Cellulitis and erysipelas: antimicrobial prescribing

NICE guideline

Draft for consultation, April 2019

This guideline sets out an antimicrobial prescribing strategy for cellulitis and erysipelas. These skin infections are usually caused by *Streptococcus pyogenes* or *Staphylococcus aureus* bacteria. It aims to optimise antibiotic use and reduce antibiotic resistance. It does not cover diagnosis.

For managing other skin conditions, see our web page on skin conditions.

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

Who is it for?

- Healthcare professionals
- People with cellulitis or erysipelas, their families and carers

The guideline contains:

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

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

Recommendations

1.1 Managing cellulitis and erysipelas

Treatment

1.1.1 Before treating cellulitis or erysipelas, consider drawing around the extent of the infection with a single-use surgical marker pen to monitor progress. Be aware that redness may be less visible on darker skin tones.

1.1.2 Offer an antibiotic for people with cellulitis or erysipelas. When choosing an antibiotic (see the recommendations on choice of antibiotic) take account of:

- the severity of symptoms
- the site of infection
- the risk of developing complications
- previous antibiotic use.

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

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

Advice

1.1.5 When prescribing antibiotics for cellulitis or erysipelas, give advice about:

- possible adverse effects of the antibiotic
- the skin taking some time to return to normal after the course of antibiotics has finished
- seeking medical help if symptoms worsen rapidly or significantly at any time, or do not start to improve within 2 to 3 days.

Reassessment

1.1.6 Reassess people with cellulitis or erysipelas if symptoms worsen rapidly or significantly at any time, do not start to improve within 2 to 3 days, or the person:

- becomes systemically very unwell, **or**
- has severe pain out of proportion to the infection, **or**
- has redness or swelling spreading beyond the initial presentation (taking into account that some initial spreading may occur, and that redness may be less visible on darker skin tones).

1.1.7 When reassessing people with cellulitis or erysipelas, take account of:

- other possible diagnoses, such as an inflammatory reaction to an insect bite, gout, superficial thrombophlebitis, eczema, allergic dermatitis or deep vein thrombosis
- any symptoms or signs suggesting a more serious illness or condition, such as lymphangitis, necrotising fasciitis or sepsis
- previous antibiotic use, which may have led to resistant bacteria.

Referral and seeking specialist advice

1.1.8 Refer people with cellulitis or erysipelas to hospital if they have any symptoms or signs suggesting a more serious illness or condition, such as lymphangitis, necrotising fasciitis or sepsis.

1.1.9 Consider referring or seeking specialist advice for people with cellulitis or erysipelas if they:

- are severely unwell, **or**
- have a higher risk of complications, **or**
- have infection near the eyes or nose, **or**
- could have uncommon pathogens, **or**
- have spreading infection that is not responding to oral antibiotics, **or**

- cannot take oral antibiotics (exploring locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital, where appropriate).

See the committee discussion on managing cellulitis and erysipelas.

1.2 Choice of antibiotic

1.2.1 When prescribing antibiotics for cellulitis or erysipelas follow:

- table 1 for adults aged 18 years and over
- table 2 for children and young people under 18 years.

Table 1. Antibiotics for adults aged 18 years and over

Antibiotic[1]	**Dosage and course length[2]**
First choice oral antibiotic	
Flucloxacillin	500 mg four times a day for 7 days[3]
Alternative first choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable	
Clarithromycin	500 mg twice a day for 7 days[3]
Erythromycin (in pregnancy)	500 mg four times a day for 7 days[3]
First choice oral antibiotic if infection near the eyes or nose[4] (consider seeking specialist advice)	
Co-amoxiclav	500/125 mg three times a day for 7 days[3]
Alternative first choice oral antibiotics if infection near the eyes or nose[4] for penicillin allergy or if co-amoxiclav unsuitable (consider seeking specialist advice)	
Clarithromycin ***with***	500 mg twice a day for 7 days[3]
Metronidazole	400 mg three times a day for 7 days[3]
First choice intravenous antibiotic (if unable to take oral antibiotics or severely unwell)[5,6]	
Flucloxacillin	500 mg to 2 g four times a day
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]	
Clarithromycin	500 mg twice a day
Co-amoxiclav (not if penicillin allergy)	1.2 g three times a day
Cefuroxime	750 mg to 1.5 g three or four times a day
Clindamycin	600 mg to 2.7 g daily in two to four divided doses, increased if necessary to 4.8 g daily (maximum per dose 1.2 g)
Gentamicin	Initially 5 to 7 mg/kg once a day, subsequent doses

	adjusted according to serum gentamicin concentration[7]
Vancomycin	15 to 20 mg/kg two or three times a day (maximum 2 g per dose), adjusted according to serum-vancomycin concentration[8]
Linezolid (if vancomycin cannot be used; specialist advice only)	600 mg twice a day

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.

[2] Oral doses are for immediate release medicines.

[3] A longer course (up to a further 7 days) may be needed based on clinical assessment. However, skin does take some time to return to normal, and full resolution of symptoms at 7 days is not expected.

[4] Infection around the eyes or the nose (the triangle from the bridge of the nose to the corners of the mouth, or immediately around the eyes) is of more concern because of risk of a serious intracranial complication.

[5] Give oral antibiotics first-line if the person can take oral medicines, and the severity of their symptoms does not require intravenous antibiotics.

[6] Review intravenous antibiotics by 48 hours and consider switching to oral antibiotics where possible for a total of 7 days.

[7] Therapeutic drug monitoring and assessment of renal function is required (BNF, February 2019).

[8] Therapeutic drug monitoring and assessment of renal function is required. A loading dose of 25 to 30 mg/kg (maximum per dose 2 g) can be used in seriously unwell people to facilitate rapid attainment of the target trough serum vancomycin concentration (BNF, February 2019).

Table 2 Antibiotics for children and young people under 18 years

Antibiotic[1]	**Dosage and course length[2]**
First choice oral antibiotic	
Flucloxacillin	1 month to 1 year, 62.5 mg to 125 mg four times a day for 7 days[3] 2 to 9 years, 125 mg to 250 mg four times a day for 7 days[3] 10 to 17 years, 250 mg to 500 mg four times a day for 7 days[3]
Alternative first choice oral antibiotics for penicillin allergy or if flucloxacillin unsuitable	
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 7 days[3] 8 to 11 kg, 62.5 mg twice a day for 7 days[3] 12 to 19 kg, 125 mg twice a day for 7 days[3] 20 to 29 kg, 187.5 mg twice a day for 7 days[3]

	30 to 40 kg, 250 mg twice a day for 7 days[3] 12 to 17 years: 250 mg to 500 mg twice a day for 7 days[3]
Erythromycin (in pregnancy)	8 to 17 years, 250 mg to 500 mg four times a day for 7 days[3]
First choice oral antibiotic if infection near the eyes or nose[4] (consider seeking specialist advice)	
Co-amoxiclav	1 to 11 months, 0.25 ml/kg of 125/31 suspension three times a day for 7 days[3] (dose doubled in severe infection) 1 to 5 years, 0.25 ml/kg of 125/31 suspension or 5 ml of 125/31 suspension three times a day for 7 days[3] (dose doubled in severe infection) 6 to 11 years, 0.15 ml/kg of 250/62 suspension or 5 ml of 250/62 suspension three times a day for 7 days[3] (dose doubled in severe infection) 12 to 17 years, 250/125 mg or 500/125 mg three times a day for 7 days[3]
Alternative first choice oral antibiotics if infection near the eyes or nose[4] for penicillin allergy or if co-amoxiclav unsuitable (consider seeking specialist advice)	
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 7 days[3] 8 to 11 kg, 62.5 mg twice a day for 7 days[3] 12 to 19 kg, 125 mg twice a day for 7 days[3] 20 to 29 kg, 187.5 mg twice a day for 7 days[3] 30 to 40 kg, 250 mg twice a day for 7 days[3] 12 to 17 years: 250 mg to 500 mg twice a day for 7 days[3]
with (if anaerobes suspected): Metronidazole	1 month, 7.5 mg/kg twice a day for 7 days[3] 2 months to 11 years, 7.5 mg/kg three times a day (maximum per dose 400 mg) for 7 days[3] 12 to 17 years, 400 mg three times a day for 7 days[3]
First choice intravenous antibiotic (if unable to take oral antibiotics or severely unwell[5,6]	
Flucloxacillin	1 month to 12 years, 12.5 mg to 25 mg/kg four times a day (maximum 1 g four times a day)
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]	
Clarithromycin	1 month to 11 years, 7.5 mg/kg twice a day (maximum 500 mg per dose) 12 to 17 years, 500 mg twice a day
Co-amoxiclav (not if penicillin allergy)	1 to 2 months, 30 mg/kg twice a day 3 months to 17 years, 30 mg/kg three times a day (maximum 1.2 g three times a day)
Cefuroxime	1 month to 17 years, 20 mg/kg three times a day (maximum 750 mg per dose), increased to 50 to 60 mg/kg three or four times a day (maximum 1.5 g per dose) for severe infections
Clindamycin	1 month to 17 years, 3.75 to 6.25 mg/kg four times a day, increased if necessary to 10 mg/kg four times a day (maximum per dose 1.2 g); total daily dose may alternatively be given in three divided doses (maximum per dose 1.2 g)
Gentamicin	Initially 7 mg/kg once a day, subsequent doses adjusted according to serum gentamicin concentration[7]
Vancomycin	1 month to 11 years, 10 to 15 mg/kg four times a day, adjusted according to serum-vancomycin concentration[8] 12 to 17 years, 15 to 20 mg/kg two or three times a day (maximum 2 g per dose), adjusted according to serum-vancomycin concentration[8]
Linezolid[9] (if vancomycin cannot be used; specialist advice only)	1 month to 11 years, 10 mg/kg three times a day (maximum 600 mg per dose) 12 to 17 years, 600 mg twice a day

[1] See BNFC for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding, and administering intravenous antibiotics.

[2] The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age. Oral doses are for immediate release medicines.

[3] A longer course (up to a further 7 days) may be needed based on clinical assessment. However, skin does take some time to return to normal, and full resolution of symptoms at 7 days is not expected.

[4] Infection around the eyes or the nose (the triangle from the bridge of the nose to the corners of the mouth, or immediately around the eyes) is of more concern because of risk of a serious intracranial infection.

[5] Give oral antibiotics first-line if the child or young person can take oral medicines, and the severity of their symptoms does not require intravenous antibiotics.

[6] Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible for a total of 7 days.

[7] Therapeutic drug monitoring and assessment of renal function is required (BNFC, February 2019).

[8] Therapeutic drug monitoring and assessment of renal function is required. A loading dose of 25 to 30 mg/kg (maximum per dose 2 g) can be used in seriously unwell people to facilitate rapid attainment of the target trough serum vancomycin concentration (BNFC, February 2019).

[9] Linezolid is not licensed in children and young people under 18 years, so use would be off label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

See the evidence and committee discussions on choice of antibiotics, antibiotic dose frequency, antibiotic course length, and antibiotic route of administration.

1.3 Preventing recurrent cellulitis or erysipelas

1.3.1 Do not routinely offer antibiotic prophylaxis to prevent recurrent cellulitis or erysipelas. Give advice about seeking medical help if symptoms of cellulitis or erysipelas develop.

1.3.2 For adults who have had treatment in hospital, or under specialist advice, for at least 2 episodes of cellulitis or erysipelas in the previous 12 months, consider a trial of antibiotic prophylaxis. Involve the person in a shared decision by discussing and taking account of:

- the severity and frequency of previous symptoms
- the risk of developing complications
- underlying conditions (such as oedema, diabetes or venous insufficiency) and their management
- the person's preference for antibiotic use.

1.3.3 When choosing an antibiotic (see the recommendations on choice of antibiotic prophylaxis) take account of any previous microbiological results and previous antibiotic use.

1.3.4 When antibiotic prophylaxis is given, give advice about:

- possible adverse effects of the antibiotic
- returning for review within 6 months
- seeking medical help if symptoms of cellulitis or erysipelas recur.

1.3.5 Review antibiotic prophylaxis for recurrent cellulitis or erysipelas at least every 6 months. The review should include:

- assessing the success of prophylaxis
- discussion of continuing, stopping or changing prophylaxis (taking into account the person's preferences for antibiotic use and the risk of antimicrobial resistance)

Antibiotic prophylaxis should be stopped or switched to an alternative antibiotic if cellulitis or erysipelas recurs.

See the evidence and committee discussion on antibiotic prophylaxis for the prevention of recurrent cellulitis and erysipelas.

1.4 Choice of antibiotic prophylaxis

1.4.1 When prescribing antibiotics to prevent recurrent cellulitis or erysipelas in adults follow table 3.

Table 3. Antibiotic prophylaxis for adults 18 years and over

Antibiotic prophylaxis[1,2]	**Dosage[3]**
First choice	
Phenoxymethylpenicillin	250 mg twice a day
Alternative first choice for penicillin allergy	
Erythromycin	250 mg twice a day
For alternative antibiotics, seek specialist advice	
[1]See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast feeding.	

[2]Choose antibiotics according to recent microbiological results where possible. Avoid using the same antibiotic for treatment and prophylaxis.
[3]Doses given are by mouth using immediate release medicines, unless otherwise stated.

See the evidence and committee discussion on antibiotic prophylaxis for the prevention of recurrent cellulitis and erysipelas.

Terms used in the guideline

Cellulitis and erysipelas

Infections of the tissues under the skin (subcutaneous), which usually result from contamination of a break in the skin. Both conditions are characterised by acute localised inflammation and oedema, with lesions more superficial in erysipelas with a well-defined, raised margin (World Health Organization 2018).

Summary of the evidence

This is a summary of the evidence, for full details see the evidence review.

Managing cellulitis and erysipelas

- Cellulitis and erysipelas are infections of the tissues under the skin, which are treated with antibiotics.
- The main bacteria causing cellulitis and erysipelas are *Streptococcus pyogenes* and *Staphylococcus aureus*, but infection can also be caused by *Streptococcus pneumoniae, Haemophilus influenza*, Gram negative bacilli and anaerobes (NICE CKS – Cellulitis 2016).
- The evidence identified in this guideline was for antibiotics compared with other antibiotics for managing non-surgically acquired cellulitis or erysipelas in adults, young people and children. Most studies did not report the site of infection, but where this was reported most cases had a lower limb infection or less frequently an upper limb infection. One systematic review excluded a study of facial cellulitis.

Committee discussion on managing cellulitis and erysipelas

- The committee agreed based on experience that in order to monitor the progression of cellulitis or erysipelas, and help assess the effectiveness of antibiotic treatment, it may be useful to draw around the extent of the infected area using a single use surgical marker pen before treatment. The committee discussed that a single use surgical pen should be used as it is designed for purpose (unlike other pen types which may damage skin or leave permanent marking) and would not risk cross infection. The committee also noted that in people with certain conditions (for example lymphoedema) drawing around the infected area may be difficult or not possible because the rash may be ill-defined.
- The committee agreed that it may take time for antibiotic treatment to take effect, and initially redness or swelling may extend beyond the marked line (if used).
- The committee agreed that, in line with the NICE guideline on antimicrobial stewardship (NG15), prescribers should provide 'safety netting' advice to people with cellulitis or erysipelas about when to seek further help if they become more unwell or have side effects of antibiotic treatment, but to also discuss that skin can take some time to return to normal even after a course of effective antibiotics. The committee was aware that the time taken for skin to return to normal appearance is variable, but in their experience could be a number of weeks.
- The committee agreed that if a person's symptoms worsen rapidly or significantly at any time they should be reassessed taking into account other possible diagnoses, the development of serious complications, such as lymphangitis, necrotising fasciitis or sepsis, and the possibility of an antimicrobial resistant infecting organism.
- The committee agreed that people with cellulitis or erysipelas should be referred to hospital if they have symptoms or signs suggestive of necrotising fasciitis or sepsis.
- The committee discussed and agreed that in some cases the prescriber may need to consider referring or seeking specialist advice on inpatient

treatment or locally available options for intravenous treatment at home or in a community setting. These cases include people who are severely unwell, at higher risk of complications, have infection near the eyes or nose, could have uncommon pathogens, have lymphangitis, have a spreading infection that is not responding to oral antibiotics or cannot take oral antibiotics. They discussed that children under 1 year and people who are frail or have underlying disease (such as diabetes or immunosuppression) are at a higher risk of developing complications, as are those who could have an uncommon causative organism, for example following a wound exposed to water [surfers for example] or during farm work.

Choice of antibiotics

Effectiveness of antibiotics versus other antibiotics in adults

- There were no differences in the clinical effectiveness of the following antibiotic comparisons in adults with cellulitis or erysipelas:
  - an oral penicillin or cephalosporin compared with an oral macrolide or oral clindamycin (adults and children) (Ferreira et al 2016),
  - oral azithromycin compared with oral cefalexin (Kilburn et al 2010),
  - oral azithromycin compared with oral erythromycin (Kilburn et al 2010),
  - IV then oral moxifloxacin compared with IV then oral co-amoxiclav (Vick-Fragaso et al 2009),
  - IV or oral linezolid compared with IV vancomycin (Kilburn et al 2010),
  - IV dalbavancin compared with IV vancomycin (Boucher et al 2014),
  - IV ampicillin with sulbactam compared with IV cefazolin (Kilburn et al 2010),
  - IV flucloxacillin compared with IV ceftriaxone (Kilburn et al 2010),
  - IV moxifloxacin compared with IV piperacillin with tazobactam (Kilburn et al 2010),
  - IV daptomycin compared with IV penicillin or IV vancomycin (Konychev et al 2013),
  - IV tigecycline compared with IV ampicillin with sulbactam or IV co-amoxiclav (Matthews et al 2012),

  - newer cephalosporins compared with older cephalosporins (Kilburn et al 2010),
  - IV ceftaroline compared with IV vancomycin plus aztreonam (Frampton 2013),
  - IV daptomycin compared with IV vancomycin (Pertel et al 2009),
  - IV meropenem compared with IV imipenem with cilastatin (Kilburn et al 2010).

- Some differences were seen for some effectiveness outcomes for the following antibiotic comparison in adults with cellulitis or erysipelas:
  - oral macrolides or oral streptogramins improved the number of people who were symptom free, or had reduced symptoms, at 7 to 14 days follow-up compared with a penicillin (Kilburn et al 2010).

Based on 3 systematic reviews (Frampton 2013, Ferreira et al 2016 and Kilburn et al 2010) and 5 RCTs (Boucher et al 2014, Konychev et al 2013, Matthews et al 2012, Pertel et al 2009, and Vick-Fragaso et al 2009).

Effectiveness of antibiotics versus other antibiotics in children

- There was no difference in the clinical effectiveness of the following antibiotic comparison in children with cellulitis or erysipelas:
  - IV linezolid compared with IV vancomycin (Yogev et al 2003).

Based on 1 RCT (Yogev et al 2003).

Dual therapy in adults or children

- There were no differences in the clinical effectiveness of the following antibiotic comparisons in adults or children with cellulitis or erysipelas:
  - oral cefalexin plus oral co-trimoxazole compared with oral cefalexin alone (Bowen et al 2017),
  - IV then oral flucloxacillin plus IV then oral benzylpenicillin compared with IV then oral flucloxacillin alone (Kilburn et al 2010),
  - IV or oral flucloxacillin plus oral clindamycin compared with IV or oral flucloxacillin alone (Brindle et al 2017),

- IV ceftazidime plus IV vancomycin compared with IV ceftobiprole alone (Noel et al 2008).

Based on 2 systematic reviews (Bowen et al 2017 and Kilburn et al 2010) and 2 RCTs (Brindle et al 2017 and Noel et al 2008).

Safety of antibiotics

- Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE Clinical Knowledge Summary [CKS]: diarrhoea – antibiotic associated).
- About 10% of the general population claim to have a penicillin allergy; this is often because of a skin rash that occurred while taking a course of penicillin as a child. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. See the NICE guideline on drug allergy: diagnosis and management for more information.
- People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta lactam antibiotics (BNF, February 2019).
- Cholestatic jaundice and hepatitis can occur with flucloxacillin up to 2 months after stopping treatment; risk factors are increasing age and use for more than 14 days (BNF, February 2019).
- Cholestatic jaundice can occur with co-amoxiclav, and is more common in people over 65 years and in men; treatment should not exceed 14 days (BNF, February 2019).
- Macrolides should be used with caution in people with a predisposition to QT interval prolongation. Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side effects of macrolides. These are less frequent with clarithromycin than with erythromycin (BNF, February 2019).
- Aminoglycoside doses are based on weight and renal function, and whenever possible treatment should not exceed 7 days (BNF, February 2019).
- Loading and maintenance doses of vancomycin are calculated on the basis of the person's weight and renal function, with adjustments made according to serum vancomycin concentrations (BNF, February 2019).

- Severe optic neuropathy can occur with linezolid, particularly if used for longer than 28 days. Blood disorders have also been reported and weekly full blood counts are recommended (BNF, February 2019).
- See the summaries of product characteristics for information on contraindications, cautions and adverse effects of individual medicines.
- Data on adverse events in the included studies were limited due to cellulitis or erysipelas often being a subgroup in larger skin and skin structure infection studies, where adverse event data were presented for the whole study not cellulitis or erysipelas subgroups.
- There were no differences in the adverse events of the following antibiotic comparisons in adults or children with cellulitis or erysipelas:
  - oral cefazolin compared with IV ceftriaxone (Kilburn et al 2010),
  - oral cefalexin plus oral co-trimoxazole compared with oral cefalexin alone (Bowen et al 2017),
  - oral cefalexin or oral clindamycin compared with IV cefazolin or IV clindamycin (Aboltins et al 2015),
  - oral levofloxacin for 5 days compared with 10 days (Kilburn et al 2010),
  - IV ceftriaxone compared with IV flucloxacillin (Kilburn et al 2010),
  - IV daptomycin compared with IV vancomycin (Pertel et al 2009).
- Some differences were seen for some adverse event outcomes for the following antibiotic comparisons in adults or children with cellulitis or erysipelas:
  - flucloxacillin plus clindamycin was significantly worse for adverse events (most commonly diarrhoea) compared with flucloxacillin alone (Brindle et al 2017),
  - IV penicillin was significantly worse for adverse events (no details provided) compared with IM penicillin (Kilburn et al 2010).

Based on 2 systematic reviews (Bowen et al 2017 and Kilburn et al 2010) and 3 RCTs (Brindle et al 2017, Pertel et al 2009 and Aboltins et al 2015).

Committee discussion on choice of antibiotics

- The committee noted that most antibiotics compared with another antibiotic showed no difference in clinical outcomes in adults or children. The committee also noted that dual therapy was no more effective than single antibiotic therapy in adults. Adverse event data were very limited and there were no differences in adverse events between most of the antibiotic comparisons. Given the very limited amount of evidence in children, the committee agreed that antibiotic choice for children can be extrapolated from the choice for adults.
- The committee agreed based on their experience that choice of antibiotic treatment should be based on the severity of symptoms and the risk of developing complications, whilst minimising the risk of the development of antibiotic resistance.
- The committee discussed that in practice erysipelas can often be difficult to tell apart from cellulitis, and recognised that both infections may be caused by *Streptococcus pyogenes* or *Staphylococcus aureus,* although there is uncertainty around the evidence for erysipelas which may be more associated with streptococcus. Therefore management of both infections, with regard to antibiotic choice, is the same.
- The committee were aware that severity scoring tools (for example Eron 2000 and 'Dundee' Koerner & Johnson 2010) have been developed and may be used in practice. However these have not to date been used in randomised clinical trials. The committee agreed that recommendations for antibiotic treatment should reflect the available evidence and provide guidance on oral and intravenous treatment as this would fit with current severity scoring tools and the risks of developing complications without needing evidence of the effectiveness of such tools.
- The committee agreed that the evidence for dual therapy (a combination of 2 antibiotics) showed no benefit over monotherapy for treating cellulitis or erysipelas, and dual therapy should not be routinely used given the increased risk of antimicrobial resistance and more side effects.

- The committee agreed based on the evidence, their experience and resistance data that the first choice **oral antibiotic** should be **flucloxacillin** (a relatively narrow spectrum penicillin). The committee discussed that flucloxacillin has activity against *Staphylococcus aureus* (because it is not inactivated by penicillinases produced by staphylococci) and *Streptococcus pyogenes.*
- The committee were aware that a narrow spectrum penicillin with a specific antistreptococcal penicillin is sometimes prescribed for cases of cellulitis or erysipelas, because these infections can involve either streptococci or staphylococci, but there is no evidence that dual therapy is more effective than, for example, flucloxacillin alone. Additionally, the committee considered that dual therapy may increase the risk of antimicrobial resistance and side effects.
- The committee agreed that oral macrolides, **clarithromycin** or **erythromycin** (in pregnancy), are suitable alternatives to flucloxacillin in people who have penicillin allergy or where flucloxacillin is not a suitable option. Oral macrolide antibiotics were shown to be at least as effective as an oral penicillin in studies, and have a similar spectrum of activity to penicillins. There was limited, very low quality, evidence that oral macrolides or oral streptogramins were more effective than a penicillin (oral or IV). However, the committee considered this evidence was limited because oral macrolides and oral streptogramins were analysed together, not as separate classes. Additionally, the oral streptogramin (pristinamycin) and the only oral penicillin (cloxacillin) are not licensed in the UK. There was no head to head comparison of either oral macrolides or oral streptogramins with flucloxacillin.
- The committee discussed and agreed based on limited evidence and their experience that for infection near the eyes or nose (the triangle from the bridge of the nose to the corners of the mouth, or immediately around the eyes), the first choice oral antibiotic should be **co-amoxiclav** (a penicillin with a beta-lactamase inhibitor) because of the risk of a serious intracranial complication. The committee agreed this extended spectrum antibiotic was needed to prevent treatment failure and reduce

complications of infection in people who are at higher risk due to the location and nature of the infection, and the possibility of uncommon pathogens. For people with infection around the eyes or nose, consulting a specialist was recommended because of the particular risk of complications with this infection site.

- The committee discussed and agreed based on their experience that although routine dual therapy was not recommended, **clarithromycin** (a macrolide) **with metronidazole** (an antibiotic with high activity against anaerobic bacteria) is a suitable alternative to co-amoxiclav in adults with infection near the eyes or nose, if co-amoxiclav is not suitable or there is penicillin allergy. In children, the committee discussed that anaerobic bacteria are less of a concern and that clarithromycin alone may be sufficient. However, if anaerobes are suspected, the addition of metronidazole was recommended.
- The committee agreed based on evidence, their experience and resistance data that the first choice **intravenous antibiotic** for people unable to take oral antibiotics or with severe illness should be the relatively narrow spectrum penicillin, **flucloxacillin**.
- Based on evidence, their experience and resistance data, the committee agreed to recommend a choice of alternative intravenous antibiotics for people with penicillin allergy, or if flucloxacillin is unsuitable or if the infection is near the eyes or nose. These are as follows (antibiotics may be combined if susceptibility or sepsis is a concern):
  - **clarithromycin**
  - **co-amoxiclav** (not in penicillin allergy)
  - **cefuroxime**
  - **clindamycin**
  - **gentamicin**
  - **vancomycin** (or if this cannot be used, under specialist advice, **linezolid**.

Antibiotic dose frequency

- There was no difference in the clinical effectiveness of the following antibiotic comparison in adults with cellulitis or erysipelas:
  - oral cefalexin four times a day compared with twice a day, using the same total daily dose.

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

Based on 1 systematic review (Kilburn et al 2010).

Antibiotic course length

- There were no differences in the clinical effectiveness of the following antibiotic comparisons in adults with cellulitis:
  - oral tedizolid for 6 days compared with 10 days (Hanretty et al 2018),
  - oral levofloxacin for 5 days compared with 10 days (Kilburn et al 2010).

Based on 2 systematic reviews (Hanretty et al 2018 and Kilburn et al 2010).

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

Antibiotic route of administration

- There were no differences in the clinical effectiveness of the following antibiotic comparisons in adults with cellulitis:
  - oral cefalexin or oral clindamycin compared with intravenous [IV] cefazolin or IV clindamycin (Aboltins et al 2015),
  - IV benzylpenicillin compared with intramuscular [IM] benzylpenicillin (Kilburn et al 2010).

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

Based on 1 systematic review (Kilburn et al 2010) and 1 RCT (Aboltins et al 2015).

Committee discussion on antibiotic dose frequency, course length and route of administration

- The committee acknowledged that there was very limited evidence identified for antibiotic dose frequency.
- The committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and minimise the risk of side effects.
- Based on limited evidence and their experience, the committee agreed that a shorter course of antibiotics was generally as effective as a longer course of antibiotics for cellulitis or erysipelas, and a 7-day course was sufficient for most people. The committee discussed that a longer course (up to a further 7 days) may be needed for some people based on a clinical assessment of their symptoms and history. However, skin does take some time to return to normal, even after an effective course of antibiotics, and a full resolution of symptoms at 7 days would not be expected.
- Based on limited evidence, the committee agreed that oral antibiotics were as effective as intravenous antibiotics for treating cellulitis and erysipelas.
- In line with the NICE guideline on antimicrobial stewardship and Public Health England's Start smart – then focus, the committee agreed that oral antibiotics should be used in preference to intravenous antibiotics where possible. Intravenous antibiotics should only be used for people who are severely ill, unable to tolerate oral treatment, or where oral treatment would not provide adequate coverage or tissue penetration. The use of intravenous antibiotics should be reviewed by 48 hours (taking into account the person's response to treatment and any microbiological results) and switched to oral treatment where possible, for a total of 7 days. Again, a longer course (up to a further 7 days) may be needed for some people based on clinical assessment.

Antibiotic prophylaxis for the prevention of recurrent cellulitis and erysipelas

- Antibiotic prophylaxis (with an intramuscular or oral penicillin, or oral erythromycin) significantly lowered the risk of recurrence of cellulitis or erysipelas compared with no treatment or placebo in a meta-analysis of 5 RCTs in adults (approximately 46 to 70 years) with 1 to 2 previous episodes of cellulitis or erysipelas in the past 3 months to 3 years depending on the RCT.
- Antibiotic prophylaxis significantly lowered the incidence rate (episodes per person month) compared with no treatment or placebo in a meta-analysis of 4 RCTs in adults with 1 to 2 previous episodes of cellulitis or erysipelas.
- Antibiotic prophylaxis significantly lowered the risk of an episode (time to next episode) of cellulitis or erysipelas compared with no treatment or placebo in a meta-analysis of 3 RCTs in adults with 1 to 2 previous episodes of cellulitis or erysipelas.
- Antibiotic prophylaxis was not significantly different to no treatment or placebo for mortality or risk of hospitalisation in adults with 1 to 2 previous episodes of cellulitis or erysipelas.
- There were no differences in the adverse events of antibiotic prophylaxis compared with no treatment or placebo in adults with cellulitis or erysipelas:
- No systematic reviews or randomised controlled trials in children met the inclusion criteria.

Based on 1 systematic review (Dalal et al 2017).

Committee discussion on antibiotic prophylaxis of recurrent cellulitis or erysipelas

- The committee noted that recurrence is not uncommon in people who have had cellulitis or erysipelas. The committee also noted the limitations of the evidence for antibiotic prophylaxis, which was in adults only and mainly related to lower limb cellulitis. There was variation in the populations in the included studies for the number of previous episodes (1 to 2) and the time periods over which recurrence was defined (up to 3

years).

- The committee discussed the evidence for prophylactic antibiotics in adults. Overall, antibiotics reduced the risk of cellulitis or erysipelas recurring but did not reduce the risk of hospitalisation or mortality, and the long-term effects on antibiotic resistance are unknown.
- The committee agreed based on evidence and experience that antibiotic prophylaxis should not be routinely offered to prevent recurrent cellulitis or erysipelas because of the balance of risks and benefits in the overall population.
- However, they agreed based on evidence and experience that a trial of antibiotic prophylaxis could be considered for a higher-risk population, which the committee defined as adults who have had at least 2 previous episodes of cellulitis or erysipelas in the previous 12 months which were managed in hospital, or where the care was under specialist advice. The populations in the antibiotic prophylaxis trials were more varied (having 1 or 2 previous episodes over up to 3 years) but the committee wanted to ensure that prophylaxis would only be considered for those at highest risk.
- The committee agreed that prophylaxis should only be considered following a discussion with the person to ensure shared decision making, and should be reviewed every 6 months. Prophylaxis may be appropriate in this higher-risk population because the benefits of prophylaxis may outweigh the risks. However, it is important to ensure that the previous episodes of cellulitis and erysipelas have been correctly diagnosed, any underlying condition (such as oedema, diabetes or venous insufficiency) is being managed optimally, and prophylaxis is reviewed at least every 6 months.
- The choice of antibiotic was low-dose **phenoxymethylpenicillin** which was used in the majority of the trials in the systematic review, or low-dose **erythromycin** in penicillin allergy, which was used in 1 trial in the systematic review. The committee discussed that alternative antibiotics may be appropriate with specialist advice, and that choice should be based on recent microbiological results where possible. Based on their

experience and resistance data, the committee agreed that using the same antibiotic for treatment and prophylaxis should be avoided.

- The committee recognised the importance of reviewing antibiotic prophylaxis, and considered that up to every 6 months was reasonable based on possible adverse effects of antibiotics, the risk of resistance with long-term antibiotics, the possible need for any further investigations if recurrence of cellulitis or erysipelas, and to allow time to assess treatment success. People should also know to seek medical help if cellulitis or erysipelas recurs despite taking prophylaxis.
- To reduce the risk of antimicrobial resistance, the committee agreed that each review, should include a discussion around the success of prophylaxis and whether antibiotics should be continued, stopped or changed, taking into account the person's preferences for antibiotic use and the potential risk of antimicrobial resistance with long-term use of antibiotics. If treatment failure occurs and cellulitis or erysipelas recurs, the committee agreed that antibiotic prophylaxis should be stopped or switched to an alternative prophylactic antibiotic once the acute infection has been treated.
- No recommendation for antibiotic prophylaxis in children was made because there was no evidence in this population.

Other considerations

Medicines adherence

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

Resource implications

- Recommended antibiotics are available as generic formulations. See Drug Tariff or BNF for costs.

See the full evidence review for more information.