolones in the management of cellulitis and erysipelas.
7	Association of British Clinical Diabetologists				In pts with diabetes higher doses of flucloxacillin are regularly needed – 1-2 grams qds for 5-10 days depending on severity	Thank you for your comment. The committee discussed dosing of flucloxacillin and have recommended 500 mg to 1 g orally four times a day **or** 1 to 2 g four times a day IV in line with your comment. The evidence review found no evidence for higher doses specifically for people with diabetes.
8	British Infection Association	Table 1	Page 4	9	'First choice oral antibiotic': Flucloxacillin 500 mg four times a day for 7 days 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 *Staph aureus* and group A Streptococci	Thank you for your response to our question asked at consultation. The committee discussed dosing of flucloxacillin and have recommended 500 mg to 1 g four times a day orally or 1 to 2 g four times a day IV in line with your comment.
9	British Infection Association	Table 1 and Table 2	Page 4 and page 7	9 and bottom of page 6 and top of page 7	'Alternative choice intravenous antibiotics for penicillin allergy, if flucloxacillin unsuitable, or if infection near the eyes or nose4 (consider seeking specialist advice). Antibiotics may be combined if susceptibility or sepsis a concern': - This section needs further clarity. As it is currently, it is not clear when to use which antibiotic - A large number of our members were concerned at the inclusion of gentamicin in these tables. Gentamicin should never be used as a single agent for skin/soft tissue infection as it has no streptococcal cover and is not generally used for cellulitis/erysipelas in combination (though may be in e.g. necrotising fasciitis) - Teicoplanin should be included as an alternative to vancomycin. • Clarithromycin alone is sub-optimal cover e.g. for *Haemophilus influenza* for cellulitis related to the face/eye – oral alternative in penicillin allergic patients in such cases	Thank you for your comment. The committee have reviewed all the comments received on antibiotic choice and have amended the tables in the guideline in response to stakeholder comments by: • being clearer when to use each antibiotic • removing gentamicin as an option from the guideline • including teicoplanin as an option • including clarithromycin plus metronidazole as an option • including clindamycin as an option (although the committee did not wish to add ciprofloxacin) • including clarithromycin plus metronidazole as anaerobic cover for infection near eyes/nose in people with penicillin allergy • agreed the dosing of flucloxacillin, recommending 500 mg to 1 g four times a day orally **or** 1 to 2 g four times a day IV in line with your comment.

					could be ciprofloxacin plus clindamycin (albeit with high risk of *C difficile* infection). • There is no mention of anaerobic cover for patients with penicillin allergy and infection near eyes/nose in this section which needs to be included. First choice intravenous antibiotic (if unable to take oral antibiotics or severely unwell): Flucloxacillin 500 mg to 2 g four times a day 500mg fluclox is a sub-optimal dose for a severely unwell patient, 2g qds would be optimal (if normal renal function). It is not out practice to use a lower dose than 2g qds unless patient has significant renal impairment.	
10	British Infection Association	Table 2	Page 6	1	Alternative first choice oral antibiotics if infection near the eyes or nose4 for penicillin allergy or if co-amoxiclav unsuitable (consider seeking specialist advice) *with (if anaerobes suspected):* Clarification needed as to when anaerobes would be suspected.	Thank you for your comment. The committee agreed that it would be a clinical decision when to suspect anaerobic involvement as diagnostics are out of scope for this guideline.
11	British Infection Association	Tables 1 and 2	Pages 4 and 5	n/a	Add specific empirical oral and IV antibiotic choices for patients known to be colonised with MRSA.	Thank you for your comment. The committee have amended the antibiotic choice table adding a section for MRSA which includes vancomycin, teicoplanin and linezolid in response to stakeholder comments.
12	British Infection Association	Guideline	Page 2		It would be useful to include guidance of what samples are appropriate in terms of making a microbiological diagnosis and when these samples should be taken in relation to when antibiotics are started.	Thank you for your comment. Diagnosis (including microbiological diagnosis of cellulitis and erysipelas) is out of scope for this guideline. However, new recommendations have been added on when to take a swab in order to guide antibiotic choice, see recommendations 1.1.2, 1.1.10, 1.1.11 and 1.1.12. The committee discussed that most people with cellulitis or erysipelas will not need a swab taking at all so should it should not be routinely undertaken, and empirical antibiotic treatment should not be delayed in any case.
13	British Infection Association	Guideline	Page 2	Section 1.1.2	Emphasise the need to review previous positive microbiology including infection alerts on the patient's medical records especially MRSA.	Thank you for your comment. The committee have added a bullet in recommendation 1.1.4 to reflect your comment to take account of previous microbiological results from a swab and a person's MRSA status if known.

14	British Infection Association	Guideline	General	18 1.1.4	“Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics if possible” could be reworded as “Only use intravenous antibiotics where there is clear reason and then review intravenous antibiotics by 48 hours and switch to oral therapy. If there is a concern of lack of response at this time then re-assess for an alternative cause of ongoing symptoms. Only continue IV therapy in exceptional circumstances such as if the patient is vomiting.” There is little evidence for a requirement for IV antibiotics beyond 48 hours for example in lower limb leg cellulitis and in our clinical experience prolonged IV antibiotics are often given without being required (e.g. when an underlying source is missed).	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 1.1.6 recommends reviewing IV antibiotics by 48 hours and switching to oral treatment if possible. Recommendations 1.1.1, 1.1.10 and 1.1.13 cover considering alternative diagnoses if no improvement.
15	British Infection Association	Guideline	General		Include information on when out-patient intravenous antibiotic therapy may be appropriate for treatment of cellulitis/erysipelas and potential antibiotics choices e.g. ceftriaxone/teicoplanin/daptomycin/dalbavancin combined with the requirement to switch to oral antibiotics at 48 hours in general.	Thank you for your comment. The committee have added a suitable antibiotic choice (ceftriaxone) for ambulatory care (which includes outpatient parenteral antibiotic therapy [OPAT]) in response to stakeholder comments. The committee agreed that other antibiotic choices may be appropriate and have therefore recommended seeking specialist advice for specific populations or antibiotic choices.
16	British Infection Association	Guideline	General		Please remove gentamicin alone as an option in this guideline and review the evidence as to whether it should be used in combination. Most of those responding to the consultation stated they would not use gentamicin in cellulitis or erysipelas. The recommendation to use gentamicin may introduce toxicity without benefit and the evidence needs to be carefully reviewed if this option is to be included in the guideline.	Thank you for your comment. The committee have removed gentamicin as an option from the guideline in response to stakeholder comments.
17	British Infection Association	Guideline	General		Include information on when intravenous therapy is in fact not recommended and should be discontinued. For example there is a paucity of evidence for intravenous therapy in simple cellulitis and prolonged courses are not recommended. In such cases without resolution within such a time-frame further examination and	Thank you for your comment. Please note the guideline recommends only commencing intravenous therapy when the person is unable to take oral antibiotics or is severely unwell, and it is recommended (see recommendation 1.1.6) that intravenous antibiotics are reviewed by 48 hours and an oral switch considered.

					consideration of a potential missed source of infection is important and should be highlighted.	
18	British Infection Association	Guideline	General		Doxycyline and co-trimoxazole do not appear to be included in this guideline but are commonly used by infection specialists for skin and soft tissue infections where appropriate.	Thank you for your comment. The committee have included doxycycline as an option in response to stakeholder comments. The committee discussed that the risk associated with co-trimoxazole use generally outweighs the level of benefit in people with cellulitis or erysipelas, and there are other available options.
19	British Infection Association	Guideline	General		It would be helpful to include a recommendation that a patient with sepsis be fully assessed to exclude necrotising fasciitis as cellulitis alone would be an uncommon cause of sepsis.	Thank you for your comment. The committee have added a bullet point about excluding necrotising fasciitis in recommendation 1.1.9 (pain out of proportion to the infection).
20	UK Clinical Pharmacy Association	Guideline review	General		We were interested to see the inclusion of gentamicin in this guideline. Not often the drug that we would generally use in the treatment of cellulitis, even in combination – if I was concerned about Gram negative infection then we would be more likely to use an extended spectrum penicillin or carbapenem.	Thank you for your comment. The committee have removed gentamicin as an option in response to stakeholder comments.
21	UK Clinical Pharmacy Association	Guideline review	Page 4		No mention of MRSA and treatment options if patient is colonised e.g doxycycline	Thank you for your comment. In response to stakeholder comments, the committee have amended the antibiotic table to include a section on MRSA treatment which includes vancomycin, teicoplanin and linezolid; doxycycline has also been added as an option and may be considered as part of combination therapy for MRSA.
22	UK Clinical Pharmacy Association	Guideline review	General		No mention of reviewing previous swab results to guide treatment.	Thank you for your comment. The committee has added a new recommendation on reviewing previous microbiology results, see recommendation 1.1.12.
23	UK Clinical Pharmacy Association	Guideline review	Page 4		Linezolid – There is no mention of monitoring requirements as per BNF	Thank you for your comment. The committee have amended the footnote text in the guideline regarding monitoring requirements.
24	UK Clinical Pharmacy Association	Guideline review	2	16	The severity of their condition does not require intravenous antibiotics" I think it would be useful to have something in here to describe when a patient's condition is severe enough to warrant IV antibiotics. E.g. SIRs response, blistering or would it be patients with end organ dysfunction? Or it is refer to 1.1.8 for IV criteria?	Thank you for your comment. The antibiotic table footnote states 'give oral antibiotics first-line if the person can take oral medicines, and the severity of their symptoms does not require intravenous antibiotics'. The committee agreed it would not be feasible to give further examples as individual patient

						condition, extent and severity of infection and presence of comorbidities can vary extensively.
25	UK Clinical Pharmacy Association	Guideline review	3	28	Not responding after how long? 48-72 hours?	Thank you for your comment. The committee did not wish to place a time period on this recommendation as there are too many individual patient factors which may occur and this should be based on clinical judgement.
26	UK Clinical Pharmacy Association	Evidence review	4	9	7 days is recommended but the IDSA and the Hepburn 2004 advocate 5 days if patient has responded to antibiotics (not referenced in here). The Kilburn paper suggests 5 days is enough, Hanretty suggests 6 days. Why have NICE chosen 7? Why a dose range for flucloxacillin? There is wide variation in doses prescribed (Brindle published on the variation in fluclox dosing in the SW of England). Would it not be more useful to advocate a dose? 1g qds?	Thank you for your response to our question asked at consultation. The committee have discussed and amended the duration of antibiotic to 5 to 7 days. The committee have given a dose range to allow for different settings (primary and secondary care) treating different severity and extents of infection and individual patient factors (such as age and frailty).
27	UK Clinical Pharmacy Association	Guideline review	11		Second bullet point “may take time for the antibiotic to take effect” may be better worded “ although the bacteria are likely rapidly killed it may take time for the redness to resolve due to toxins and inflammatory processes.	Thank you for your comment. The committee agree that this is a correct rationale, but the plain English language summary was preferred, and no change was made to the recommendation.
28	UK Clinical Pharmacy Association	Evidence review	General		Daptomycin is not recommended under any circumstances, whereas it is mentioned in the IDSA guidelines. We tend to use daptomycin in severe cellulitis in preference to flucloxacillin (because of the additional MRSA coverage) or in preference to vancomycin as daptomycin requires no levels and may require fewer adjustments in relation to renal function, though would not use daptomycin in severe renal impairment.	Thank you for your comment. The committee agreed that the narrow spectrum antibiotic flucloxacillin is the preferred first line antibiotic choice (both orally and IV) as it will cover almost all causative organisms of cellulitis or erysipelas. The committee discussed that *MRSA* cases account for <1% of infections, so routine use of broader spectrum antibiotics in the absence of known or suspected *MRSA* will increase resistance and not rate of cure. The evidence for this topic found no difference between daptomycin and vancomycin in practice. For known or suspected *MRSA,* the committee have added teicoplanin as an option because it requires less monitoring than vancomycin and it can be used from birth, whereas the SPC for daptomycin states that it can be used from 1 year. Additionally, daptomycin is more costly per dose than either teicoplanin or vancomycin (see BNF cost prices).

29	UK Clinical Pharmacy Association	Evidence review	General		Cellulitis near the eyes and nose: NICE recommends co-amoxiclav instead of flucloxacillin "because of risk of a serious intracranial complication". We would normally be happy with flucloxacillin. As far as we know, there is no evidence that facial erysipelas or pre-septal cellulitis in adults/adolescents has a different etiology and we tend to broaden the antibiotic coverage (to include Gram-negatives and anaerobes) only in very specific settings such as clinical or radiological evidence of sinusitis or abscess formation or intra-cranial infection or cavernous sinus thrombosis.	Thank you for your comment. The committee agreed that the risk of serious complication is low from infection around the eyes and nose. However, the consequences of such a serious complication would likely be very serious, so in order to reduce first line treatment failure they have indicated that co-amoxiclav is suitable option.
30	UK Clinical Pharmacy Association	Guideline Review	6		Cellulitis near the eyes and nose: is there no scope for a separate guideline for periorbital / preseptal cellulitis?	Thank you for your comment. The recommendations presented are suitable for periorbital / preseptal cellulitis. The committee agreed that there is likely insufficient evidence for a separate guideline on this topic.
31	UK Clinical Pharmacy Association	Guideline Review	6		Cellulitis near the eye and nose: recommendation for penicillin allergy if anaerobes suspected to add metronidazole to clarithromycin – clindamycin is often recommended in preference to the combination of clarithromycin and metronidazole although appreciate that both clarithromycin and metronidazole are available commercially as a suspensions whereas clindamycin is not.	Thank you for your comment. The committee agreed that only a small proportion of individuals would have infection around the eyes and nose, and only a small proportion of those would require an alternative choice of therapy for penicillin allergy. The committee agreed that what is important in this situation is to offer antibiotic cover for both aerobic and anaerobic organisms. They agreed that the first-choice antibiotic for people with infection near the eyes and nose is co-amoxiclav, with clarithromycin plus metronidazole for people with penicillin allergy. Clindamycin is recommended but is reserved as an alternative choice for severe infection.
32	UK Clinical Pharmacy Association	Guideline Review	6		Interesting that there is no recommendation for use of ceftriaxone – this is used frequently in preference to cefuroxime to allow ambulation i.e. ONCE daily dosing.	Thank you for your comment. Ceftriaxone has been added as an option for ambulatory care only, in response to stakeholder comments.
33	UK Clinical Pharmacy Association	Guideline Review	7		Gentamicin also not usually used for treatment of cellulitis in paediatrics.	Thank you for your comment. The committee have removed gentamicin as an option in response to stakeholder comments.
34	Nottingham University	Evidence review	2	8	1.1.2 When choosing an antibiotic, suggest also need to take into account:	Thank you for your comment.

	Hospitals NHS Trust				• Severity of signs- i.e. speed of spread, and systemic signs of moderate or high risk sepsis • Previous history of MRSA (meticillin-resistant Staphylococcus aureus) and/or macrolide resistant Gram positive infection/colonisation • Antibiotic allergies • A history of animal bite or water-based injury at the site (Possible Gram negative pathogens) • Need more mention of preceding injuries (scratches, bites, water, soil etc) referral to Microbiology for advice. • Resistance due to repeated use of second-line agents) including in the prophylaxis section specifically about previous macrolide resistance and Staph.aureus/MRSA. If they are severely immunocompromised or have poorly controlled diabetes (Need to consider possible Gram negative pathogens)	• Severity of symptoms - sepsis risk would need to be managed by immediate referral please see recommendation 1.1.13 • Previous microbiology result has been added (MRSA history) to recommendations 1.1.4 and 1.1.12 • Antibiotic allergy – please see antibiotic choice recommendation tables 1 and 2 where alternative antibiotic options are given for those with penicillin allergy • There are separate planned NICE guidelines for human and animal bites and insect bites and stings. A note about water-borne infection has been added to recommendations 1.1.2, 1.1.4 and 1.1.14 • Preceding injury has been added to recommendation 1.1.4 • The committee agreed that as the incidence of *MRSA* related cellulitis is <1% of infections, flucloxacillin is still the first line antibiotic of choice even where other antibiotics have been used previously • Previous resistance (macrolides) microbiology result has been added to recommendations 1.1.4 and 1.1.12 • We have added a new recommendation about managing underlying conditions (see recommendation 1.1.5) including diabetes, no evidence was found to suggest that in the absence of (for example) a penetrating injury (which should be considered for swabbing see recommendation 1.1.2) a cellulitis infection in someone with diabetes will be caused by a gram negative organism.
35	Nottingham University Hospitals NHS Trust	Evidence review	3	22	1.1.9 Consider referring or seeking specialist advice for people with cellulitis or erysipelas if they: • Have a history of animal bite or water-based injury at the site (Possible Gram negative pathogens)	Thank you for your comment. • There are separate planned NICE guidelines for human and animal bites and insect bites and stings. A note about water-borne infection has been added to recommendations 1.1.2, 1.1.4 and 1.1.14 • We have added a new recommendation about managing underlying conditions (see

					• Are severely immunocompromised or have poorly controlled diabetes (Possible Gram negative pathogens) • Need more mention of preceding injuries (scratches, bites, water, soil etc) to prompt referral to Microbiology for advice.	recommendation 1.1.5) including diabetes, but the committee did not agree with the comment that these individuals would need referral beyond the reasons given in recommendation 1.1.14.
36	Nottingham University Hospitals NHS Trust	Evidence review	4 and 9	9 and 1	Table 1 and 2 • To reduce slow response/ failure of oral treatment the oral dose of flucloxacillin should be flucloxacillin 500mg-1g qds. • IV dose of flucloxacillin starting at 500mg qds is too low- suggest equivalent of 1-2 g qds (and equivalent higher starting dose for children) majority of patients are obese too so 500mg will not be effective. • The IV dose of flucloxacillin says 500mg – 2g – if 'severely unwell' should just go with 2g. • Don't like how they have just listed antibiotics as alternatives to IV flucloxacillin with no mention on why / when you would use these. • No mention of teicoplanin or dalbavancin as suitable IV agents • If penicillin allergy and risk of adverse effects or known macrolide resistance or known MRSA need an alternative antibiotic choice - suggest doxycycline • The dose of IV clindamycin at 600mg daily dose is too low and should the 2.7 g qds dose be 2.4 g qds? • It should be clearer that the co-amoxiclav option in table 1 and 2 is only for infection near the eyes or nose and add indication for animal bites (or refer to separate guidance)	Thank you for your comment. Following stakeholder comments: • The committee discussed dosing of flucloxacillin and have recommended 500 mg to 1 g four times a day orally or 1 to 2 g four times a day IV in line with your comment. Please note that intravenous dose range is for those unable to take oral antibiotic **and** those who are more severely unwell. For those unable to take oral flucloxacillin (as opposed to those with more severe illness) the SPC reports that peak serum levels 1 hour after administration are similar for oral and parenteral 500 mg dose. • The committee discussed and amended the table to make it clearer when to use each antibiotic, the rationale for the use of each is given in the discussion section of the guideline. • The committee added teicoplanin as an option if MRSA is suspected or confirmed and recommended that other antibiotics (which could include dalbavancin) may be appropriate based on microbiological results and specialist advice. • The committee added doxycycline as an alternative first choice option, but did not add it to antibiotics to be given if MRSA suspected or confirmed. • The committee agreed that the correct dose range for clindamycin, given in the table is in line with the SPC for serious infection and higher doses for more severe infection • The committee amended the table to make it clear that the choice of co-amoxiclav is for infection near the eyes or nose

					• IV gentamicin is NOT a suitable agent for cellulitis/erysipelas and should be removed	• The committee removed gentamicin as an option.
37	Nottingham University Hospitals NHS Trust		8	5	Need to consider resistance due to repeated use of second-line agents) including in the prophylaxis section specifically about previous macrolide resistance and Staph.aureus/MRSA.	Thank you for your comment. The committee agreed that as the incidence of MRSA related cellulitis is <1% of infections, flucloxacillin is still the first line antibiotic of choice even where other antibiotics have been used previously.
38	Royal College of General Practitioners	Guideline	General		The RCGP has developed an antibiotic toolkit for prescribers, which can be found here: https://www.rcgp.org.uk/clinical-and-research/resources/toolkits/target-antibiotic-toolkit.aspx	Thank you for your comment. Unfortunately, it does not appear that any of the resources in the toolkit are specific to cellulitis and erysipelas.
39	Royal College of General Practitioners	Guideline	9	21	The committee should consider making a recommendation on those with a BMI >33. Thomas 2013 shows standard dose prophylaxis is less effective in those with BMI>33. It may be pragmatic to recommend a higher dose for people with BMI >33 based on biological plausibility. Furthermore, people with a raised BMI are more likely to get recurrent episodes, so it is even more important to get ensure appropriate dosing. Although Thomas 2013 has been excluded from the evidence review as it has been included in a prioritised systematic review, this detail has not been highlighted. We suggest that the evidence related to BMI should be highlighted in the linking evidence to recommendations section and that the committee should consider making a recommendation in this area https://www.nejm.org/doi/full/10.1056/nejmoa1206300	Thank you for your comment. The reported study (Thomas et al 2013) was prognostic and as such did not meet the criteria for inclusion in our evidence review. NICE is aware that increasing the dose of an antibiotic based solely on the weight of an individual may be inappropriate and the following need to be considered: • How the individual drug is broken down, absorbed, transported, distributed and broken down or eliminated • How lipophilic or water-soluble the individual drug is In many cases all the information may not be known or the SPC for the individual drug may need to be used.
40	Royal College of General Practitioners	Guideline	General		The committee should consider higher antibiotic doses for acute treatment, as well as in prophylaxis, according to body weight. 2 articles that highlight this consideration -	Thank you for your comment. NICE is aware that increasing the dose of an antibiotic based solely on the weight of an individual may be inappropriate and the following need to be considered:

					(1) Adjustment of dosing of antimicrobial agents for bodyweight in adults: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2809%2960743-1/fulltext (2) How should antibiotics be dosed in obesity? https://www.sapg.scot/media/2918/howshouldantibioticsbedosedinobesity_2016_update.pdf	• How the individual drug is absorbed, transported, distributed and broken down or eliminated • How lipophilic or water-soluble the individual drug is In many cases all the information may not be known or the SPC for the individual drug may need to be used.
41	Royal College of General Practitioners	Guideline	General		Additionally is there the need to consider reduced antibiotic dose in renal impairment? https://www.bfwh.nhs.uk/mobile/amformulary/renal.shtml	Thank you for your comment. Please note Table 1 and 2 footnote 1 refers the reader to the BNF for dose adjustment for renal impairment.
42	Royal College of General Practitioners	Guideline	General		The committee should consider making a recommendation on recording the side effects of treatment and their tolerability for the patient. The choice of antibiotics depends on multiple factors, one of them is the patient allergies and sensitivities, unfortunately most of the times patient will have intolerance to side effect rather than allergy, so mentioning that in record is vital to help in choosing antibiotics when needed.	Thank you for your comment. While NICE recognise the importance of recording and reporting side effects, adverse effects and allergies in relation to future prescribing we consider this to be a part of good medical practice in prescribing as described by the GMC and out-of-scope for this guideline.
43	Royal College of General Practitioners	Guideline	General		The committee should consider making a recommendation highlighting the need to consider potential drug interactions when choosing an antibiotic	Thank you for your comment. While NICE recognise the importance of potential drug interactions the footnote in the prescribing table directs the reader to the BNF for appropriate use (which would include interactions).
44	Royal College of General Practitioners	Guideline	2	24	The committee should consider specifying a timeframe that patients might expect to continue having symptoms, for example 'this may take up to three weeks to get better'	Thank you for your comment. The committee found no evidence on the natural history of the resolution of the skin or symptoms and so were unable to provide a time frame.
45	Royal College of General Practitioners	Guideline	General		The committee should consider making a recommendation for shared decision making with patients having acute cellulitis, in line with the recommendation for shared decision making for people with recurrent cellulitis or erysipelas (1.3.2,	Thank you for your comment. Shared decision making is a key pillar of NICE guidance and there is a NICE guideline on shared decision making in development. The committee regarded shared decision making as implicit within the prescribing decision-making process.

					page 8, line 12). The shared decision making process is appropriate for all decisions, especially negotiating over arrangements for follow up.	It is highlighted under the prophylaxis section as the decision to take prophylactic antibiotics is much more of a preference sensitive decision than a decision to take antibiotics for the treatment of an infection that is not self-limiting.
46	Royal College of General Practitioners	Guideline	1	4	The mentioned 2-page visual summary is actually 3 pages	Thank you for your comment. We have amended the text in the guideline.
47	Royal College of General Practitioners	Guideline	1	4	This is a guideline rather than a strategy	Thank you for your comment. The guideline lays out a plan for prescribing based on patient need and choice which consistent with the term prescribing strategy.
48	Royal College of General Practitioners	Guideline	2	23	This will need to say antibiotic(s)- adding an S in cases when 2 antibiotics can be used	Thank you for your comment. We have amended the text in the guideline.
49	Royal College of General Practitioners	Guideline	4	9	Is committee assured that clarithromycin is the best first choice alternative antibiotic in view of safety concerns of clarithromycin? Please see this BMJ article stating that the use of clarithromycin in the setting of acute exacerbations of chronic obstructive pulmonary disease or community acquired pneumonia may be associated with increased cardiovascular events- https://www.bmj.com/content/346/bmj.f1235	Thank you for your comment. NICE is aware of the recent research findings in relation to clarithromycin. However, the related publication from 2013 (prospective cohort study) concluded more data was needed to confirm its results. The guideline includes the following safety information from the BNF relating to macrolides, 'Macrolides should be used with caution in people with a predisposition to QT interval prolongation.'
50	Royal College of General Practitioners	Guideline	5		Linezoid typically a specialist only prescribable medication. NHS England guidance states that "Linezolid should be initiated only in a hospital environment and after consultation with a relevant specialist such as a microbiologist" (https://www.gov.uk/drug-safety-update/linezolid-restricted-indication) The phrase "specialist use only" would be preferable here.	Thank you for your comment. The committee have amended the wording in the prescribing tables to confirm specialist use only.

51	Royal College of General Practitioners	Guideline	5	1	The guideline appears to give dose ranges in children as per the BNF. Yet the BNF adult dose range for flucloxacillin, for example, is 250-500mg times a day, whilst this guideline advises 500mg. The committee should consider giving clearer direction as to the dose within a given age group.	Thank you for your comment. The committee discussed that there was available evidence from the evidence review for the specified doses given for adults in the guideline. As no studies using the first line choice antibiotic (flucloxacillin) were in children the committee took the decision to advocate the normal dose ranges given in the BNF and BNFC.
52	Royal College of General Practitioners	Guideline	8	11	The committee should provide clearer guidance on when a trial of antibiotic prophylaxis should be introduced (immediately after the 2nd episode?) and who should be making the recommendation	Thank you for your comment. The committee have clarified that this decision should be made, and therapy initiated, by a specialist. A lack of evidence for when a trial of prophylaxis should be considered led the committee to the decision that as this will be specialist led this would be discussed by the specialist and the person with recurrent cellulitis, this would also be dependent on local service factors (for example referral waiting times).
53	Royal College of General Practitioners	Guideline	8	18	The person's preference for antibiotic use', in the context of shared decision making, should not reduce the threshold at which the prescriber if offering antibiotics. The committee should ensure that this is captured in the guideline to avoid antimicrobial resistance.	Thank you for your comment. The committee agreed that they have adequately specified the factors that should lead to a discussion about prophylactic antibiotics. The committee would reasonably expect that a specialist led discussion of the individual risk and benefit would include the risk of antimicrobial resistance.
54	Royal College of General Practitioners	Guideline	9	8	The committee should consider a recommendation to stop antibiotics after any given 6-month period. From an antibiotic resistance consideration, there should be other management advice that the patient has at the start of prophylaxis that may reduce or remove the need for subsequent prophylaxis- e.g. weight loss, improved diabetic control, improved activity levels	Thank you for your comment. The duration of treatment in the prophylaxis studies varied from 1 month to 38 months, there is no evidence for stopping therapy at 6 months. However, recommendation 1.3.5 states that there should be a 6 month review of the trial of prophylaxis, which the committee believe is reasonable. Please note that other non-antimicrobial interventions for the prevention of cellulitis recurrence are out-of-scope for this guideline.
55	Royal College of General Practitioners	Guideline	1		Suggest addition of a subheading- pages 2 and 3 are subtitled as choice of antibiotic treatment. Page 1 would sit with a title such as 'general	Thank you for your comment. The NICE publishing team considered wording but did not agree this change as there are already headings for treatment, advice, reassessment and referral.

					management considerations'.	
56	Royal College of General Practitioners	Visual summary	1		Within the first box, rephrase 'Offer an antibiotic' to state 'offer a suitable antibiotic'	Thank you for your comment. The NICE team considered this wording but did not agree this change as the suitable antibiotics are given in tables.
57	Royal College of General Practitioners	Visual summary	1		The 2nd box for do not routinely offer antibiotic prophylaxis, 2 points: (1) when it states consider a trial of antibiotic prophylaxis, it would be better to put this together with the bottom right paragraph in the grey box where it mentions as which antibiotic and dose to use, and the duration of such treatment; (2) 'advise seeking medical help if symptoms recur'- is this guidance a GP should be offering to a patient, or is it stating a GP should be referring the patient for further medical assessment?	Thank you for your comment. (1) The visual summary has been amended to more closely reflect your comments. The wordings are now adjacent but due to space limitations could not be combined. (2) This is advice for the individual to seek help if symptoms recur.
58	Royal College of General Practitioners	Visual summary	1		Both boxes could perhaps have a header- acute presentation for box 1, and antibiotic prophylaxis for box 2	Thank you for your comment. Unfortunately, this is not consistent with the NICE style for visual summaries.
59	Royal College of General Practitioners	Visual summary	1		Background - are skin infections usually caused by strep pyrogens AND staph aureus, or should the and be an OR?	Thank you for your comment. This has been amended in line with your comment.
60	Royal College of General Practitioners	Visual summary	1		The grey background and antibiotic box should be on the left side, so you read it first, rather than being on the right. For route of antibiotics, it states "give oral antibiotics first line if possible". And alternative form of words could be "antibiotics should preferentially be given orally when clinically appropriate…If receiving antibiotics intravenously, review by 48 hours and switch to oral administration if possible"	Thank you for your comment. The layout has been amended in line with your comment. Unfortunately, due to limitations of space the wording could not be amended.
61	Royal College of General Practitioners	Visual summary	2 And 3		Would it be possible to make it clearer that page 2 refers to adults and page 3 to children?	Thank you for your comment. The tables are headed adults aged 18 years and over, and children and young people under 18 years, this is in line with NICE style

						and the committee considered this clear for users of the visual summary.
62	Royal College of General Practitioners	Visual summary	2 and 3		Would it be possible to give a clearer visual distinction between 1st form 2nd line antibiotics?	Thank you for your comment. We have amended the tables to clarify this.
63	Royal College of General Practitioners	Visual summary	2 and 3		Infections near the nose or eye - just to make sure that Metronidazole is not at the right side of the box	Thank you for your comment. We have amended the tables to clarify this.
64	Neonatal & Paediatric Pharmacists Group	Guideline	General		This guideline does not state that neonates are excluded from the recommendations, and yet does not provide any advice on this population. Should the exclusion be more explicit? It is unlikely that patients in this age group would present with these symptoms and be managed following this guideline.	Thank you for your comment. The guideline prescribing table now has wording for children under 1 month advising that antibiotic choice should be based on specialist advice. The scope of all antimicrobial prescribing guidelines excludes neonates under 72 hours.
65	Neonatal & Paediatric Pharmacists Group	Guideline	6	Table 2	Co-amoxiclav dose recommendations do not include the 400/57 suspension. We would advocate use of this strength of the preparation in children and young people because it can be given twice daily. Using twice daily dosing eliminates the need for a lunchtime dose which can cause problems for children and young people at nursery or school and may optimise compliance and completion of the course.	Thank you for your comment. The committee discussed and agreed that the 400/57 suspension could be useful; it has been added to table 2 as a footnote to reflect your comment.
66	Neonatal & Paediatric Pharmacists Group	Guideline	6	Table 2	Erythromycin (in pregnancy) – by this do you mean that erythromycin should be the preferred 2nd line choice during pregnancy? If so, this is not clear – could it be stated more explicitly?	Thank you for your comment. Please note that the heading for the table section is *Alternative first choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable.*
67	Neonatal & Paediatric Pharmacists Group	Guideline	6	Table 2	Erythromycin – the total daily dose can also be given twice daily (500 mg to 1g twice a day) which may be better in school-age children and young people.	Thank you for your comment. The committee discussed the comment but did not recommend giving erythromycin twice a day because of concerns about tolerability.
68	Neonatal & Paediatric Pharmacists Group	Guideline	7	Table 2	Gentamicin – we would recommend adding age restriction of “1 month to 17 years,” to this dose recommendation. Use of gentamicin in neonates for neonatal sepsis is at a lower dose (5mg/kg) with the frequency varying depending on the age of the neonate.	Thank you for your comment. The committee have removed gentamicin as an option in response to stakeholder comments.

69	Neonatal & Paediatric Pharmacists Group	Guideline	6-7	Table 2	Section heading "Alternative choice intravenous antibiotics for penicillin allergy, if flucloxacillin unsuitable, or if infection near the eyes or nose[4] (consider seeking specialist advice). Antibiotics may be combined if susceptibility or sepsis a concern[6]" This is quite a vague statement and there is no information on preference of choice here. It would be useful if guidance on which antibiotics could be combined was included.	Thank you for your comment. The table has been amended for clarity in response to stakeholder comments.
70	Neonatal & Paediatric Pharmacists Group	Guideline	7	Table 2	Linezolid has an oral bioavailability of approximately 100% (Summary of Product Characteristics - Zyvox 600 mg Film-Coated Tablets (linezolid). Pfizer Limited. Date of revision of the text 09/2018. https://www.medicines.org.uk/emc/product/1688/smpc). Therefore, unless the patient is nil by mouth, we would tend to use oral route. For this indication, it would be unusual to need to use IV. It would seem counter to the antimicrobial stewardship statement on p20 of the guideline to recommend IV treatment if it is not necessary.	Thank you for your comment. The committee discussed this comment and have amended the table to recommend either oral or IV linezolid in response to stakeholder comments.
71	Neonatal & Paediatric Pharmacists Group	Guideline	General		Flucloxacillin suspensions are unpalatable and frequently not tolerated in children and young people. This has an impact on completion of courses. In some areas of the UK, they are recommending using cefalexin suspension as an alternative.	Thank you for your comment. The committee discussed the palatability of oral flucloxacillin versus it being the best antibiotic for the treatment of cellulitis and have added footnote 5 in table 2, which says 'If flucloxacillin oral solution is not tolerated because of poor palatability, consider capsules (see Medicines for Children, helping your child to swallow tablets leaflet).'
72	Neonatal & Paediatric Pharmacists Group	Guideline	General		Some of our members have reported local practice of treating cellulitis with a combination of phenoxymethylpenicillin (or benzylpenicillin if IV) and flucloxacillin. We would welcome this combination being discouraged in the guidance as there is little benefit to it.	Thank you for your comment. The committee reviewed the evidence for dual therapy (see Committee discussion on choice of antibiotic page 16, 5th bullet) and have stated that dual therapy should not be routinely used given the increased risk of antimicrobial resistance and more side effects.
73	Neonatal & Paediatric Pharmacists Group	Guideline	General		*Question 3: is 7 days an appropriate duration of antibiotic treatment, with a footnote to explain that a longer course of up to a further 7 days may be needed based on clinical assessment?* We would support this approach.	Thank you for your response to our question asked at consultation. The committee have discussed and amended the duration of antibiotic treatment to 5 to 7 days in response to stakeholder comments.

74	Royal Pharmaceutical Society	Draft guideline	General		Course length of 7 days with option for additional 7 days seems reasonable	Thank you for your response to our question asked at consultation. The committee have discussed and amended the duration of antibiotic treatment to 5 to 7 days in response to stakeholder comments.
75	Royal Pharmaceutical Society	Draft guideline	General		There is no mention of OPAT which is an increasingly common approach to managing patients with cellulitis to reduce hospital stay	Thank you for your comment. The committee have added ceftriaxone as a treatment option which is suitable for ambulatory care only (which includes OPAT), in response to stakeholder comments.
76	Royal Pharmaceutical Society	Draft guideline	4 and 5	Table	• Doxycycline/cotrimoxazole is not mentioned as an alternative and probably should be for penicillin allergic outpatient treatment or step down. • Clindamycin needs a warning around for those at risk of CDI. • Query use of Cefuroxime given the range of alternatives • Unsure why Gentamicin is included – only useful in someone very unwell and should be indicated that this is when used. Add cautions around linezolid use in view of the many interactions/ contraindications and monitoring requirements due to toxicity	Thank you for your comment. In response to stakeholder comments: • Doxycycline has been added as an option. • The committee discussed that the risks associated with co-trimoxazole use generally outweigh the level of benefit in people with cellulitis or erysipelas and there are other available options. The committee discussed that it should only ever be given on specialist advice for cellulitis. • Footnote 1 refers the reader to the BNF for specific information for each antibiotic (including for clindamycin the risk of antibiotic associated colitis). The guideline also gives safety information from the BNF that 'Clindamycin has been associated with colitis and diarrhoea. Although this can occur with most antibiotics, it is more frequent with clindamycin'. • The committee considered your comment but agreed that cefuroxime is a suitable treatment option. • The committee have removed gentamicin as an option. • Linezolid is now described as specialist use only (if vancomycin or teicoplanin cannot be used).
77	British Association of Dermatologists		General		The NICE guideline should consider evidence that multiple studies have shown that over 30% of people initially treated or referred with lower limb cellulitis turn out to have other diagnoses. Therefore patients who do not respond to antibiotics should be reassessed at 48 hours and other diagnoses considered. Levell NJ,	Thank you for your comment. Please note that recommendation 1.1.9 asks for people not improving at 2 to 3 days be reassessed. Recommendations 1.1.1 has been amended in line with your comment about excluding other possible diagnoses, also recommendation 1.1.10 on reassessment states that alternative diagnoses should be considered.

					Wingfield CG, Garioch JJ .Severe lower limb cellulitis is best diagnosed by dermatologists and managed with shared care between primary and secondary care. Br J Dermatol. 2011 Jun;164(6):1326-8.	
78	British Association of Dermatologists		General		All patients with lower limb cellulitis should be assessed for treatable predisposing factors (eg tinea, venous eczema, lymphoedema, obesity etc). This helps to prevent recurrent cellulitis which then leads to a common, deteriorating and expensive cycle of lymphoedema, decreased mobility, obesity, diabetes (with all its sequelae) and leg ulceration.	Thank you for your comment. The committee have added a new recommendation regarding the management of underlying conditions (see recommendation 1.1.7).
79	British Association of Dermatologists		General		Failure to consider these misses an opportunity for early intervention in a Cinderella disease, to improve health and prevent chronic disease.	Thank you for your comment. The committee have added a new recommendation regarding the management of underlying conditions (see recommendation 1.1.7).
80	British Association of Dermatologists		General		We cannot see a recommendation re. taking swabs for microbiological culture from broken skin at affected sites. Though often negative, positive results, for instance showing resistant organisms, can influence antibiotic choice.	Thank you for your comment. The committee have added new recommendations regarding microbiological sampling to guide antibiotic choice (see recommendation 1.1.2, 1.1.11 and 1.1.12).
81	Royal College of Nursing	General	General		The Royal College of Nursing (RCN) welcomes proposals to develop NICE guidelines for Cellulitis and erysipelas: antimicrobial. The RCN invited members with expertise in this area to review the draft documents on its behalf. The comments below reflect the views of our reviewers.	Thank you for your comment.
82	Royal College of Nursing	Guideline	General		The guidelines appear well written and easy to use. They could potentially have most impact on prescribing practice within general practice, particularly regarding the use of prophylactic antibiotics.	Thank you for your comment.
83	Royal College of Nursing	Guideline	4	9	With regard to section 1.2 (table 1 and 2) - 7 days seeks an appropriate duration of antibiotic treatment. The document makes clear that further treatment of additional 7 day may be appropriate	Thank you for your response to our question asked at consultation. The committee have discussed and amended the duration of antibiotic treatment to 5 to 7 days in response to stakeholder comments.

					although needs to be based on clinical assessment.	
84	Royal College of Nursing	General	4 onwards	9 onwards	Clear visual summary which presents the key points of the guideline	Thank you for your comment.
85	Royal College of Nursing	Guideline	General		Our reviewers consider that the biggest impact would be on primary care. Some areas run ulcer/cellulitis clinics, and therefore, the recommended guideline could potentially reduce variation; learning from established units could potentially support implementation.	Thank you for your comment.
86	Royal College of Nursing	Guideline	General		Ambulatory services within tertiary care will need to be included as this is where General Practice services refer. All areas will need to follow the same guidelines to prevent confusion for the patient and inconsistent treatment.	Thank you for your comment. We have added an antibiotic suitable for ambulatory care to the antibiotic choice tables.
87	Royal College of Nursing	Guideline	General		Our reviewers consider that there may not be a significant challenge/change in practice; most areas already draw around areas to monitors spread. A review at 7 days is good practice is welcome.	Thank you for your comment.
88	Royal College of Nursing	Guideline	General		We note the committee discussion on antibiotic dose frequency, course length and route of administration- The evidence indicates that oral antibiotics are equal in effectiveness to IV. This will have an impact on care pathways in hospital cellulitis programmes especially as it also indicates that oral should be used in preference to IV- this will make cellulitis far more treatable in the community setting. For Prophylaxis - should the guidelines indicate who should decide on and monitor prophylaxis treatment? Can this decision be made in primary care or is it a specialist only decision like prophylaxis in UTI? Guidance here would be helpful.	Thank you for your comments. The committee discussed your comment and have amended the text of the recommendation to state that specialists should be responsible for initiating prophylaxis.

89	Royal College of Paediatrics and Child Health	Full version and summary	Table 2	5-7	There are no clear specifics apart from Gentamicin for those < 1 month of age. Could this be an omission? The dose for neonates in the guidance is not correct as dosing and frequency depends on age and gestation if premature. Either neonates need excluding completely from this information or this needs to be included and elaborated on somewhere.	Thank you for your comment. The committee have removed gentamicin as an option. Additionally, for those aged <1 month the prescribing table now states that specialist advice should be sought around antibiotic choice. The scope of all antimicrobial prescribing guidelines excludes neonates under 72 hours.
90	Royal College of Paediatrics and Child Health	Full version and summary	Table 2	5-7	Flucloxacillin liquid is considered unpalatable by many children, and therefore having another oral alternative such as cefalexin may be worth considering. Palatability is an important factor in ensuring treatment compliance in children, and therefore it is recommended that this should be considered within the guidance.	Thank you for your comment. The committee discussed the palatability of oral flucloxacillin versus it being the best antibiotic for the treatment of cellulitis and have footnote 5 in table 2, which says 'If flucloxacillin oral solution is not tolerated because of poor palatability, consider capsules (see Medicines for Children, helping your child to swallow tablets leaflet).'
91	Royal College of Paediatrics and Child Health	Full version and summary	Table 2	5-7	It might also be worth considering the co-amoxiclav 400/57 preparation which can be used twice so aiding compliance in the older age groups in children.	Thank you for your comment. The committee discussed and agreed that the 400/57 suspension could be useful, and a footnote has been added to table 2 to reflect your comment.
92	Royal College of Paediatrics and Child Health	Full version and summary	Table 2	6-7	Regarding the comment 'Alternative choice intravenous antibiotics for penicillin allergy, if flucloxacillin unsuitable, or if infection near the eyes or nose (consider seeking specialist advice). Antibiotics may be combined if susceptibility or sepsis a concern'. This statement is not particularly clear, seeking specialist advice is fine, but otherwise there is no information on preference of choice here and which antibiotics could be combined. Does this need to be added for clarity?	Thank you for your comment. The committee have discussed your comment and have clarified the antibiotic options in the antibiotic prescribing table in response to stakeholder comments.
93	Royal College of Paediatrics and Child Health	Full version	1.1.7	3	Other possible diagnoses/more serious illnesses should also include Septic Arthritis and Osteomyelitis especially in children with cellulitis over a joint. This is important as anti-microbial choice will differ. The reviewer has personally seen two misdiagnosed cases of cellulitis.	Thank you for your comment. The committee have amended the wording in recommendation 1.1.11 to include these conditions in response to your comments.

94	Royal College of Paediatrics and Child Health	Full version	1.1.8	3	Refer if more serious illness or condition should also include Septic Arthritis and Osteomyelitis. This is important as anti-microbial choice will differ. The reviewer has personally seen two misdiagnosed cases of cellulitis.	Thank you for your comment. The committee have amended the wording in the recommendation 1.1.10 to include these conditions.
95	Correvio Ltd	Draft Guideline	12	1	Overview Dalbavancin is a novel lipoglycopeptide antibiotic with a long terminal half-life (14.4–15.5 days), Jackson KA, et al. *Drugs.* 2015;75(11):1281–1291. Dalbavancin is administered as a 30-minute intravenous (IV) infusion as a single-dose or 2-dose regimen, which eliminates the need for a peripherally inserted central catheter. This single-dose regimen may help optimize adherence especially in the outpatient setting and enable patients to be treated as outpatient who otherwise would not be eligible (Russo 2016, 2018). Dalbavancin is approved in the US and Europe as a single-dose or 2-dose treatment for adults with ABSSSIs caused by susceptible gram positive organisms, and it has been evaluated in multiple phase 3 clinical trials of skin infection. Boucher, 2014; DalvanceR (dalbavancin). Full Prescribing Information, Durata Therapeutics US Ltd., Parsippany, NJ, 2016. Dunne, 2016; Jauregui 2005; Xydalba™ (dalbavancin) EU SmPC December, 2018 Greater clarity around dalbavancin effiacacy and safety is being further elucidated as large registries begin to publish their real world experience, Gonzalez, P1907, ECCMID 2019. These post-authorisation data are specifically valuable since they provide data on clinical efficacy and safety in specific and vulnerable patient groups with significant comorbidities, often excluded form clinical studies. With activity against the gram-positive organisms most frequently implicated in ABSSSIs, including	Thank you for your comment. Please note that dalbavancin was an antibiotic included within the guideline search strategy. • Jackson KA (incorrect author reference is Scott LJ 2015) is not an RCT or systematic review. • Russo A et al 2016 does not appear to be an RCT or systematic review. • Russo 2018 – unfortunately NICE were unable to identify this specific publication. • Boucher 2014 is an included study within the evidence review. • The studies by Dunne 2016 and Jauregui 2005 were excluded as they did not report cellulitis results separate to main ABSSI results (please see the guideline evidence review appendix for excluded studies).

					MRSA, dalbavancin provides a convenient and well tolerated treatment option for the management of ABSSSI.	
96	Correvio Ltd	Draft Guideline	12	1	Efficacy and safety Acute bacterial skin and skin structure infections (ABSSSIs) are a cause of significant morbidity, while therapy can be a burden to the healthcare system. New antibiotics that simplify treatment and avoid hospitalization can offer benefits to the patients, the hospital and the payer. Studies DISCOVER 1 and 2 were identically designed noninferiority trials of dalbavancin versus vancomycin–linezolid for the treatment of acute bacterial skin and skin-structure infection. When these studies were pooled, 525 of 659 patients (79.7%) in the dalbavancin group and 521 of 653 (79.8%) in the vancomycin–linezolid group had an early clinical response indicating treatment success. Adverse events and study days with an adverse event were less frequent in the dalbavancin group than in the vancomycin–linezolid group. The most common treatment-related adverse events in either group were nausea, diarrhoea, and pruritus. The authors concluded that once-weekly intravenous dalbavancin was not inferior to twice-daily intravenous vancomycin followed by oral linezolid for the treatment of acute bacterial skin and skin-structure infection Boucher, 2014. When comparing the single dose regimen of dalbavancin versus the two dose regimen, patients were randomized to dalbavancin 1500 mg either as a single intravenous (IV) infusion or 1000 mg IV on day 1 followed 1 week later by 500 mg IV. The primary endpoint was a ≥20% reduction in the area of erythema at 48–72 hours in the intent-to-treat population. Dalbavancin delivered as a single dose was noninferior to a 2-dose regimen (81.4% vs 84.2%; difference, −2.9% [95% CI, −8.5% to 2.8%]). Clinical	Thank you for your comment. Please note that dalbavancin was an antibiotic included within the guideline search strategy. • Boucher 2014 (DISCOVER 1 and 2) is an included study within the evidence review. • Gonzales 2019 – unfortunately NICE were unable to identify this specific publication.

					outcomes were also similar at day 14 (84.0% vs 84.8%), day 28 (84.5% vs 85.1%), and day 14 in clinically evaluable patients with MRSA in a baseline culture (92.9% vs 95.3%) in the single and 2-dose regimens, respectively. Treatment-emergent adverse events occurred in 20.1% of the single-dose patients and 19.9% on the 2-dose regimen. Data on the efficacy and safety of dalbavancin in clinical practice are derived from a phase 4 observational, multicenter, retrospective cohort study (DRIVE). Data were abstracted from medical charts of 1168 adult patients treated with dalbavancin during 2016–2018 at 34 sites across the United States (Gonzales 2019). The safety population included 1010 ABSSSI patients (86.5%) and 158 non-ABSSSI patients (13.5%), the evaluable population 953 (87.3%) ABSSSI and 139 (12.7%) non-ABSSSI patients. Mean age was 57.3 (±17.7) years, mean body mass index 30.5 (±8.6) kg/m^2, with 25% of patients presenting with a Charlson Comorbidity Index of ≥5. Comorbidities and specific conditions included myocardial infarction (77%), congestive heart failure (9%). peripheral vascular disease (11%), cerebrovascular disease (5%), dementia (2%), chronic obstructive pulmonary disease (7%), diabetes mellitus (32%), moderate to severe chronic kidney disease (11%), blood or solid tumours (8%), alcohol abuse (7%), and non-alcohol drug abuse (11%). Overall success rate (95% CI) was 73.5% (70.8–76.1), with similar results for patients with ABSSSI (73.8%) and non-ABSSSI (71.9%). Adverse events during the DRIVE study were consistent with those noted in clinical trials of dalbavancin and dalbavancin-related serious adverse events were observed in 7/1010 (0.7%) of ABSSSI patients and 1/158 (0.6%) of non-ABSSSI patients. Conclusions. A single 1500-mg infusion of dalbavancin is noninferior to a 2-dose regimen,	

					has a similar safety profile, and removes logistical constraints related to delivery of the second dose. Data from the large DRIVE registry assessing patients with significant comorbidities treated in a real-world setting supports the overall positive benefit-risk balance of dalbavancin.	
97	Correvio Ltd	Draft Guideline	12	1	Cost effectiveness There are scenarios where dalbavancin offers a potential cost saving. Where the patient is not suitable for OPAT and therefore would require admission to hospital for an extended period of time, such as patients who are homeless, alcohol or drug abuse patients, or where a patient has learning disabilities, dementia or Alzheimer's. These conditions may require an extended hospital stay, even though this is undesirable for the patient, the treating health care professionals and the hospital. The SMC concluded that dalbavancin could be cost effective when avoiding an inpatient stay, https://www.scottishmedicines.org.uk/medicines-advice/dalbavancin-xydalba-fullsubmission-110515/ Jan 2017. Falconer S, Poster #P2296 recently presented two years' worth of data that demonstrated dalbavancin can be cost saving, should it allow admissions avoidance, when patients are unable to travel in daily for OPAT care, or where capacity issues exist within a hospital.	Thank you for your comment. Please note that dalbavancin was an antibiotic included within the guideline search strategy. The committee were aware of the SMC decision regarding dalbavancin. • Falconer is not a full publication (conference abstract) and therefore was not included in the review. • The committee have indicated in the prescribing table that other antibiotics for ambulatory care may be appropriate based on specialist advice for certain populations.
98	Correvio Ltd	Draft Guideline	23	2	Patient groups: Homeless and PWID (Patients Who Inject Drugs) Gonzalez, 2018, analysed Patients Who Inject Drugs (PWID) in the single-dose study, and concluded that dalbavancin as a single-dose or 2-dose regimen had similar efficacy for the treatment of ABSSSI at all timepoints in the PWID and non-PWID populations.. Clinical success by baseline pathogen was also similar in the PWID	Thank you for your comment. Please note that dalbavancin was an antibiotic included within the guideline search strategy. • Gonzalez 2018 does not present data for cellulitis outcomes alone and therefore was not eligible for inclusion. • Nathwani et al 2016 was excluded from the evidence review as it is not an RCT or systematic review.

					and non-PWID subgroups, with comparable efficacy in the treatment of MRSA as in MSSA. The single-dose therapy may be particularly useful in populations with poor adherence or at high risk for loss to follow-up, and therefore where there is greater potential for emergence of recurrent infection with resistant strains of bacteria. In this study subgroup analysis, 10.3% of the PWID group in the 2-dose dalbavancin arm did not receive the second dose on day 8, compared to 4.1% of the non-PWID group in the 2-dose dalbavancin arm (*p*=0.047). The most common reasons for missing the second dose in the PWID subgroup were related to social circumstances that may be seen in this population: loss to follow-up (n=4), withdrawal of consent (n=2), or incarceration (n=2), while the most common reasons in the non-PWID subgroup were related to the infection or treatment and were due to investigator judgment to prematurely discontinue study drug: adverse events (n=5), or only gram-negative bacteria identified from ABSSSI infection site (n=2). The PWID population, which is more likely to be nonadherent than the non-PWID population, could benefit from single-dose therapy with dalbavancin in a community setting, or in a hospital setting Nathwani, 2016 In hospitalized patients, nonadherence to oral antibiotics after discharge is an important predictor of poor outcome and relapse, Mertz, 2008 In a study by Eells, 2016, researchers found that patients with S. aureus skin and soft tissue infections took, on average, just 57% of their prescribed antibiotic doses after leaving the hospital. This resulted in approximately half of them developing a new infection or needing additional treatment for the existing skin infection.	• Mertz 2008 – unfortunately NICE were unable to identify this specific publication, it may be Mertz et al 2009 which is not an RCT or systematic review and therefore was not eligible for inclusion. • Eells et al 2016 is not an RCT or systematic review and therefore was not an includable study. • Hemmige et al 2015 is not an RCT or systematic review and therefore was not eligible for inclusion. • Waldron 2015 – – unfortunately NICE were unable to identify this specific publication. • Buehrle DJ et al 2017 is not an RCT or systematic review and therefore was not eligible for inclusion.

					In this study, researchers followed 188 patients who had been hospitalized and had S. aureus associated skin and soft tissue infections; researchers were able to obtain complete records on 87 of the patients. Of these, 40 required additional treatment within 30 days of leaving the hospital due to: a new skin infection, requirement of incision and drainage of their infections, or new antibiotics. The researchers also found higher rates of non-adherence to antibiotic regimens among patients who were prescribed more than one antibiotic after leaving the hospital, who did not see the same healthcare provider for follow up visits or who felt they did not have a regular healthcare provider. These findings suggest that an antibiotic with fewer treatment administrations (e.g. single dose or two-dose regimen) would be beneficial to patients and potentially improve compliance and efficacy outcomes. In a community setting, adherence can be further compromised; PWID are at higher risk of recurrent ABSSSIs Hemmige, 2015, and more likely to have severe disease with adverse outcomes Waldron, 2015. Reasons for outpatient antibiotic failure in PWID also include missed follow-up visits, noncompliance with antibiotic therapy, and documented line manipulation Buehrle, 2017.	
99	Correvio Ltd	Draft Guideline	14	5	Tolerance to medication There is a growing body of evidence, that antibiotics that have been used for years, e.g. vancomycin are associated with adverse events such as nephrotoxicity at higher doses without any significant additional clinical benefit (Jeffres 2017; Filippone 2017). Antibiotics like dalbavancin offer a solution to the difficult to tolerate antibiotics, when given as a single dose infusion or two-dose regimen. This dosing regimen minimises the compliance issue. In	Thank you for your comment. Please note that dalbavancin was an antibiotic included within the guideline search strategy. • The systematic review by Jeffres 2017 is out-of-scope for this guideline as it does not include the guideline population (people with cellulitis). • Filippone et al 2017 is not an RCT or systematic review and is out-of-scope for this guideline. • The study by Dunne 2016 was excluded as it did not report cellulitis results separate to main ABSSI results (please see the guideline evidence review appendix for excluded studies)

					addition, dalbavancin does not require dose adjustments in the following populations: • Elderly • Up to moderate renal failure (dose reduction recommended if CrCl below 30 ml/min) • Mild hepatic impairment • Overweight or obese (higher BMI) • Patients on dialysis. A recent article by Jeffres, 2017, suggested that Vancomycin-associated nephrotoxicity is linked with increased duration of hospitalization, costs, and risk of mortality. Elevated trough concentrations are associated with a higher incidence of nephrotoxicity, but not clinical cure. Monitoring vancomycin concentrations is time consuming and resource intensive, therefore use of an alternative antibacterial could save time and resources that could then be devoted to initiatives like antibiotic stewardship, which has demonstrated improved patient outcomes. In pooled analysis of seven Phase II and Phase III clinical trials evaluated adverse events in 3002 patients, Dunne, 2016 demonstrated that patients receiving dalbavancin were associated with lower overall adverse event rates than those patients receiving comparator agents (44.9% vs 46.8%, respectively; P=0.012). Relative to those treated with comparator, patients receiving dalbavancin experienced also fewer treatment-related adverse events (18.4 vs. 20.1 %, respectively, p = 0.014), and fewer treatment-related serious adverse events (0.2 vs. 0.7 %, respectively, p = 0.021). The duration of adverse events was similar for dalbavancin and the comparator regimens, with a median of 3.0 and 4.0 days. In this analysis, nephrotoxicity rates were numerically lower in patients receiving dalbavancin than in those receiving vancomycin for at least 10 days [dalbavancin 3.3 vs. vancomycin 9.3 % (p = 0.06)], supported by	

					rates of nephrotoxicity in a smaller subset of patients, controlling for factors related to continuation of intravenous therapy [dalbavancin 1.7 % vs. vancomycin 9.3 % (p = 0.21)].	
100	Public Health England	Visual summary	1	Box on 'Advise'	PHE recommends that a new box is added before the box titled 'Advise'. This new box should include: "Assess and consider: Other possible diagnoses, such as non-infectious inflammation, symptoms or signs of something more serious (such as lymphangitis, necrotising fasciitis or sepsis). Previous antibiotic use, which may have led to resistant bacteria." This text has been predominantly taken from the box titled "Reassess if". If the suggested new box is added to the visual summary, the last paragraph from the "Reassess if" box should be deleted.	Thank you for your comment. The visual summary has been amended in line with your comment. However, please note that it is only a summary of the guideline and cannot be as comprehensive as the full guideline. Other possible diagnosis are covered by the guideline.
101	Public Health England	Visual summary	1	Background	Acute cellulitis and erysipelas are: • skin infections • usually caused by Streptococcus pyogenes and Staphylococcus aureus bacteria • treated with antibiotics Exclude non-infective causes of inflammation (this is because many insect bites and allergic reactions are treated as a mild cellulitis)	Thank you for your comment. The visual summary is for the management of cellulitis and erysipelas. It is only a summary of the guideline and cannot be as comprehensive as the full guideline. Other possible diagnoses are covered by the guideline.
102	Public Health England	Visual summary	1	Background	PHE recommends that the background should include the following addition "Give oral antibiotics first line if possible and if there are no systematic symptoms. Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics if possible".	Thank you for your comment. The grey left hand box now recommends oral antibiotics first line if possible and a review of IV antibiotics by 48 hours with a switch to oral antibiotics if possible in response to stakeholder comments.
103	Public Health England	Visual summary	1	Antibiotics	It is better to put all information on prophylactic antibiotics together on the document	Thank you for your comment. The visual summary has been amended to take account of your comments. The wordings are now adjacent but due to space limitations could not be combined.

104	Public Health England	Visual summary	1	Antibiotics	PHE recommends that clarithromycin is prescribed for a penicillin allergy and not erythromycin because side effects are less and compliance is better.	Thank you for your comment. Please note that clarithromycin is the first treatment option in the guideline for penicillin allergy, erythromycin is noted for use in pregnancy.
105	Public Health England	Choice of antibiotic	4	9	PHE wishes to bring to the attention of NICE two peer review publications which show that shorter courses (five days) are just as effective as longer courses in patients with uncomplicated cellulitis in adults • Hepburn et al. 2004 https://www.ncbi.nlm.nih.gov/pubmed/15302637 • Brindle et al. 2017 https://www.ncbi.nlm.nih.gov/pubmed/28314743 Shorter courses will support tackling AMR as well as reduce risk of adverse/side effects on patients	Thank you for your comment. The committee discussed and have amended the flucloxacillin course length to 5 to 7 days in response to stakeholder comments.
106	Scottish Antimicrobial Prescribing Group & Healthcare Improvement Scotland	Guideline	General		Challenges to implementation – see comment 1 re layout to ensure staff in various settings can access correct information. To make information clearer a flowchart may be helpful separating out community versus hospital treatment and options for standard and penicillin allergic patients. Course length of 7 days with option for additional 7 days seems reasonable.	Thank you for your comment. The guideline prescribing tables have been amended following consultation to make them clearer in response to stakeholder comments. We are unable to provide a flowchart and we do not separate out community and hospital options as such. The committee discussed and have amended the flucloxacillin course length to 5 to 7 days in response to stakeholder comments.
107	Scottish Antimicrobial Prescribing Group & Healthcare Improvement Scotland	Guideline	General		Sections would be better broken up into those requiring admission and outpatient/primary care management. Also there is no mention of OPAT which is an increasingly common approach to managing patients with cellulitis to reduce hospital stay.	Thank you for your comment. The committee have discussed at length the layout of the table following consultation. We do not separate out community and hospital options as such. However, the committee have included ceftriaxone as an option for ambulatory care in response to stakeholder comments.
108	Scottish Antimicrobial Prescribing	Guideline	4	Table 1	• Oral treatment - Dosing of oral flucloxacillin.500mg dose may be ineffective suggest 1g is appropriate in adults.	Thank you for your comment. In response to stakeholder comments, the committee have agreed that:

	Group & Healthcare Improvement Scotland				• Dosing of IV flucloxacillin – range given is 500mg to 2g QDS. Unsure where the lower figure comes from and would not expect it to be effective. Suggest considering 2g QDS for all adult patients unless eGFR is < 10, in which case 1g QDS. • The need and reasoning for coamoxiclav for infections close to the nose and eyes is unclear. The reasoning for an alternative to fluclox is first and foremost the occasional isolation of pathogens other than Staph aureus and Strep pyogenes which would warrant a broad spectrum antibiotics and secondarily the complications. • The alternatives to coamoxiclav for penicillin allergic patients with eye/nose involvement are not suitable as gram negative cover is required (otherwise adding metronidazole to fluclox would be suitable for the non-pen allergic). • Doxycycline/cotrimoxazole is not mentioned as an alternative and probably should be for pen allergic outpatient treatment or step down. • Clindamycin needs a warning around for those at risk of CDI. • Cefuroxime given the range of alternatives would never be part of our recommendations given, use leads to cultural changes within prescribing which leads to its use out with guideline directed use. • No idea why Gentamicin is in the guidelines. May add to someone very unwell but this is not how it is outlined. Suggest caveats included regarding linezolid use in view of the many interactions/ contraindications and monitoring requirements due to toxicity.	• The dosing of flucloxacillin should be 500 mg to 1 g four times a day orally or 1 to 2 g four times a day IV. • The risk of serious complication is low from infection around the eyes and nose. However, the consequences of such a serious complication would likely be very severe so in order to reduce first line treatment failure they have indicated that co-amoxiclav is suitable option. • The important factor is to offer antibiotic cover for both aerobic and anaerobic organisms for people with infection around the eyes and nose. The first choice antibiotic is co-amoxiclav, with clarithromycin plus metronidazole for people with penicillin allergy. • Doxycycline should be included as an option. The committee discussed that the risk of co-trimoxazole use generally outweighs the level of benefit and there are other available options. The committee discussed that so it should only ever be given for cellulitis on specialist advice. • Footnote 1 refers the reader to the BNF for specific information for each antibiotic (including for clindamycin the risk of antibiotic associated colitis). The guideline also gives safety information from the BNF that 'Clindamycin has been associated with colitis and diarrhoea. Although this can occur with most antibiotics, it is more frequent with clindamycin'. • Cefuroxime is a suitable treatment option. • Gentamicin should be removed as a treatment option. • Linezolid is should be for specialist use only (if vancomycin or teicoplanin cannot be used).
109	Scottish Antimicrobial	Guideline	8	1.3	What is the evidence for prophylaxis? More useful approach is anticipatory prescribing – giving	Thank you for your comment. The evidence for prophylaxis comes from the Cochrane systematic

	Prescribing Group & Healthcare Improvement Scotland				patients a treatment course to start at the first signs of infection – but this does not seem to have been considered.	review on Interventions for the prevention of recurrent erysipelas and cellulitis by Dalal et al 2017 (see also the NICE evidence review). The evidence search and review found no evidence for anticipatory prescribing.