National Institute for Health and Care Excellence

Final

Cellulitis and erysipelas: antimicrobial prescribing guideline

Evidence review

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1 Context

1.1 Background

Cellulitis and erysipelas are infections of the subcutaneous tissues, 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). Cellulitis can affect any part of the body, but usually affects the hands (causing swollen fingers), the feet (sometimes near toes if there is athletes foot) and lower legs (NHS – cellulitis). This guideline and evidence review covers cellulitis and erysipelas, but does not include surgical cellulitis, infections of skin pores (folliculitis, furuncles or carbuncles) or layers of the skin deeper than dermis and subcutaneous tissue (for example fasciitis).

Cellulitis is a common infection seen in both primary and secondary care. Prescribing in primary care in England for cellulitis from 2013 to 2015 accounted for 12.0% of antibiotics prescribed for skin and wounds, and around 2% of all prescribed antibiotics in primary care with a linked diagnostic code (Dolk et al 2018). In 2017-18 there were over 88,000 recorded admissions to hospital in England for cellulitis, with more than 80,000 of these being emergency admissions, and accounting for over 430,000 bed days (NHS Digital, Hospital Admitted Patient Care Activity, 2017-18).

Recurrence of cellulitis is common with 10–30% of people who suffer an episode of cellulitis having further subsequent episodes at different time intervals (Dalal et al 2010).

Factors that increase the risk of developing cellulitis include venous insufficiency (Jorup-Ronstrom & Britton 1989), lymphoedema (Keely 2008), peripheral vascular disease, diabetes mellitus, obesity (Cox et al 1998), white ethnicity and preceding injury to the limb (Halpern et al 2008). Local factors include tinea pedis, ulcers, trauma, and insect bites (Cox et al 1998). It has been suggested that age is a predisposing factor with elderly people more at risk of developing cellulitis due to a compromised immune response (Nazarko 2012). However, no proven link between age or gender, has been established (Phoenix et al 2012).

This guideline and evidence review does not cover diagnosis, and starts from the point in the care pathway when a diagnosis of cellulitis or erysipelas has been made. Health professionals should ensure that they follow best practice in diagnosing any skin infection before prescribing. There is evidence that misdiagnosis of cellulitis may occur in up to a third of cases seen in the UK (Levell et al 2011), and it has been suggested as one reason for the wide variation in treatment failures in randomised controlled trials of antibiotics, from 6% to 37% (Obaitan et al 2016). Misdiagnosis of cellulitis could potentially expose people to an inappropriate, or over use, of antibiotics. Misdiagnosis delays effective treatment and clinical improvement that may be avoided through, for example, a dermatology review of people admitted with cellulitis (Ko et al 2018).

In cellulitis and erysipelas, the most common causative pathogens are *Streptococcus pyogenes* and *Staphylococcus aureus.* Less common organisms include: *Streptococcus pneumoniae, Haemophilus influenza,* Gram negative bacilli and anaerobes (NICE, Clinical Knowledge Summaries Cellulitis – acute, Chira & Miller 2010, Blackberg et al 2014).

Cellulitis and erysipelas are treated with antibiotics, and can be serious if not treated quickly (NHS-cellulitis). A systematic review comparing cure rates from before (1900 to 1950, before widespread penicillin resistance) and after the introduction of antibiotics (Spellberg et al 2009) found that for cellulitis and erysipelas cure rates increased from 66% (95% confidence

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interval [CI], 64%–68%) without antibiotics to 98% (95% CI, 96%–99%) for penicillin-treated patients, with penicillin reducing mortality by 10%.

People who have typical symptoms of cellulitis (red, hot, painful skin; possibly swollen, painful glands) are advised to see their GP (NHS – cellulitis), with an urgent appointment advised in some cases, such as if the face or area around the eye is affected, or symptoms are rapidly getting worse (which could be a sign of something more serious like the rare condition necrotising fasciitis).

1.2 Antimicrobial stewardship

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks. This guideline also recommends that safety netting advice should be given to everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include: how long symptoms are likely to last with antimicrobials, wat to do if symptoms get worse, what to do if they experience adverse effects from the treatment, and when they should ask again for medical advice.

In line with the Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship , intravenous antibiotic prescriptions should be reviewed at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.3 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

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When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2018 reported that antimicrobial prescribing declined significantly between 2013 and 2017, with the total consumption of antibiotics in primary and secondary care declining by 4.5%. This reflected a 13.2% decrease in primary care and a 7.7% increase in secondary care prescribing. The peak of antibiotic consumption over the last 20 years occurred in 2014, with levels falling since then. The most commonly used antibiotics in England remained stable between 2013 and 2017, and were: penicillins (44.6% in 2017), tetracyclines (22.2% in 2017) and macrolides (14.7% in 2017).

Over the 5-year period, significant declining trends of use were seen for penicillins (inhibitor combinations only), first and second-generation cephalosporins, sulfonamides and trimethoprim, and anti-*C. difficile* agents. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

In the 5-year period from 2013 to 2017, primary care use of penicillins declined by 10.9%, with use of penicillins in the dental setting remaining largely the same. In the hospital setting, prescribing of penicillins was higher in 2017 for both inpatients (2.4%) and outpatients (14.7%) compared with 2013. Prescribing of co-amoxiclav and amoxicillin between 2013 and 2017 decreased by 11.3% and 7.4%, respectively.

Overall use of tetracyclines was unchanged between 2013 and 2017, with doxycycline (49.7% in 2017) and lymecycline (36.3% in 2017) most commonly used. Macrolide use declined by 5.8% from 2013 to 2017. Azithromycin use continued to increase in 2017, with overall use rising by 31.3% since 2013. In contrast, erythromycin use declined over the same period by 40.7%.

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2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for acute sinusitis.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing cellulitis and erysipelas (see appendix C: literature search strategy for full details). The literature search identified 5,886 references. These references were screened using their titles and abstracts and 480 full text references were obtained and assessed for relevance. Sixteen full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Fifteen of the 16 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 1 reference that was not prioritised for inclusion is listed in appendix I: not prioritised studies, with reasons for not prioritising the study. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 464 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in table1 to Table 5. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

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Table 1: Summary of included studies: antibiotic choice

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Boucher et al 2014 DB RCT Multicentre international Follow-up at 48 to 72 hours after treatment starting	n=1,312	People with ABSSSI (cellulitis as a subgroup)	Glycopeptide (intravenous [IV] dalbavancin) weekly on days 1 and 8	Glycopeptide (IV vancomycin) for 3 days with option for switch to oral linezolid (10 to 14 days)	Days to no advance in condition
Bowen et al 2017 Systematic review Multiple countries Follow-up period not reported	n=53,286 (10 RCTs and 5 observational studies)	Adults and children with SSSI (cellulitis as a subgroup)	Co-trimoxazole (oral) alone or with cefalexin (7 to 14 days)	Clindamycin, cefalexin or placebo (oral) (7 to 14 days)	Clinical cure (or other outcome as per included study)
Ferreira et al 2016 Systematic review and meta-analysis Multiple countries Follow-up period varied by study	n=3,032 (15 RCTs)	Adults or children with community-acquired cellulitis or erysipelas	Penicillin or cephalosporin (oral)[1]	Macrolide or lincosamide (oral)[2]	Treatment failure (not cured)
Frampton 2013 Systematic review Multiple countries Follow-up at 8 to 15 days post treatment	n=1,378 (2 RCTs)	Adults (aged ≥18 years) with cSSSI (cellulitis as a subgroup)	Cephalosporin (IV ceftaroline fosamil [5 to 14 days])	Glycopeptide (IV vancomycin with aztreonam [5 to 14 days])	Clinical cure rate
Killburn et al 2010 Systematic review and meta-analysis Multiple countries Follow-up period varied by study	n=2,488 (25 RCTs)	Adults (aged 16 to 90 years) with SSSI with cellulitis as a subgroup or cellulitis and erysipelas as the main cohort	Antibiotic (by class, oral or IV)[3]	Other antibiotics (by class, oral or IV)[4]	Duration and intensity of symptoms

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Konychev et al 2013 Open-label RCT Multicentre international Follow-up at 7 to 14 days post treatment	n=120	Older adults (aged ≥65 years) with cSSSI (cellulitis as a subgroup)	Lipopetide (IV daptomycin [5 to 28 days])	Penicillin (IV semi-synthetic penicillins or vancomycin [5 to 28 days])	Clinical success at 7 to 14 days post treatment
Matthews et al 2012 Open-label RCT Multicentre international Follow-up at 8 to 50 days post treatment	n=531	People with cSSSI (cellulitis as a subgroup)	Glyclycycline (IV tigecycline [4 to 14 days])	Penicillin (IV ampicillin-sulbactam or IV co-amoxiclav [4 to 14 days]) with glycopeptide (IV vancomycin) if *MRSA*	Clinical response rate at end of therapy
Pertel et al 2009 SB RCT Multicentre international Follow-up at up to 20 days post treatment	n=103	Adults (aged ≥18 years) with cellulitis	Lipopeptide (IV daptomycin [7 to 14 days])	Glycopeptide (IV vancomycin [7 to 14 days])	Clinical efficacy
Vick-Fragaso et al 2009 Open-label RCT Multicentre international Follow-up at 14 to 28 days post treatment	n=804	Adults (aged ≥18 years) with cSSSI (complicated erysipelas as a subgroup)	Fluoroquinolone (IV then oral moxifloxacin [7 to 21 days])	Beta-lactam plus beta-lactamase inhibitor (IV then oral co-amoxiclav [7 to 21 days])	Clinical success rate
Yogev et al 2003 Open-label RCT Multicentre international Follow-up at 7 to 35 days post treatment	n=120	Children (aged <12 years) with cSSSI (cellulitis as a subgroup)	Oxazolidinone (IV or oral linezolid [10 to 28 days])	Glycopeptide (IV vancomycin [10 to 28 days])	Clinical cure rate
Abbreviations: RCT, Randomised controlled trial; SSSI, Skin and Skin Structure Infection; cSSTI, Complicated Skin and Skin Structure Infection; IV, Intravenous; DB, double blind; ABSSSI, Acute Bacterial Skin and Skin Structure Infection; PC, Placebo controlled.					

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome

[1] Penicillin or cephalosporin (oral) included flucloxacillin [7 to 14 days], cloxacillin [7 to 10 days], cefalexin [7 to 10 days], cefprozil [5 to 10 days], dicloxacillin [7 to 14 days], cefaclor [7 to 10 days] or cefdinir [5 days].

[2] Macrolide or lincosamide (oral) included erythromycin [5 to 14 days], clindamycin [7 to 14 days], azithromycin [3 to 5 days], roxithromycin [7 days] or telithromycin [5 days].

[3] Antibiotic (by class, oral or IV) included roxithromycin [until apyrexial for 10 days], pristinamycin [14 days], cefditoren [10 to 11 days], ampicillin with sulbactam [unclear duration], azithromycin [5 days], cefalexin [4 to 10 days], meropenem [3 to 14 days], moxifloxacin [14 days], ceftriaxone [6 to 14 days], levofloxacin [5 days], cefonicid [at least 3 days], flucloxacillin / benzyl penicillin [unclear duration], ticaricillin with clavulanic acid [5 to 25 days], ampicillin with sulbactam [unclear duration], cefepime [3 to 18 days], cefdinir [mean duration 10 days], gatifloxacin [7 to 10 days], linezolid [7 to 21 days], benzyl penicillin [10 days].

[4] Other antibiotics (by class, oral or IV) included penicillin [10 to 14 days], cefuroxime [10 days], cefadroxil [10 days], cefazolin [minimum 3 days], erythromycin [7 days], cloxacillin [7 days], cefalexin [4 to 10 days], imipenem with cilastatin [3 to 14 days], piperacillin with tazobactam [3 days], cefazolin plus probenecid [7 to 14 days], levofloxacin [7 to 10 days], flucloxacillin [unclear duration], moxalactam [3 to 20 days], ceftazidime [4 to 16 days], vancomycin [7 to 21 days].

Table 2: Summary of included studies: antibiotic dual therapy (treatment with more than 1 antibiotic)

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Bowen et al 2017 Systematic review Multiple countries Follow-up period not reported	n=53,286 (10 RCTs and 5 observational studies)	Adults and children with SSSI (cellulitis as a subgroup)	Cephalosporin (oral cefalexin) plus co-trimoxazole (oral [7 to 14 days])	Cephalosporin alone (oral cefalexin [7 to 14 days])	Clinical cure (or other outcome as per included study)
Brindle et al 2017 DB RCT UK Follow-up at day 5 after treatment starting	n=410	People with cellulitis	Penicillin plus lincosamide (oral flucloxacillin plus oral clindamycin [5 days])	Penicillin alone (oral flucloxacillin [5 days])	Clinical improvement
Killburn et al 2010 Systematic review and meta-analysis Multiple countries Follow-up period varied by study	n=2,488 (25 RCTs)	Adults (aged 16 to 90 years) with SSSI with cellulitis as a subgroup or cellulitis and erysipelas as the main cohort	Flucloxacillin plus benzyl penicillin (IV then oral [unclear duration])	Flucloxacillin (IV then oral [unclear duration])	Duration and intensity of symptoms

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Noel et al 2008 DB RCT Multicentre international Follow-up at 7 to 14 days post treatment	n=828	Adults (aged ≥18 years) with cSSSI (cellulitis as a subgroup)	Cephalosporin (IV ceftobiprole [7 to 14 days])	Glycopeptide plus cephalosporin (IV vancomycin plus IV ceftazidime [7 to 14 days])	Clinical cure rate
Abbreviations: RCT, Randomised controlled trial; SSSI, Skin and Skin Structure Infection; DB, double blind.					

Table 3: Summary of included studies: antibiotic course length

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Hanretty et al 2018 Systematic review Multiple countries Follow-up period varied by study	n=1420 (with skin and soft tissue infection). (23 RCTs)	People with community acquired pneumonia, intra-abdominal infection, skin and soft tissue infection, cystitis, pyelonephritis	Oxazolidinone (oral tedizolid [6 days])	Oxazolidinone (oral tedizolid [10 days])	Cure rate
Killburn et al 2010 Systematic review and meta-analysis Multiple countries Follow-up period varied by study	n=2,488 (25 RCTs)	Adults (aged 16 to 90 years) with SSSI with cellulitis as a subgroup or cellulitis and erysipelas as the main cohort	Fluoroquinolone (oral levofloxacin [5 days])	Fluoroquinolone (oral levofloxacin [10 days])	Duration and intensity of symptoms
Abbreviations: RCT, Randomised controlled trial; SSSI, Skin and Skin Structure Infection.					

Table 4: Summary of included studies: antibiotic route of administration

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Aboltin et al 2015 Randomised non-inferiority trial Australia	n=47	Adults (aged ≥16 years) with cellulitis.	Cephalosporin (oral cefalexin [10 days])	Cephalosporin (IV then oral cefazolin [10 days total])	Days to no advance in condition

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Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Follow-up up to day 28 post enrolment					
Killburn et al 2010 Systematic review and meta-analysis Multiple countries Follow-up period varied by study	n=2,488 (25 RCTs)	Adults (aged 16 to 90 years) with SSSI with cellulitis as a subgroup or cellulitis and erysipelas as the main cohort	Penicillin (IV benzyl penicillin [10 days])	Penicillin (IM penicillin [10 days])	Duration and intensity of symptoms
Abbreviations: DB, Double blind; RCT, Randomised controlled trial; SSSI, Skin and Skin Structure Infection.					

Table 5: Summary of included studies: antibiotic dose frequency

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Killburn et al 2010 Systematic review and meta-analysis Multiple countries Follow-up period varied by study	n=2,488 (25 RCTs)	Adults (aged 16 to 90 years) with SSSI with cellulitis as a subgroup or cellulitis and erysipelas as the main cohort	Cephalosporin (oral cefalexin [twice daily for 4 to 10 days])	Cephalosporin (oral cefalexin [four times daily for 4 to 10 days])	Duration and intensity of symptoms
Abbreviations: RCT, Randomised controlled trial; SSSI, Skin and Skin Structure Infection.					

Table 6: Summary of included studies: antibiotic prophylaxis for recurrence of cellulitis

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Dalal et al 2017 Systematic review and meta-analysis Follow-up period varied by study	n=513 (5 RCTs)	Adults with 1 to 2 previous episodes of cellulitis or erysipelas	Prophylactic antibiotics (erythromycin or penicillin)	No treatment or placebo	Risk of recurrence
Abbreviations: RCT, randomised controlled trial.					

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3 Evidence summary

Full details of the evidence are shown in appendix H: GRADE profiles.

The main results are summarised below for adults, young people and children with cellulitis or erysipelas.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNFC) for information on drug interactions, contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

3.1 Antibiotics in adults

3.1.1 Antibiotic prescribing strategies in people with cellulitis or erysipelas

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

3.1.2 Choice of antibiotic in adults with cellulitis or erysipelas

The evidence for choice of antibiotic in adults with cellulitis comes from 1 systematic review (Bowen et al 2017), 3 systematic reviews with meta-analyses (Ferreira et al 2016; Frampton et al 2013 and Kilburn et al 2010) and 6 RCTs (Boucher et al 2014; Konychev et al 2013; Matthews et al 2012; Pertel et al 2009; and Vick-Fragaso et al 2009).

Population in all included studies

Two systematic reviews (Frampton et al 2013 and Kilburn et al 2010) included only RCTs with adults (aged ≥18 years and ≥16 years respectively). Two systematic reviews (Bowen et al 2017 and Ferreira et al 2016) included RCTs with children, or adults and children.

Three RCTs included only adults aged ≥18 years (Pertel et al 2009; Stryjewski et al 2012 and Vick-Fragaso et al 2009) and 1 RCT included only older adults aged ≥65 years (Konychev et al 2013). One RCT did not report age inclusion criteria (Matthews et al 2012) and is therefore limited in interpretation to adults only.

Two systematic reviews included only RCT data for cellulitis or erysipelas (Ferreira et al 2016 and Kilburn et al 2010). The other 2 systematic reviews (Bowen et al 2017 and Frampton et al 2013) included RCTs of skin and skin structure infection (SSSI) or complicated skin and skin structure infection (cSSSI), but only the cellulitis population results are reported here. Only 1 RCT which was included in a systematic review (Bowen et al 2017) included a placebo arm (3-arm RCT with clindamycin compared with co-trimoxazole or placebo), but the population of this study is limited because all participants had an abscess and cellulitis rather than cellulitis alone, and had incision and drainage of the abscess in addition to antibiotics.

In 1 RCT the population was only people with cellulitis or erysipelas (Pertel et al 2009). Four RCTs included people with cSSSI (Boucher et al 2014; Konychev et al 2013; Matthews et al 2012 and Vick-Fragaso et al 2009) and cellulitis or erysipelas was a subgroup of the main study population. These subgroup data are limited as often only clinical cure is reported as an outcome for cellulitis or erysipelas, and the

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RCT subgroups for cellulitis or erysipelas may not include enough people to have sufficient statistical power.

The systematic reviews by Kilburn et al (2010) and Dalal et al (2017) state that the clinical definition of cellulitis infection was signs of skin inflammation and evidence of bacterial infection. In Kilburn et al (2010) studies of cellulitis only used more specific signs consistent with the condition. In 3 RCTs included within the systematic review there was a population of more severe infection, but the definitions of the population are subjective (for example 'complicated', 'deep tissue involvement' or 'the presence of co-morbid conditions'). The authors also used setting to imply severity of infection, with 16 RCTs being in the hospital setting, 4 RCTs in the outpatient setting, 2 RCTs in a mixture of hospital inpatients, outpatients, and primary care, 1 RCT in accident and emergency and 2 RCTs in the community care setting. Two included studies within the systematic review used a more objective measure of severity (a severity score based on oedema, erythema, and pain 0 to 3; and severity and treatment failure) but it is unclear if these are validated scores or criteria. Results were not presented by severity in the systematic reviews. The other included systematic reviews (Bowen et al 2017; Frampton 2013; Ferreira et al 2016 and Hanretty et al 2018) did not present data for diagnosis or infection severity.

In the included RCTs of skin infection rather than cellulitis alone, 1 RCT included people with complicated erysipelas or cellulitis (Vick-Fragaso et al 2009). The authors stated that the complicating factors were fever, leucocytosis, increased respiratory rate or C-reactive protein, plus 2 or more of the following symptoms and signs <24 hours before enrolment: "local pain or tenderness, anesthesia or hypoesthesia of the affected area, swelling of the presumed affected area, purulent, serosanguinous, 'dishwater' or foul-smelling discharge, gas formation detected under the skin, and changes in the appearance of the involved area, such as discoloration of skin, presence of black necrotic areas, red-brown or hemorrhagic bullae, or skin color changes from red-blue to patches of bluegrey". Similarly in the RCTs by Matthews et al (2012) and Yogev et al (2003) people with skin infections who had cellulitis had to have deep infection or complicating factors. The RCT by Konychev et al (2013) included people with skin infections who warranted hospital admission and intravenous therapy. The RCTs by Boucher et al (2014) and Noel et al (2008) had subgroups of increased severity according to the presence of objective clinical findings including systematic inflammatory response syndrome (SIRS), C-reactive protein and the involvement of fascia or muscles but not for the cellulitis subgroup.

In the RCTs with populations who just had cellulitis, 1 RCT by Aboltin et al (2015) included participants with cellulitis who had more severe infection or infection that had progressed despite oral treatment. In the RCT (and *post hoc* data) by Pertel et al (2009), all of the participants had a co-morbid condition but results were not detailed by infection severity. In the RCT by Brindle et al (2017), severity was examined as a SIRS score of 0 or more than 0; duration of local features (area, skin temperature and swelling) of between 48 and 84 hours, or <48 hours prior to randomisation; duration of antibiotics prior to the study drug of >12 or <12 hours. But no statistically significant difference in improvement in any subgroup was found.

Four of the 6 included systematic reviews did not report the site of infection (Kilburn et al 2010; Frampton 2013; Bowen et al 2017; Hanretty et al 2018). The systematic review by Dalal et al 2017 reported that most cases had a lower, or in a few cases, upper limb site of infection. The systematic review by Ferreira et al (2016) reported that they excluded a study of facial cellulitis. Five RCTs (Boucher et al 2014; Konychev et al 2013; Noel et al 2008; Vick-Fragaso et al 2009; Yogev et al 2003) did not report the site of infection. The RCT by Aboltin et al (2015) reported that participants had an upper or lower limb cellulitis. The RCT by Brindle et al (2017)

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reported that 299 of 410 participants had a leg infection and no other infection site data was reported. Similarly, the RCT by Matthews et al 2012 reported that the most common sites of infection were the lower extremity (61.6%) and upper extremity (16.2%) and no other infection site details were reported. In the RCT by Pertel et al (2009) it was reported that infection site was mostly arm and leg, only 14 of 101 participants had 'other' as the site of infection but again no further details were reported.

No included study (systematic review or RCT) used either the Eron (2003) or Dundee (2010) classifications as part of the study.

Data on adverse events was not available for all comparisons, often because diagnostic subgroup data was available for clinical efficacy but was not available for adverse events.

3.1.2.1 Penicillins as intervention or comparator

Penicillin versus macrolide or oral streptogramin

One systematic review (Kilburn et al 2010) included 3 RCTs comparing an IV or oral penicillin (IV penicillin or oral cloxacillin [not available in the UK]) with either an oral macrolide (roxithromycin [not available in the UK] or azithromycin) or an oral streptogramin (pristinamycin [not available in the UK]).

IV or oral penicillin was significantly worse than an oral macrolide or oral streptogramin for the outcome of 'symptom free or reduced symptoms' at the end of therapy (7 to 14 days; 3 RCTs, n=419, 56.9% versus 68.1%, relative risk [RR] 0.83, 95% confidence interval [CI] 0.71 to 0.96, number needed to treat [NNT] 9, 95% CI 5 to 52; very low quality evidence).

IV penicillin was significantly worse for 'symptom free or reduced symptoms' compared with an oral macrolide (roxithromycin) or oral streptogramin (pristinamycin) at the end of therapy (7 to 14 days; 2 RCTs, n=357, 57.4% versus 68.6%, RR 0.83, 95% CI 0.71 to 0.97, NNT 8, 95% CI 1 to 21; low quality evidence). Oral penicillin (cloxacillin) was not significantly different to an oral macrolide (azithromycin) in 1 RCT for the outcome of 'symptom free or reduced symptoms' at the end of therapy (7 to 14 days). See GRADE table 20.

Oral penicillin (roxithromycin) or oral streptogramins (pristinamycin) was not significantly different to IV penicillin for any adverse event (very low to low quality evidence) or adverse events leading to study withdrawal (low quality evidence). See GRADE tables 43 and 44.

Penicillin or cephalosporin versus macrolide or lincosamide

One systematic review (Ferreira et al 2016) included 9 RCTs comparing either an oral penicillin (flucloxacillin, cloxacillin [not available in the UK], penicillin, or dicloxacillin [not available in the UK]) or an oral cephalosporin (cefalexin, cefaclor or cefdinir [not available in the UK]) with an oral macrolide (erythromycin, azithromycin, roxithromycin [not available in the UK] or telithromycin [not available in the UK]) or an oral lincosamide (clindamycin).

A penicillin or cephalosporin was not significantly different to a macrolide or a lincosamide for the outcome of treatment failure (follow-up period not reported) for adults or children with cellulitis or erysipelas (9 RCTs, n=462, 12.2% versus 8.7%, RR 1.29, 95% CI 0.76 to 2.17; low quality evidence). See GRADE table 21.

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Penicillin versus cephalosporin

One systematic review (Kilburn et al 2010) included 3 RCTs comparing a penicillin (IV ampicillin with sulbactam [not available in the UK] or IV flucloxacillin) with a cephalosporin (IV cefazolin [not available in the UK] or IV ceftriaxone) in adults with cellulitis.

An IV penicillin was not significantly different to an IV cephalosporin for the outcome of 'symptom free or reduced symptoms' 0 to 72 hours after the end of therapy (3 RCTs, n=88, 75% versus 83.3%, RR 0.99, 95% CI 0.68 to 1.43; very low quality evidence). See GRADE table 22.

IV penicillin (flucloxacillin) was not significantly different to IV cephalosporin (ceftriaxone) for any adverse event or adverse event leading to study withdrawal (very low to low quality evidence). See GRADE tables 43 and 44.

Fluoroquinolone versus penicillin plus beta-lactamase inhibitor

One systematic review (Kilburn et al 2010) included 1 RCT comparing a fluoroquinolone (IV moxifloxacin) with an ureidopenicillin plus beta-lactamase inhibitor (IV piperacillin with tazobactam) in adults with cellulitis. Both arms of the RCT could switch to oral therapy at day 3. One additional RCT (Vick-Fragaso et al 2009) compared a fluoroquinolone (IV then oral moxifloxacin) with a penicillin plus beta-lactamse inhibitor (IV then oral co-amoxiclav) in a subgroup of adult patients with complicated erysipelas or complicated cellulitis.

IV moxifloxacin was not significantly different to IV piperacillin with tazobactam for rate of cure, follow-up period not reported (1 RCT, n=86, 83.7% versus 88.4%, RR 0.95, 95% CI 0.80 to 1.12; moderate quality evidence).

IV then oral moxifloxacin was not significantly different to IV then oral co-amoxiclav for clinical success in complicated erysipelas at 14 to 28 days follow-up (1 RCT, n=225 in the intention-to-treat [ITT] population, 89.5% versus 90.1%, RR 0.99, 95% 0.91 to 1.08; low quality evidence) or complicated cellulitis at 14 to 28 days follow-up (1 RCT, n=31, 91.7% versus 84.2%, RR 1.09, 95% CI 0.84 to 1.41; very low quality evidence). There were also no significant differences in the per protocol population for the same outcomes. See GRADE table 23 and 24.

Lipopeptide versus penicillin

One RCT (Konychev et al 2013) compared a lipopeptide (IV daptomycin) with a semi-synthetic penicillin (not defined; also a small number may have received IV vancomycin) in a subgroup of older adults (aged ≥65 years) with cellulitis.

IV daptomycin was not significantly different to a penicillin for clinical success (defined as complete or partial resolution of symptoms and signs without the need for further antibiotics) at 7 to 14 days (1 RCT, n=30, 77.8% versus 83.3%, RR 0.93, 95% CI 0.66 to 1.33; very low quality evidence). See GRADE table 25.

Once weekly lipoglycopeptide versus glycopeptide

One RCT (Boucher et al 2014) compared a once weekly dose (doses given on days 1 and 8) of intravenous (IV) lipoglycopeptide (dalbavancin) with daily doses of IV glycopeptide (vancomycin).

Once weekly dalbavancin was not significantly different to daily doses of vancomycin for the outcome of clinical response as assessed by a study investigator at 48 to 72 hours follow-up (1 RCT, n=703, 79.4% versus 77.1%, RR 1.03, 95% CI 0.95 to

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1.11; moderate quality evidence) or at the end of therapy (1 RCT, n=625, 90.7% versus 91.7%, RR 0.99, 95% CI 0.94 to 1.04; moderate quality evidence). See GRADE table 19.

Glycycline versus penicillin plus beta-lactamase inhibitor

One RCT (Matthews et al 2012) compared a glycycline (IV tigecycline) with a penicillin plus a beta-lactamase inhibitor (IV ampicillin with sulbactam or co-amoxiclav; plus IV vancomycin if the infection was methicillin-resistant *Staphylococcus Aureus*) in a subgroup of adults with deep soft tissue infection (92% of whom had cellulitis).

IV tigecycline was not significantly different to a penicillin plus beta-lactamase inhibitor for clinical success (cure) at the test of cure visit at 8 to 50 days follow-up (1 RCT, n=282, 76% versus 78%, RR 0.97, 95% CI 0.86 to 1.11; low quality evidence). See GRADE table 26.

3.1.2.2 Cephalosporins as intervention or comparator

Cephalosporins (newer) versus cephalosporins (older)

One systematic review (Kilburn et al 2010) included 6 RCTs comparing a newer generation cephalosporin (cefonicid, cefditoren, ceftriaxone, cefdinir and cefepime [not all available in the UK]) with an older generation cephalosporin (cefazolin, cefadroxil, cefalexin, cefuroxime, ceftazidime [not all available in the UK]) in young people and adults with cellulitis.

Newer generation cephalosporins were not significantly different to older generation cephalosporins for the outcome of 'symptom free or reduced symptoms' at 0 to 16 days follow-up (6 RCTs, n=538, 87.3% versus 86.6%, RR 0.99, 95% CI 0.93 to 1.06; low quality evidence). In subgroup analysis, no significant differences were seen for second versus first generation, third versus first generation, third versus second generation or fourth versus third generation cephalosporins. See GRADE table 27.

Oral cefazolin [not available in the UK] was not significantly different to IV ceftriaxone for any adverse event (not further defined, moderate quality evidence). See GRADE table 43.

Cephalosporin versus glycopeptide plus monobactam

One systematic review (Frampton et al 2013) included 2 RCTs comparing a cephalosporin (IV ceftaroline) with a glycopeptide plus a monobactam (IV vancomycin plus IV aztreonam) in adults with cellulitis.

IV ceftaroline was not significantly different to IV vancomycin plus IV aztreonam for cure rate at 8 to 15 days follow-up (2 RCTs, n=472, 93% versus 91.4%, RR 1.02, 95% CI 0.97 to 1.07; moderate quality evidence). See GRADE table 28.

Macrolide versus cephalosporin

One systematic review (Kilburn et al 2010) included 1 RCT comparing a macrolide (oral azithromycin) with a cephalosporin (oral cefalexin) in adults with cellulitis.

Oral azithromycin was not significantly different to oral cefalexin for cure rate at 11 days follow-up (1 RCT, n=47, 95.8% versus 95.7%, RR 1.00, 95% CI 0.89 to 1.13; moderate quality evidence). See GRADE table 29.

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3.1.2.3 Glycopeptides as intervention or comparator

Oxazolidinone versus glycopeptide

One systematic review (Kilburn et al 2010) included 1 RCT comparing an oxazolidinone (IV or oral linezolid) with a glycopeptide (IV vancomycin) in adults with cellulitis.

IV or oral linezolid was not significantly different to IV vancomycin for cure rate at 7 days follow-up (1 RCT, n=425, 91.5% versus 91.5%, RR 1.00, 95% CI 0.94 to 1.06; low quality evidence). See GRADE table 30.

Cyclic lipopeptide versus glycopeptide

One RCT (Pertel et al 2009) compared a lipopeptide (IV daptomycin) with a glycopeptide (IV vancomycin) in a subgroup of adults with cellulitis; the study also included subgroup data from 2 RCTs which were pooled for a cellulitis population.

IV daptomycin was not significantly different to IV vancomycin for cure or improvement at 7 to 14 days follow-up (1 RCT, n=101, 94% versus 90.2%, RR 1.04, 95% CI 0.93 to 1.17; moderate quality evidence) or 6 to 20 days follow-up (2 RCTs, n=50, 78.6% versus 72.7%, RR 1.08, 95% CI 0.78 to 1.49; very low quality evidence). No significant difference was found for microbiological eradication, follow-up period not reported (2 RCTs, n=36, 72.7% versus 50%, RR 1.45, 95% CI 0.81 to 2.61; very low quality evidence), or other secondary outcomes. See GRADE table 31.

IV daptomycin was not significantly different to IV vancomycin for any adverse event (very low quality evidence). See GRADE table 43.

3.1.2.4 Other antibiotic comparisons

Macrolide versus macrolide

One systematic review (Kilburn et al 2010) included 1 RCT comparing a macrolide (oral azithromycin) with another macrolide (oral erythromycin) in adults with cellulitis.

Oral azithromycin was not significantly different to oral erythromycin for the outcome of cure rate at 48 hours post-treatment (1 RCT, n=122, 70.8% versus 74%, RR 0.96, 95% CI 0.77 to 1.19; low quality evidence). See GRADE table 32.

Carbapenem versus carbapenem

One systematic review (Kilburn et al 2010) included 1 RCT comparing a carbapenem (IV meropenem) with (IV imipenem with cilastatin) in young people and adults with cellulitis.

IV meropenem was not significantly different to IV imipenem with cilastatin for the outcome of cure rate at 7 to 14 days follow-up (1 RCT, n=81, 69.2% versus 78.6%, RR 0.88, 95% CI 0.68 to 1.15; low quality evidence). See GRADE table 33.

3.1.3 Dual therapy in children or adults with cellulitis or erysipelas

The evidence for dual therapy (using 2 antibiotics to treat the infection) comes from 1 systematic review (Bowen et al 2017), 1 systematic review and meta-analysis (Kilburn et al 2010) and 2 randomised controlled trials (Brindle et al 2017 and Noel et al 2008).

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One systematic review (Kilburn et al 2010) included an RCT of dual therapy in adults, as did one RCT (Noel et al 2008). The other systematic review (Bowen et al 2017) included an RCT of children (aged ≥12 years) and adults. One RCT (Brindle et al 2017) did not specify if it included adults and children.

In 1 systematic review (Bowen et al 2017) and 1 RCT (Brindle et al 2017) the population was only cellulitis or erysipelas. In 1 systematic review (Kilburn et al 2010) it was unclear if the population was cellulitis or a subgroup of a larger population of skin and skin structure infection. In 1 RCT cellulitis was a subgroup of a larger population of skin and skin structure infection. These subgroup data are limited as only clinical response is often reported as an outcome for cellulitis or erysipelas, and the RCT subgroups for cellulitis or erysipelas may not include enough people to have sufficient statistical power.

Penicillin plus penicillin versus penicillin plus placebo

One systematic review (Kilburn et al 2010) compared a penicillin plus a penicillin (IV then oral flucloxacin plus IV benzylpenicillin) with a penicillin plus placebo (IV then oral flucloxacillin plus placebo) for cellulitis in adults.

IV then oral flucloxacillin plus benzylpenicillin was not significantly different to IV then oral flucloxacillin alone for the outcome of treatment failure at 1 to 2 days follow-up (1 RCT, n=81, 7.3% versus 5%, relative risk [RR] 1.46, 95% confidence interval [CI] 0.26 to 8.30; very low quality evidence). See GRADE table 35.

Penicillin plus lincosamide versus penicillin plus placebo

One RCT (Brindle et al 2017) compared a penicillin plus lincosamide (oral or IV flucloxacillin plus oral clindamycin) with penicillin plus placebo (oral or IV flucloxacillin plus placebo) for cellulitis.

Oral or IV flucloxacillin plus oral clindamycin was not significantly different to oral or IV flucloxacillin alone for the outcome of improvement at 5 days in the evaluable population (1 RCT, n=328, 87.2% versus 81.4%, RR 1.07, 95% CI 0.98 to 1.18; high quality evidence). There was no significant difference for the same outcome in the randomised population, or for compliance with study medication or any other secondary outcome (apart from a slightly lower mean systolic blood pressure in the co-treatment arm at day 10 [difference 3 mmHg, p=0.02] and a lower median lymphocyte count in the co-treatment arm at days 5 and 10 [0.18X10^9/L and 0.19X10^9/L, respectively, p=0.01]). See GRADE table 36.

Oral or IV flucloxacillin plus oral clindamycin was significantly worse than oral or IV flucloxacillin alone for any adverse event, mostly diarrhoea, at 5 days follow-up (1 RCT, n=336, 28.8% versus 15.3%, RR 1.87, 95% CI 1.23 to 2.86, NNH 8, 95% CI 4 to 21; moderate quality evidence) but not at 10 days follow-up (low quality evidence). See GRADE table 43.

Cephalosporin plus co-trimoxazole versus cephalosporin plus placebo

One RCT (Bowen et al 2017) included 2 RCTs comparing a cephalosporin plus co-trimoxazole (oral cefalexin plus oral co-trimoxazole) with a cephalosporin plus placebo (oral cefalexin plus placebo) in children (aged ≥12 years) and adults with cellulitis.

Oral cefalexin plus co-trimoxazole was not significantly different to oral cefalexin alone for the outcome of clinical cure at 12 to 21 days follow-up in an intention-to-treat population (2 RCTs, n=642, 78.2% versus 72%, RR 1.09, 95% CI 0.99 to 1.19; moderate quality evidence). See GRADE table 37.

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Oral cefalexin plus co-trimoxazole was not significantly different to oral cefalexin alone for any adverse event (moderate quality evidence). See GRADE table 43.

Cephalosporin plus glycopeptide versus cephalosporin plus placebo

One RCT (Noel et al 2008) compared a cephalosporin plus glycopeptide (IV ceftazidime plus IV vancomycin) with a cephalosporin plus placebo (IV ceftobiprole) in adults with cellulitis.

IV ceftazidime plus IV vancomycin was not significantly different to IV ceftobiprole alone for clinical cure rate at 6 to 17 days follow-up (1 RCT, n=122, 88.9% versus 93%, RR 1.05, 95% CI 0.92 to 1.19; moderate quality evidence). See GRADE table 38.

3.1.4 Antibiotic dose in adults with cellulitis or erysipelas

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

3.1.5 Antibiotic dose frequency in adults with cellulitis or erysipelas

The evidence for antibiotic dose frequency comes from 1 systematic review and meta-analysis (Kilburn et al 2010) which included 1 RCT of a cephalosporin (oral cefalexin) four times daily versus a cephalosporin (oral cefalexin) twice daily with the equivalent daily dose in each arm. It is unclear if this was a subgroup or a larger cohort of adults with skin and soft tissue infection, which would have limitations.

Oral cefalexin four times daily was not significantly different to oral cefalexin twice daily for the outcome of cure (number resolved), follow-up period not defined (1 RCT, n=19, 100% versus 100%, relative risk [RR] 1.00, 95% confidence interval [CI] 0.81 to 1.23; low quality evidence). See GRADE table 39.

3.1.6 Antibiotic course length in adults with cellulitis or erysipelas

The evidence for antibiotic course length in adults with cellulitis comes from 1 systematic review (Hanretty et al 2018) and 1 systematic review and meta-analysis (Kilburn et al 2010). One systematic review (Hanretty et al 2018) included 3 RCTs but was limited in the reporting of outcomes. The other systematic review (Kilburn et al 2010) reported 1 RCT also included Hanretty et al (2018) but in more detail.

Six days versus 10 days of oxazolidinone

One systematic review (Hanretty et al 2018) included 2 RCTs which compared 6 days of an oxazolidinone (oral tedizolid) with 10 days of an oxazolidinone (oral tedizolid) at the same daily dose.

Oral tedizolid for 6 days was not significantly different to oral tedizolid for 10 days for the outcome of clinical response at 48 to 72 hours follow-up in an intention-to-treat [ITT] population (2 RCTs, n=608, 78.1% versus 76.5%, relative risk [RR] 1.02, 95% confidence interval [CI] 0.94 to 1.11; low quality evidence). There was also no significant difference for the outcome of sustained clinical response at the end of therapy (11 days follow-up) in the ITT or per protocol population, or in the investigators assessment at post-therapy evaluation (7 to 14 days follow-up) in the ITT or per protocol population (low quality evidence). See GRADE table 40.

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Five days versus 10 days of a fluoroquinolone

One systematic review (Kilburn et al 2010) included 1 RCT which compared 5 days of a fluoroquinolone (oral levofloxacin) with 10 days of a fluoroquinolone (oral levofloxacin) at the same daily dose.

Oral levofloxacin for 5 days was not significantly different to oral levofloxacin for 10 days for the outcome of 'symptom free or reduced' at end of treatment, 14 days follow-up (1 RCT, n=87, 97.7% versus 97.7%, RR 1.00, 95% CI 0.94 to 1.07; high quality evidence). See GRADE table 41.

Oral levofloxacin for 5 days was not significantly different to oral levofloxacin for 10 days for any adverse event (low quality evidence). See GRADE table 43.

3.1.7 Antibiotic route of administration in adults with cellulitis or erysipelas

The evidence for route of antibiotic administration in adults with cellulitis comes from 1 randomised controlled trial (Aboltins et al 2015) and 1 systematic review and meta-analysis (Kilburn et al 2010). One RCT (Aboltins et al 2015) compared an oral cephalosporin or an oral lincosamide with an IV cephalosporin or an IV lincosamide. One systematic review (Kilburn et al 2010) included 1 RCT which compared IV penicillin with intramuscular (IM) penicillin.

Oral cephalosporin or oral lincosamide versus IV cephalosporin or IV lincosamide

One RCT (Aboltins et al 2015) compared an oral cephalosporin (cefalexin) or an oral lincosamide (clindamycin) with an IV cephalosporin (cefazolin [not available in the UK]) or an IV lincosamide (clindamycin) in adults with cellulitis.

Oral antibiotics were not significantly different to IV antibiotics for the outcome of the mean number of days to no advancement of infection (1 RCT, n=47, mean difference [MD] -0.49 days, 95% confidence interval [CI] -1.02 to +0.04; low quality evidence) and treatment failure rate, follow-up period not defined (1 RCT, n=47, 4.2% versus 21.7%, relative risk [RR] 0.20, 95% CI 0.03 to 1.59; very low quality evidence). There were also no significant differences in pain score at 7 and 28 days follow-up (measured using a visual analogue scale) but pain scores were significantly higher on day 1 in the oral antibiotic group (1 RCT, n=47, MD +2.00, 95% CI +0.47 to +3.53; low quality evidence).

Oral antibiotics were not significanty different to IV antibiotics for any adverse event (1 RCT, n=47, 29.2% versus 30.4%, RR 0.96, 95% CI 0.40 to 2.31; very low quality evidence). Adverse events were mostly gastrointestinal in the oral antibiotic arm and pain or erythema at the injection site for the IV antibiotic arm. See GRADE table 17.

Intravenous penicillin versus intramuscular penicillin

One systematic review (Kilburn et al 2010) included 1 RCT comparing an IV penicillin (benzylpenicillin) with an IM penicillin (benzylpenicillin plus the local anaesthetic procaine) in adults with cellulitis.

IV benzylpenicillin was not significantly different to IM benzylpenicillin for the outcome of treatment failure at 10 days follow-up (1 RCT, n=112, 14% versus 20%, RR 0.70, 95% CI 0.31 to 1.61; very low quality evidence). See GRADE table 18.

IV benzylpenicillin was significantly worse than IM benzylpenicillin for any adverse events, mostly due to phlebitis (1 RCT, n=112, 25.5% versus 0%, RR 30.04, 95% CI 1.84 to 491.55, number needed to harm [NNH] 4, 95% CI 2 to 7; low quality

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evidence) but not for adverse events leading to study withdrawal (low quality evidence). See GRADE tables 43 and 44.

3.1.8 Antibiotic prophylaxis for the prevention of recurrent cellulitis or erysipelas in adults

The evidence for antibiotic prophylaxis for the prevention of recurrent cellulitis comes from 1 systematic review and meta-analysis (Dalal et al 2017), which included 6 RCTs. Five of these RCTs compared antibiotic prophylaxis with a pencillin or macrolide compared with no treatment or placebo in adults who had between 1 and 2 previous episodes of cellulitis or erysipelas.The other RCT included in the systematic review did not meet the inclusion criteria for the NICE guideline as it was not an antimicrobial intervention and was therefore excluded from the analysis.

Population of the included studies

In the 6 RCTs there were 573 people (200 men and 373 women), aged (in 5 of the RCTs) between 50 and 70 years. One RCT had a lower mean age of 46.2 years.

The number of previous episodes of cellulitis at recruitment was 2 episodes in 3 RCTs and 1 episode in 1 RCT, 1 RCT did not report this data. The time interval to a recurrence of cellulitis or erysipelas before a person entered an RCT was 3 years in 2 RCTs, 2 years in 1 RCT and 1 year in another. One RCT included participants with 1 previous episode within 12 weeks from inclusion and 1 RCT did not report this data.

Penicillin was used in 4 RCTs and erythromycin was used in 1 RCT. Three RCTs evaluated oral ingestion of penicillin (penicillin V), at a dose of 250 mg twice a day in 2 RCTs (for 6 and 12 months treatment course respectively) and 2 grams to 4 grams a day in 1 RCT (depending on participant's weight: 1 gram twice a day if < 90 kg; 1 gram + 2 grams a day if 90 kg to 120 kg; 2 grams twice a day if > 120 kg with an unclear length of treatment course). In 1 RCT penicillin (benzathine penicillin) was injected into the muscle at a dose of 1.2 million units every 15 days (length of treatment varied from 1 to 38 months). One RCT used erythromycin at a dose of 250 mg twice a day given by mouth (18 month course of treatment). In 2 RCTs the control group received a placebo, the other RCTs (penicillin V) used no treatment as the comparator.

Any antibiotic versus placebo or no treatment

One systematic review (Dalal et al 2017) included 5 RCTs in a meta-analysis which compared any antibiotic (IM benzathine penicillin, oral phenoxymethylpenicillin, oral penicillin V or oral erythromycin) with no treatment or placebo.

Antibiotic prophylaxis compared with no treatment (3 RCTs) or placebo (2 RCTs) significantly lowered the risk of recurrence during treatment of cellulitis in adults (5 RCTs, n=513, 13.6% versus 31.6%, relative risk [RR] 0.43, 95% confidence interval [CI] 0.30 to 0.61, number needed to treat [NNT] 6, 95% CI 4 to 10; moderate quality evidence).

Antibiotic prophylaxis compared with no treatment (2 RCTs) or placebo (2 RCTs) significantly lowered the incidence rate (episodes per person-month) of recurrence of cellulitis in adults (4 RCTs, n=4375 person months, 4% versus 7.6%, RR 0.44, 95% CI 0.22 to 0.89; very low quality evidence). However, once antibiotics were stopped in the trials the benefits of prophylaxis did not continue.

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Antibiotic prophylaxis compared with no treatment or placebo significantly lowered the risk of an episode of cellulitis (time to next episode) by 49% (3 RCTs, n=437, hazard ratio [HR] 0.51, 95% CI 0.34 to 0.78; moderate quality evidence), but had no effect on mortality (3 RCTs, n=437, 5.1% versus 4.1%, RR 1.24, 95% CI 0.53 to 2.88; very low quality evidence) or the risk of hospitalisation (3 RCTs, n=429, 5.7% versus 7.4%, RR 0.77, 95% CI 0.38 to 1.6; very low quality evidence). See GRADE table 42.

Antibiotic prophylaxis was not significantly different to no treatment or placebo for any adverse event (3 RCTs, n=469, 25% versus 28.7%, RR 0.88, 95% CI 0.65 to 1.17; low quality evidence). See GRADE table 43.

3.2 Antibiotics in children

3.2.1 Antibiotic prescribing strategies in children with cellulitis or erysipelas

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

3.2.2 Antibiotic choice in children with cellulitis or erysipelas

The evidence for choice of antibiotic in children with cellulitis comes from the systematic reviews reported in section 3.1.2 that included children and adults. Additionally, 1 RCT (Yogev et al 2003) conducted in children was identified. In the RCT, children were a subgroup of a larger cohort with skin and soft tissue infection (Yogev et al 2003). These subgroup data are limited as often only clinical cure is reported as an outcome for cellulitis or erysipelas, and the RCT subgroups for cellulitis or erysipelas may not include enough people to have sufficient statistical power.

Oxazolidinone versus glycopeptide

One RCT (Yogev et al 2003) compared an oxazolidinone (IV linezolid) with a glycopeptide (IV vancomycin) in children with skin and soft tissue infection, with cellulitis and erysipelas as subgroups. A switch from IV to oral antibiotics (either oral linezolid or 'an appropriate antibiotic') could be made at day 3.

IV linezolid was not significantly different to IV vancomycin for clinical cure rate (follow-up period not reported) for children with cellulitis (1 RCT, n=36, 95% versus 93.8%, RR 1.01, 95% CI 0.86 to 1.19; low quality evidence) See GRADE table 34.

3.2.3 Dual therapy in children with cellulitis or erysipelas

See section 3.1.3.

3.2.4 Antibiotic dose in children with cellulitis or erysipelas

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

3.2.5 Antibiotic dose frequency in children with cellulitis or erysipelas

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

3.2.6 Antibiotic course length in children with cellulitis or erysipelas

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

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3.2.7 Antibiotic route of administration in children with cellulitis or erysipelas

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

3.2.8 Antibiotic prophylaxis for the prevention of recurrent cellulitis or erysipelas in children

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

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4 Terms used in the guideline

Cellulitis and erysipelas

Cellulitis and erysipelas are infections of the subcutaneous tissues, 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).

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Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• Spellberg et al 2009 • Chira & Miller 2010 • NICE, Clinical Knowledge Summaries Cellulitis – acute • NHS Cellulitis
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NHS Cellulitis • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2018)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff

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Key area	Key question(s)	Evidence sources
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary (BNF) November 2018 • BNF for children (BNFC) November 2018 • Summary of product characteristics

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Appendix B: Review protocol

Review question	What pharmacological (antimicrobial) interventions are effective in managing cellulitis?
Types of review question	Intervention questions will primarily be addressed through the search.
Objective of the review	To determine the effectiveness of pharmacological (antimicrobial) interventions in managing cellulitis to address antimicrobial resistance. In line with the major goals of antimicrobial stewardship this includes interventions that lead prescribers to: • optimise therapy for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.
Eligibility criteria – population/ disease/ condition/ issue/domain[1]	Population: Adults and children (aged 72 hours and older) with acute cellulitis or erysipelas (including recurrent cellulitis) of any severity (measured using severity scoring system, for example, the Eron (2003) or Dundee (2010) classification systems).
Eligibility criteria – intervention(s)/ exposure(s)	The review will include studies which include: • Antimicrobial pharmacological interventions[2]. For the treatment of cellulitis (or antibiotic prophylaxis of recurrent cellulitis) in primary, secondary or other care settings (for example outpatient parenteral antimicrobial therapy, walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).
Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.
Outcomes and prioritisation	a) Clinical outcomes such as: • mortality

[1] Surgical cellulitis was excluded post hoc because the committee considered it a distinct clinical condition that can require different antibiotic treatment to non-surgical cellulitis due to the presence of more gram negative organisms, which if they followed this guideline, would result in the prescribing of antibiotics which may be consideredinappropriate or provide inadequate antibiotic cover.

2 Antimicrobial pharmacological interventions include: antibiotics, which could include back-up prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy

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	• infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. c) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. d) Ability to carry out activities of daily living. e) Service user experience. f) Health and social care related quality of life, including long-term harm or disability. g) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).
Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs. If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies.
Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers • non-pharmacological interventions.
Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these

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	categories to enable the production of management recommendations.
Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.
Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following sources will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy database, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process (including Daily Update and Epub Ahead of Print) via Ovid The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. A summary of the proposed search strategy is given in the appendix below. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates.

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	Date limits will be applied to restrict the search results to: • studies published from 2000 to the present day The results will be downloaded in the following sets: • Systematic reviews and meta analysis • Randomised controlled trials • Observational and comparative studies • Other results Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening. See Appendix for details of search terms to be used.
Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk
Highlight if amendment to previous protocol	For details please see the interim process guide (2017).
Search strategy – for one database	For details see appendix C.
Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.
Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.
Methods for assessing bias at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).
Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).

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Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).
Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).
Rationale/ context – Current management	For details please see the interim process guide (2017).
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence and conducted meta-analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	Developed and funded by NICE.
Name of sponsor	Developed and funded by NICE.
Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.

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Appendix C: Literature search strategy

Medline

1 exp CELLULITIS/ (7501)

2 ERYSIPELAS/ (1299)

3 (cellulitis or erysipelas).tw. (9715)

4 exp Soft Tissue Infections/ (3190)

5 or/1-4 (16868)

6 analgesics/ (45428)

7 exp analgesics, non-narcotic/ (309985)

8 analgesics, short-acting/ (9)

9 antipyretics/ (2547)

10 (analgesic* or antipyretic*).ti,ab. (76411)

11 Acetaminophen/ (16703)

12 (paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab. (22371)

13 Adrenal Cortex Hormones/ (61029)

14 (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab. (99438)

15 exp Prednisolone/ (48760)

16 (Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab. (37169)

17 Anti-Inflammatory Agents, Non-Steroidal/ (62636)

18 nsaid*.ti,ab. (22613)

19 ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab. (35966)

20 Ibuprofen/ (8093)

21 (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab. (12100)

22 watchful waiting/ (2825)

23 "no intervention*".ti,ab. (6855)

24 (watchful* adj2 wait*).ti,ab. (2291)

25 (wait adj2 see).ti,ab. (1317)

26 (expectant* adj2 manage*).ti,ab. (2929)

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27 (active* adj2 surveillance*).ti,ab. (6703)

28 ((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv*)).ti,ab. (25095)

29 ((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab. (2108)

30 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. (28642)

31 (delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*").ti,ab. (4028681)

32 Inappropriate prescribing/ (2301)

33 Amikacin/ (3912)

34 Amikacin.ti,ab. (8649)

35 exp Amoxicillin/ (10561)

36 Amoxicillin.ti,ab. (13414)

37 Ampicillin/ (13117)

38 Ampicillin*.ti,ab. (21532)

39 Azithromycin/ (4584)

40 (Azithromycin* or Azithromicin* or Zithromax*).ti,ab. (7157)

41 Penicillin G/ (8935)

42 (Benzylpenicillin* or "Penicillin G").ti,ab. (7981)

43 Cefalexin/ (2003)

44 (Cefalexin* or Cephalexin* or Keflex*).ti,ab. (2729)

45 (Ceftaroline* or Zinforo*).ti,ab. (574)

46 Ceftriaxone/ (5488)

47 (Ceftriaxone* or Rocephin* or Rocefin*).ti,ab. (9522)

48 Chloramphenicol/ (19107)

49 (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab. (25672)

50 Clarithromycin/ (5863)

51 (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab. (8395)

52 Clindamycin/ (5436)

53 (Clindamycin* or Dalacin* or Zindaclin*).ti,ab. (9680)

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54 Amoxicillin-Potassium Clavulanate Combination/ (2400)

55 (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab. (14520)

56 (dalbavancin* or dalvance*).ti,ab. (336)

57 Daptomycin/ (1770)

58 (daptomycin* or cubicin*).ti,ab. (2670)

59 Doxycycline/ (8941)

60 (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab. (12165)

61 (Ertapenem* or Invanz*).ti,ab. (1298)

62 Erythromycin/ (13502)

63 Erythromycin Estolate/ (148)

64 Erythromycin Ethylsuccinate/ (514)

65 (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab. (19919)

66 Floxacillin/ (695)

67 (Floxacillin* or Flucloxacillin*).ti,ab. (802)

68 Framycetin/ (493)

69 Framycetin.ti,ab. (157)

70 Fusidic Acid/ (1554)

71 ("Fusidic acid" or fusidate or Fucidin).ti,ab. (1937)

72 Gentamicins/ (17652)

73 (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab. (25267)

74 Imipenem/ (3859)

75 (Imipenem* or Primaxin*).ti,ab. (9592)

76 Levamisole/ (4233)

77 (Levamisole or ergamisol).ti,ab. (4417)

78 Levofloxacin/ (2958)

79 (Levofloxacin* or Evoxil* or Tavanic*).ti,ab. (6729)

80 Linezolid/ (2639)

81 (Linezolid* or Zyvox*).ti,ab. (5056)

82 Meropenem*.ti,ab. (5424)

83 Metronidazole/ (12108)

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84 Metronidazole.ti,ab. (14340)

85 exp Neomycin/ (9048)

86 (neom?cin or "Neo-Fradin").ti,ab. (9135)

87 Mupirocin/ (1131)

88 (Mupirocin or Bactroban).ti,ab. (1628)

89 Ofloxacin/ (5878)

90 (Ofloxacin* or Tarivid*).ti,ab. (6526)

91 (oritavancin* or orbactiv*).ti,ab. (302)

92 Penicillin V/ (2147)

93 (Phenoxymethylpenicillin or "Penicillin V").ti,ab. (1475)

94 Piperacillin/ (2595)

95 (Piperacillin* or Tazobactam* or Tazocin*).ti,ab. (6781)

96 Teicoplanin/ (2157)

97 (Teicoplanin* or Targocid*).ti,ab. (3373)

98 Tedizolid.ti,ab. (205)

99 (Tigecycline* or Tygacil*).ti,ab. (2677)

100 Trimethoprim, Sulfamethoxazole Drug Combination/ (6539)

101 (Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab. (5752)

102 Vancomycin/ (12636)

103 (Vancomycin* or Vancomicin* or Vancocin*).ti,ab. (24507)

104 exp Aminoglycosides/ (147315)

105 Aminoglycoside*.ti,ab. (17596)

106 exp Penicillins/ (78079)

107 Penicillin*.ti,ab. (52476)

108 exp beta-Lactamases/ (21005)

109 ((beta adj Lactamase*) or betaLactamase* or beta-Lactamase*).ti,ab. (25284)

110 exp beta-Lactamase inhibitors/ (7274)

111 beta-Lactams/ (6081)

112 (beta-Lactam or betaLactam or beta Lactam or beta-Lactams or betaLactams or beta Lactams).ti,ab. (19595)

113 exp Carbapenems/ (9661)

114 Carbapenem*.ti,ab. (11641)

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115 exp Cephalosporins/ (40388)

116 Cephalosporin*.ti,ab. (20606)

117 exp Fluoroquinolones/ (30211)

118 Fluoroquinolone*.ti,ab. (14784)

119 exp Macrolides/ (102375)

120 macrolide*.ti,ab. (14504)

121 Polymyxins/ (2835)

122 Polymyxin*.ti,ab. (6651)

123 exp Quinolones/ (43401)

124 Quinolone*.ti,ab. (12915)

125 exp Tetracyclines/ (45818)

126 Tetracycline*.ti,ab. (33455)

127 Chlorhexidine/ (7623)

128 (Chlorhexidine or Unisept or Hibiscrub or Hydrex or Hibi or HiBiTane).ti,ab. (9559)

129 Hydrogen Peroxide/ (52553)

130 ("Hydrogen peroxide" or crystacide).ti,ab. (47805)

131 Povidone-Iodine/ (2621)

132 (Povidone-Iodine or Betadine or Videne).ti,ab. (3106)

133 Potassium Permanganate/ (1509)

134 ("Potassium permanganate" or "EN-Potab" or Permitabs).ti,ab. (1561)

135 Proflavine/ (523)

136 proflavine.ti,ab. (636)

137 Silver Sulfadiazine/ (892)

138 (Silver Sulfadiazine or Flamazine).ti,ab. (890)

139 (reactive oxygen or surgihoney*).ti,ab. (102342)

140 Iodine/ (24285)

141 Iodine.ti,ab. (44578)

142 Honey/ or Apitherapy/ (3449)

143 (Honey* or L-Mesitran or MANUKApli or Medihoney or Melladerm or Mesitran).ti,ab. (19598)

144 (Antiseptic* or anti-infective* or anti infective or antiinfective or microbicide*).ti,ab. (13547)

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145 exp anti-infective agents, local/ (214561)

146 anti-infective agents/ or exp anti-bacterial agents/ (683980)

147 (antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab. (439021)

148 or/6-145 (5318664)

149 or/6-147 (5675327)

150 5 and 149 (8017)

151 limit 150 to yr="2000 -Current" (5310)

152 limit 151 to english language (4617)

153 Animals/ not (Animals/ and Humans/) (4456014)

154 152 not 153 (4472)

155 limit 154 to (letter or historical article or comment or editorial or news or case reports) (1569)

156 154 not 155 (2903)

157 Meta-Analysis.pt. (91651)

158 Network Meta-Analysis/ (452)

159 Meta-Analysis as Topic/ (16396)

160 Review.pt. (2418006)

161 exp Review Literature as Topic/ (10018)

162 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (134139)

163 (review$ or overview$).ti. (441402)

164 (systematic$ adj5 (review$ or overview$)).tw. (139443)

165 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (8827)

166 ((studies or trial$) adj2 (review$ or overview$)).tw. (40851)

167 (integrat$ adj3 (research or review$ or literature)).tw. (10331)

168 (pool$ adj2 (analy$ or data)).tw. (25535)

169 (handsearch$ or (hand adj3 search$)).tw. (8354)

170 (manual$ adj3 search$).tw. (5368)

171 or/157-170 (2698074)

172 156 and 171 (669)

173 Randomized Controlled Trial.pt. (467089)

174 Controlled Clinical Trial.pt. (92592)

175 Clinical Trial.pt. (511984)

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176 exp Clinical Trials as Topic/ (316953)

177 Placebos/ (34055)

178 Random Allocation/ (95544)

179 Double-Blind Method/ (147251)

180 Single-Blind Method/ (25591)

181 Cross-Over Studies/ (43534)

182 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (1085029)

183 (random$ adj3 allocat$).tw. (31247)

184 placebo$.tw. (197380)

185 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (158457)

186 (crossover$ or (cross adj over$)).tw. (78776)

187 or/173-186 (1829153)

188 5 and 148 (5802)

189 limit 188 to yr="2000 -Current" (3843)

190 limit 189 to english language (3350)

191 Animals/ not (Animals/ and Humans/) (4456014)

192 190 not 191 (3232)

193 limit 192 to (letter or historical article or comment or editorial or news or case reports) (1112)

194 192 not 193 (2120)

195 187 and 194 (403)

196 Observational Studies as Topic/ (3221)

197 Observational Study/ (51469)

198 Epidemiologic Studies/ (7753)

199 exp Case-Control Studies/ (936174)

200 exp Cohort Studies/ (1772435)

201 Cross-Sectional Studies/ (272809)

202 Controlled Before-After Studies/ (348)

203 Historically Controlled Study/ (142)

204 Interrupted Time Series Analysis/ (466)

205 Comparative Study.pt. (1806769)

206 case control$.tw. (112700)

207 case series.tw. (60873)

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208 (cohort adj (study or studies)).tw. (159994)

209 cohort analy$.tw. (6376)

210 (follow up adj (study or studies)).tw. (45491)

211 (observational adj (study or studies)).tw. (83814)

212 longitudinal.tw. (208602)

213 prospective.tw. (497009)

214 retrospective.tw. (436640)

215 cross sectional.tw. (285313)

216 or/196-215 (4203586)

217 194 and 216 (1103)

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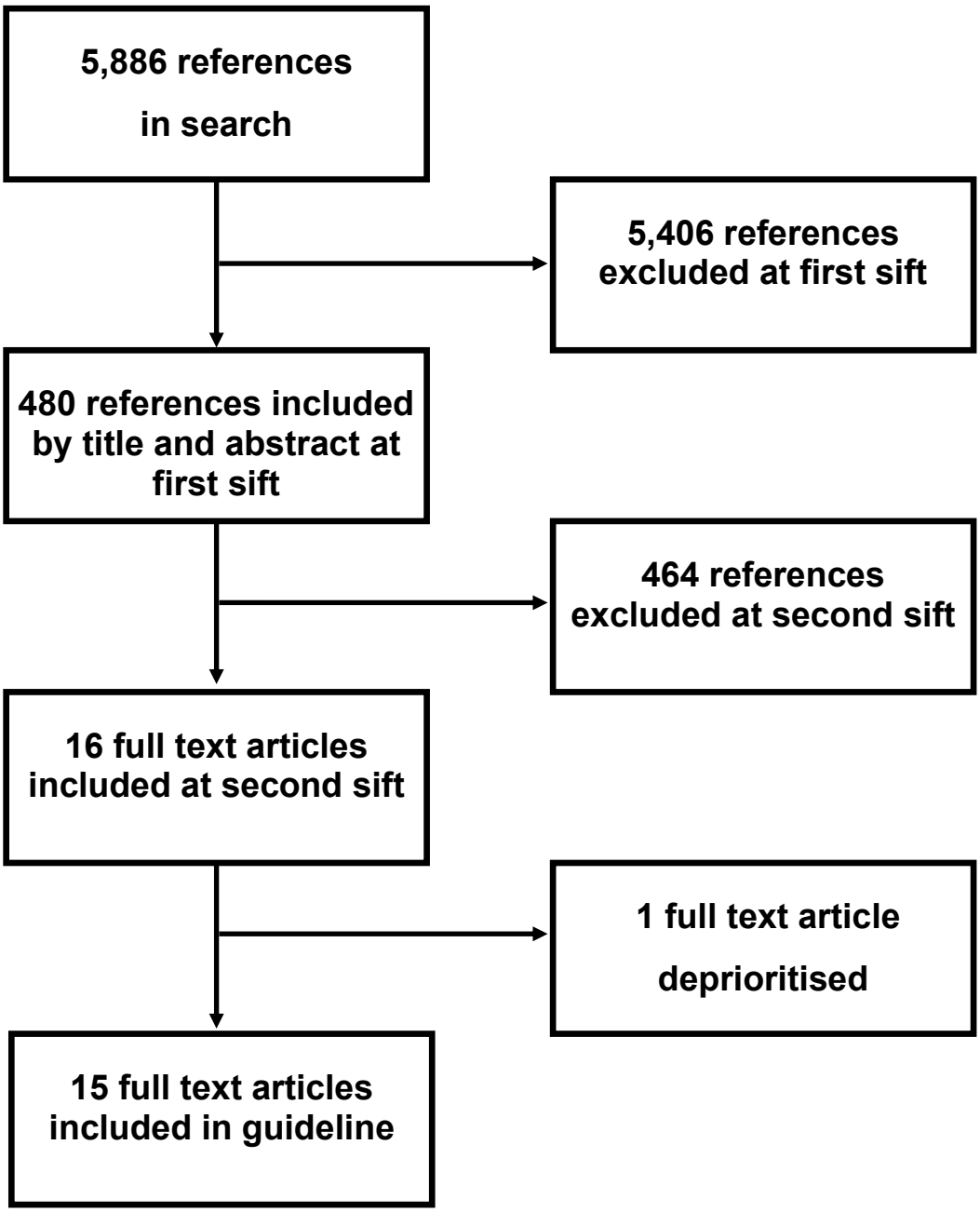
Appendix D: Study flow diagram



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Appendix E: Evidence prioritisation

Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Which antibiotic is most effective in adults with cellulitis or erysipelas?						
Antibiotic compared with another antibiotic						
Boucher et al. 2014	RCT	Once weekly dalbavancin	Vancomycin (IV) oral linezolid switch at day 3	Early clinical response (48 hours)	Prioritised	Comparator not included elsewhere
Kilburn et al. 2010	Systematic review	Antibiotics (by class)	Other antibiotics (by class)	Duration / intensity of symptoms	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Ferreira et al. 2016	Systematic review	Penicillin or cephalosporin	Macrolide or lincosamide	Treatment failure	Prioritised	Updates the Kilburn et al 2010 systematic review for these comparisons
Frampton 2013	Systematic review	Ceftaroline fosamil	Vancomycin with aztreonam	Clinical cure rate	Prioritised	Comparator not included elsewhere
Bowen et al. 2017	Systematic review	Co-trimoxazole alone or with cefalexin	Clindamycin or cefalexin	Clinical cure rate	Prioritised	Updates the Kilburn et al 2010 systematic review for these comparisons
Konychev et al. 2013	RCT	Daptomycin	Penicillin (IV semi-synthetic penicillin's or vancomycin)	Clinical success	Prioritised	Intervention and comparator not included elsewhere
Matthews et al. 2012	RCT	Tigecycline	Ampicillin-sulbactam or co-amoxiclav with vancomycin if MRSA	Clinical response	Prioritised	Intervention and comparator not included elsewhere
Pertel et al. 2009	RCT	Daptomycin	Vancomycin	Clinical response	Prioritised	Intervention and comparator not included elsewhere

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Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
Vick-Fragaso et al. 2009	RCT	Moxifloxacin	Co-amoxiclav	Clinical success	Prioritised	Comparator not included elsewhere
Which antibiotic co-treatment is most effective in adults with cellulitis or erysipelas?						
Antibiotic plus antibiotic compared with antibiotic plus placebo						
Bowen et al. 2017	Systematic review	Co-trimoxazole with cefalexin	Cefalexin alone	Clinical cure rate	Prioritised	Updates the Kilburn et al 2010 systematic review for these comparisons
Brindle et al. 2017	RCT	Flucloxacillin plus clindamycin	Flucloxacillin alone	Clinical improvement	Prioritised	Comparator not included elsewhere
Kilburn et al. 2010	Systematic review	Flucloxacillin plus benzyl penicillin	Flucloxacillin alone	Duration and intensity of symptoms	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Noel et al. 2008	RCT	Vancomycin plus ceftazidime	Ceftibiprole	Clinical cure rate	Prioritised	Comparator not included elsewhere
What is the optimal dose, dose frequency, duration and route of administration in adults with cellulitis or erysipelas?						
Short course compared to long course antibiotics						
Aboltins et al. 2015	RCT	Cefalexin (oral)	Cefazolin (IV then oral)	Days to no advance	Prioritised	Comparator not included elsewhere
Hanretty et al. 2018	Systematic review	Tedizolid (6 days)	Tedizolid (10 days)	Cure rate	Prioritised	Updates the Kilburn et al 2010 systematic review for this comparison
Kilburn et al. 2010	Systematic review	Levofloxacin (5 days - duration) Penicillin IV (route)	Levofloxacin (10 days - duration) Penicillin IM (route)	Duration and intensity of symptoms	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison

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Reference	Study type	Intervention(s)	Comparator(s)	Key outcomes	Prioritisation decision	Reason for decision
		Cefalexin (twice daily for 4 to 10 days – dose frequency)	Cefalexin (four times daily for 4 to 10 days)			
Which antibiotic is the most effective in children with cellulitis or erysipelas?						
Antibiotic compared with antibiotic						
Yogev et al. 2003	RCT	IV or oral linezolid	IV vancomycin	Clinical cure rate	Prioritised	Population and comparator and not included elsewhere
Do antibiotics prevent recurrence in adults with prior episodes of cellulitis or erysipelas?						
Antibiotic compared with no treatment or placebo						
Dalal et al. 2017	Systematic review	Prophylactic antibiotics (erythromycin or penicillin)	No treatment or placebo	Risk of recurrence	Prioritised	Highest quality (most comprehensive) systematic review identified for this comparison
Mason et al. 2014	RCT	Prophylactic penicillin	Placebo	Health economic outcomes	Not prioritised	The outcome data from 2 RCTs already included in Dalal et al 2017.

[1] See appendix F for full references of included studies
[2] See appendix I for full references of not-prioritised studies, with reasons for not prioritising these studies

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Appendix F: Included studies

Aboltins CA; Hutchinson AF; Sinnappu RN et al (2015) Oral versus parenteral antimicrobials for the treatment of cellulitis: a randomized non-inferiority trial. The Journal of antimicrobial chemotherapy 70(2), 581-6

Boucher HW; Zervou FN; Zacharioudakis IM et al (2014) Weekly dalbavancin was noninferior to daily vancomycin for acute bacterial skin infection in adults. Annals of Internal Medicine 161(8), JC9

Bowen AC; Carapetis JR; Currie BJ et al (2017) Sulfamethoxazole-Trimethoprim (Cotrimoxazole) for Skin and Soft Tissue Infections Including Impetigo, Cellulitis, and Abscess. Open forum infectious diseases 4(4), ofx232

Brindle R; Williams OM; Davies P et al (2017) Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis. BMJ open 7(3), e013260

Dalal A; Eskin-Schwartz M; Mimouni D et al (2017) Interventions for the prevention of recurrent erysipelas and cellulitis. Cochrane Database of Systematic Reviews (6),

Ferreira A; Bolland MJ; Thomas MG (2016) Meta-analysis of randomised trials comparing a penicillin or cephalosporin with a macrolide or lincosamide in the treatment of cellulitis or erysipelas. Infection 44(5), 607-15

Frampton JE (2013) Ceftaroline fosamil: a review of its use in the treatment of complicated skin and soft tissue infections and community-acquired pneumonia. Drugs 73(10), 1067-94

Hanretty AM; Gallagher JC (2018) Shortened Courses of Antibiotics for Bacterial Infections: A Systematic Review of Randomized Controlled Trials. Pharmacotherapy 38(6), 674-687

Kilburn SA; Featherstone P; Higgins B et al (2010) Interventions for cellulitis and erysipelas. Cochrane Database of Systematic Reviews (6)

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Matthews P; Alpert M; Rahav G et al (2012) A randomized trial of tigecycline versus ampicillin-sulbactam or amoxicillin-clavulanate for the treatment of complicated skin and skin structure infections. BMC Infectious Diseases 12, 297

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Pertel PE; Eisenstein BI; Link AS et al (2009) The efficacy and safety of daptomycin vs. vancomycin for the treatment of cellulitis and erysipelas. International journal of clinical practice 63(3), 368-75

Vick-Fragoso R; Hernandez-Oliva G; Cruz-Alcazar J et al (2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. Infection 37(5), 407-17

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Yogev R; Patterson LE; Kaplan SL et al (2003) Linezolid for the treatment of complicated skin and skin structure infections in children. Pediatric Infectious Disease Journal 22(9 SUPPL.), S172-S177

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Appendix G: Quality assessment of included studies

G.1 Antibiotic route of administration in adults with cellulitis or erysipelas

Table 7: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Kilburn et al 2010
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

[a] The systematic review included observational trials as well as RCTs.
[b] Only limited databases were searched, with limited search dates, no hand searches or grey literature searches mentioned.
[c] No formal assessment of study quality undertaken.
[d] Safety data were not reported.
[e] Study selection criteria are unclear.

Table 8: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Aboltins et al 2015
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes

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Were patients, health workers and study personnel blinded?	No[a]
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

[a] Open-label RCT.
[b] There was a larger number of people with Diabetes in the DISCOVER 2 trials vancomycin arm (9.4% vs. 16.8%, p=0.003).

G.2 Choice of antibiotic choice in adults and children with cellulitis or erysipelas

Table 9: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Bowen et al 2017	Ferreira et al 2016	Frampton 2013	Kilburn et al 2010
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Partially[a]	Yes	Unclear[e]	Yes
Do you think all the important, relevant studies were included?	Unsure[b]	Unsure[b]	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	No[c]	Yes	No[c]	Yes
If the results of the review have been combined, was it reasonable to do so?	N/A	Yes	N/A	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

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Can the results be applied to the local population?	Yes	Yes	Yes	Yes
Were all important outcomes considered?	No[d]	Yes	No[d]	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] The systematic review included observational trials as well as RCTs.
[b] Only limited databases were searched, with limited search dates, no hand searches or grey literature searches mentioned.
[c] No formal assessment of study quality undertaken.
[d] Safety data were not reported.
[e] Study selection criteria are unclear.

Table 10: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Boucher et al 2014	Konychev et al 2013	Matthews et al 2012	Noel et al 2008	Pertel et al 2009
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	No[a]	No[a]	Yes	Partially[c]
Were the groups similar at the start of the trial?	Yes	Partially[b]	Yes	Yes	Partially[d]
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles				
How precise was the estimate of the treatment effect?	See GRADE profiles				

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Study reference	Boucher et al 2014	Konychev et al 2013	Matthews et al 2012	Noel et al 2008	Pertel et al 2009
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles				

[a] Open-label RCT.
[b] There was a larger number of people with Diabetes in the DISCOVER 2 trials vancomycin arm (9.4% vs. 16.8%, p=0.003).
[c] There was a gender imbalance in the randomisation (58% female in treatment arm vs. 66.7% in the comparator, no p value reported).
[d] Evaluator-blinded study only.
[e] There was a gender imbalance in the randomisation (66% female in treatment arm vs. 51% in the comparator, 8% more people had diabetes in the treatment arm than comparator, no p value reported).

Table 11: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Vick-Fragaso et al 2009	Yogev et al 2003
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	No[a]	No[a]
Were the groups similar at the start of the trial?	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
How large was the treatment effect?	See GRADE profiles	

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Study reference	Vick-Fragaso et al 2009	Yogev et al 2003
How precise was the estimate of the treatment effect?	See GRADE profiles	
Can the results be applied in your context? (or to the local population)	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	

[a] Open-label RCT.

G.3 Dual therapy in children and adults with cellulitis or erysipelas

Table 12: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Bowen et al 2017	Kilburn et al 2010
Did the review address a clearly focused question?	Yes	Yes
Did the authors look for the right type of papers?	Partially[a]	Yes
Do you think all the important, relevant studies were included?	Unsure[b]	Yes
Did the review's authors do enough to assess the quality of the included studies?	No[c]	Yes
If the results of the review have been combined, was it reasonable to do so?	N/A	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes
Were all important outcomes considered?	No[d]	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles

[a] The systematic review included observational trials as well as RCTs.
[b] Only limited databases were searched, with limited search dates, no hand searches or grey literature searches mentioned.
[c] No formal assessment of study quality undertaken.

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[d] Safety data were not reported.

Table 13: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Brindle et al 2017
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.4 Antibiotic dose frequency in adults with cellulitis or erysipelas

Table 14: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Kilburn et al 2010
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles

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Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.5 Antibiotic course length in adults with cellulitis or erysipelas

Table 15: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Hanretty et al 2018	Kilburn et al 2010
Did the review address a clearly focused question?	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	No[a]	Yes
If the results of the review have been combined, was it reasonable to do so?	N/A	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes
Were all important outcomes considered?	No[b]	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles

[a] No quality assessment of included studies
[b] Only clinical cure was examined

G.6 Antibiotic prophylaxis for the prevention of recurrent cellulitis or erysipelas in adults

Table 16: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Dalal et al 2017
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes

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Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Appendix H: GRADE profiles

H.1 Antibiotic route of administration in adults with cellulitis or erysipelas

Table 17: GRADE profile – Oral antibiotics vs parenteral antibiotics for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics	Parenteral antibiotics	Relative (95% CI)	Absolute		
Mean number of days to no advancement of cellulitis (follow-up daily until no advancement; measured with: oral vs. parenteral antibiotics in ITT population; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	24[4] 1.29 (SD 0.62)	23[5] 1.78 (SD 1.13)	-	MD 0.49 lower (1.02 lower to 0.04 higher)[6]	⊕⊕OO LOW	CRITICAL
Treatment failure rate (follow-up not specified; assessed with: oral vs. parenteral antibiotics in ITT population)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	1/24 (4.2%)[4]	5/23 (21.7%)[5]	RR 0.20 (0.03 to 1.59)[8]	174 fewer per 1000 (from 211 fewer to 128 more)	⊕OOO VERY LOW	CRITICAL
Pain score at day 1 (follow-up 1 days; measured with: oral vs. parenteral antibiotics in ITT population[9]; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[10]	none	24[4] 4.8 (SD 2.4)	23[5] 2.8 (SD 2.9)	-	MD 2.00 higher (0.47 to 3.53 higher)[8]	⊕⊕OO LOW	CRITICAL

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Pain score at day 7 (follow-up 7 days; measured with: oral vs. parenteral antibiotics in the ITT population[9]; Better indicated by lower values)												
1[1]	randomised trials	Serious[2]	not applicable	no serious indirectness	no serious imprecision	none	24[4] 1.9 (SD 1.9)	23[5] 1.9 (SD 2.7)	-	MD 0.0 higher (1.30 lower to 1.30 higher)[8]	⊕⊕⊕O MODERATE	CRITICAL
Pain score at day 28 (follow-up 28 days; measured with: oral vs. parenteral antibiotics in ITT population[9]; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	24[4] 0.3 (SD 0.6)	23[5] 0.4 (SD 1.7)	-	MD 0.10 lower (0.84 lower to 0.64 higher)[8]	⊕⊕⊕O MODERATE	CRITICAL
Reduction in pain score from baseline to day 1 (follow-up 1 days; measured with: oral vs. parenteral antibiotics in ITT population[9]; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[11]	none	24[4] 0.5 (SD 1.9)	23[5] 1.0 (SD 2.5)	-	MD 0.50 lower (1.77 lower to 0.77 higher)	⊕⊕OO LOW	CRITICAL
Reduction in pain score from baseline to day 7 (follow-up 7 days; measured with: oral vs. parenteral antibiotics in ITT population[9]; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[12]	none	24[4] 3.4 (SD 3.3)	23[5] 1.9 (SD 3.0)	-	MD 1.50 higher (0.30 lower to 3.30 higher)[8]	⊕⊕OO LOW	CRITICAL
Reduction in pain score from baseline to day 28 (follow-up 28 days; measured with: oral vs. parenteral antibiotics in ITT population[9]; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[13]	none	24[4] 5.0 (SD 2.8)	23[5] 3.4 (SD 3.5)	-	MD 1.60 higher (0.22 lower to 3.42 higher)	⊕⊕OO LOW	CRITICAL
Satisfaction rating (overall) (follow-up 28 days; measured with: oral vs. parenteral antibiotics in ITT population [14]; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[15]	none	24[4] 3.9 (SD 0.3)	23[5] 3.7 (SD 0.6)	-	MD 0.20 higher (0.07 lower to 0.47 higher)[8]	⊕⊕OO LOW	IMPORTANT
Any adverse event (assessed with: complications of treatment[16])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[17]	none	7/24 (29.2%)[4]	7/23 (30.4%)[5]	RR 0.96 (0.40 to 2.31)[8]	12 fewer per 1000 (from 183 fewer to 399 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; ITT, Intention-to-treat; SD, Standard deviation; MD, Mean difference; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Aboltins et al 2015.
[2] Downgraded 1 level - RCT assessed as at risk of bias due to being open-label (non-blinded).
[3] Downgraded 1 level - at a default minimal important difference of 0.5 SD of the control (parenteral antibiotic arm = 0.565) data are consistent with no meaningful difference or appreciable benefit with oral antibiotics.
[4] Oral antibiotics were cefalexin or clindamycin.
[5] Parenteral antibiotics were IV cefazolin or IV clindamycin.
[6] Per-protocol analysis (excluded 1 patient with major protocol violation from the oral arm) was -0.48 (95% CI -1.02 to +0.07).
[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oral antibiotics, and no meaningful difference or appreciable harm with parenteral antibiotics.
[8] NICE analysis.
[9] Pain was assessed with a visual analogue scale with a range of 0–10.
[10] Downgraded 1 level - at a default minimal important difference of 0.5 SD of the control (parenteral antibiotic arm = 1.45) data are consistent with no meaningful difference or appreciable harm with

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oral antibiotics.
[11] Downgraded 1 level - at a default minimal important difference of 0.5 SD of the control (parenteral antibiotic arm = 1.25) data are consistent with no meaningful difference or appreciable benefit with parenteral antibiotics.
[12] Downgraded 1 level - at a default minimal important difference of 0.5 SD of the control (parenteral antibiotic arm = 1.50) data are consistent with no meaningful difference or appreciable benefit with oral antibiotics.
[13] Downgraded 1 level - at a default minimal important difference of 0.5 SD of the control (parenteral antibiotic arm = 1.75) data are consistent with no meaningful difference or appreciable benefit with oral antibiotics.
[14] Convenience, effectiveness and overall satisfaction measured on scale 0 - 4 (not satisfied to most satisfied) 3 surveys not returned (unclear which arm).
[15] Downgraded 1 level - at a default minimal important difference of 0.5 SD of the control (parenteral antibiotic arm = 0.3) data are consistent with no meaningful difference or appreciable benefit with oral antibiotics.
[16] Mostly gastrointestinal adverse event in the oral arm and pain, erythema at injection site in the parenteral arm.
[17] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oral antibiotics, and no meaningful difference or appreciable harm with parenteral antibiotics.

Table 18: GRADE profile – Penicillin (IV) vs. penicillin (IM) for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV penicillin**	**IM penicillin**	**Relative (95% CI)**	**Absolute**		
Treatment failure (follow-up 10 days; assessed with: IV vs. IM penicillin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	8/57 (14%)[4]	11/55 (20%)[5]	RR 0.70 (0.31 to 1.61)[6]	60 fewer per 1000 (from 138 fewer to 122 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous; IM, Intramuscular.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with IV penicillin, and no meaningful difference or appreciable harm with IM penicillin.
[4] IV benzyl penicillin.
[5] IM benzyl penicillin + procaine (a local anaesthetic).
[6] NICE analysis.

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H.2 Antibiotic choice in adults with cellulitis or erysipelas

Table 19: GRADE profile – Once weekly lipoglycopeptide vs. glycopeptide for with cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lipoglycopeptide	Glycopeptide	Relative (95% CI)	Absolute		
Clinical response (according to investigator assessment) (follow-up 48 to 72 hours; assessed with: Lipoglycopeptide vs. glycopeptide)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[2]	no serious imprecision	none	281/354 (79.4%)[3]	269/349 (77.1%)[4]	RR 1.03 (0.95 to 1.11)[5]	23 more per 1000 (from 39 fewer to 85 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical response (according to investigator assessment) (follow-up at end of therapy; assessed with: Lipoglycopeptide vs. glycopeptide)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[2]	no serious imprecision	none	294/324 (90.7%)[3]	276/301 (91.7%)[4]	RR 0.99 (0.94 to 1.04)[5]	9 fewer per 1000 (from 55 fewer to 37 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; IV, Intravenous.												

[1] Boucher et al 2014.
[2] Downgraded 1 level - cellulitis as a subgroup of acute bacterial skin and skin-structure infections.
[3] IV dalbavancin (2 dose regimen days 1 and 8).
[4] IV vancomycin with option to switch to oral linezolid to complete 10 to 14 days therapy.
[5] NICE analysis.

Table 20: GRADE profile – Penicillin vs. macrolide or oral streptogramin for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV penicillin	Oral macrolide or oral streptogramin	Relative (95% CI)	Absolute		
Symptom free or reduced at end of therapy (follow-up 7 to 14 days[1]; assessed with: IV or oral penicillin vs. oral macrolide or oral streptogramin)												
3[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	119/209 (56.9%)[6,7]	143/210 (68.1%)[8,9]	RR 0.83 (0.71 to 0.96)[10]	116 fewer per 1000 (from 27 fewer to 197 fewer)	⊕OOO VERY LOW	CRITICAL
Symptom free or reduced at end of therapy (follow-up 7 to 14 days[1]; assessed with: IV penicillin vs. oral macrolide or oral streptogramin)												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	108/188 (57.4%)[6]	116/169 (68.6%)[8]	RR 0.83 (0.71 to 0.97)[10]	117 fewer per 1000 (from 21 fewer to 199 fewer)	⊕⊕OO LOW	CRITICAL

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Symptom free or reduced at end of therapy (follow-up 7 to 10 days; assessed with: Oral penicillin vs. oral macrolide)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[11]	none	11/21 (52.4%)[7]	27/41 (65.9%)[9]	RR 0.80 (0.50 to 1.26)	132 fewer per 1000 (from 329 fewer to 171 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: IV, Intravenous; 95% CI, 95% Confidence interval; RR, relative risk; RCT, Randomised controlled trial.												

[1] Length of follow-up varied by study (from 'not stated' to 14 days).
[2] Kilburn et al 2010.
[3] Downgraded 1 level - no study assessed by the Cochrane reviewers was found to be at low risk of bias.
[4] Downgraded 1 level - 1 RCT (Daniel et al 1991, part 2) was in a population of people with skin and soft tissue infection not just people with cellulitis or erysipelas.
[5] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with macrolide or streptogramin.
[6] IV penicillin (2 RCTs).
[7] Oral cloxacillin (1 RCT).
[8] Oral macrolide (roxithromycin) or oral streptogramin (pristinamycin).
[9] Oral macrolide (azithromycin).
[10] NICE analysis using fixed effects model (I^2<50%).
[11] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oral macrolide, and no meaningful difference or appreciable harm with oral cloxacillin.

Table 21: GRADE profile – Penicillin or cephalosporin vs macrolide or lincosamide for cellulitis or erysipelas

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Penicillin or cephalosporin**	**Macrolide or lincosamide**	**Relative (95% CI)**	**Absolute**		
Treatment failure (assessed with: penicillin or cephalosporin vs. macrolide or lincosamide)												
9[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	27/221 (12.2%)[4]	21/241 (8.7%)[5]	RR 1.29 (0.76 to 2.17)[6]	25 more per 1000 (from 21 fewer to 102 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk.												

[1] Ferreira et al 2016.
[2] Downgraded 1 level - the authors assessed only 4 of the 9 included RCTs as at low risk of bias.
[3] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with penicillin or cephalosporin.
[4] Penicillin (flucloxacillin, cloxacillin, penicillin or dicloxacillin) or cephalosporin (cephalexin, cefaclor or cefdinir).
[5] Macrolide (erythromycin, azithromycin, roxithromycin or telithromycin) or lincosamide (clindamycin).
[6] NICE analysis using fixed effects model (I^2=0%).

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Table 22: GRADE profile – Penicillin vs. cephalosporin for people with cellulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV penicillin	IV cephalosporin	Relative (95% CI)	Absolute		
Symptom free or reduced at end of therapy (follow-up 0 to 72 hours post therapy; assessed with: IV penicillin vs. IV cephalosporin)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	very serious[5]	none	30/40 (75%)[6,7]	40/48 (83.3%)[8,9]	RR 0.99 (0.68 to 1.43)	8 fewer per 1000 (from 267 fewer to 358 more)	⊕OOO VERY LOW	CRITICAL
Symptom free or reduced at end of therapy (assessed with: IV ampicillin plus sulbactam vs. IV cefazolin)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	serious[10]	none	16/17 (94.1%)[6]	19/24 (79.2%)[8]	RR 1.17 (0.91 to 1.51)[11]	135 more per 1000 (from 71 fewer to 404 more)	⊕OOO VERY LOW	CRITICAL
Symptom free or reduced at end of therapy (follow-up 48 to 72 hours; assessed with: IV flucloxacillin vs. IV ceftriaxone)												
1[1]	randomised trials	Serious[2]	not applicable	no serious indirectness	serious[12]	none	14/23 (60.9%)	21/24 (87.5%)	RR 0.70 (0.48 to 1.00)	263 fewer per 1000 (from 455 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: IV, Intravenous; 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - no study assessed by the Cochrane reviewers was found to be at low risk of bias.
[3] Downgraded 1 level - I^2>50%.
[4] Downgraded 1 level - 1 RCT (Chan et al 1995) was in a population of people with skin and soft tissue infection not just people with cellulitis or erysipelas.
[5] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit/harm with IV penicillin, and no meaningful difference or appreciable harm with IV cephalosporin.
[6] IV ampicillin + sulbactam (2 RCTs).
[7] IV flucloxacillin (1 RCT).
[8] IV cefazolin, a 1st generation cephalosporin (2 RCTs).
[9] IV ceftriaxone, a 3rd generation cephalosporin (1 RCT).
[10] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit IV penicillin.
[11] NICE analysis using fixed effects model (I^2<50%).
[12] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with IV cephalosporin.

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Table 23: GRADE profile – Quinolone vs. ureidopenicillin plus beta-lactamase inhibitor for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Beta-lactamase inhibitor	Relative (95% CI)	Absolute		
Cure rate (follow-up period not reported: assessed with: IV quinolone vs. IV beta-lactamase inhibitor)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	36/43 (83.7%)[3]	38/43 (88.4%)[4]	RR 0.95 (0.80 to 1.12)[5]	44 fewer per 1000 (from 177 fewer to 106 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Quinolone antibiotic, IV moxifloxacin (oral switch at day 3).
[4] Ureidopenicillin plus beta-lactamase inhibitor, IV piperacillin-tazobactam (oral switch to co-amoxiclav at day 3).
[5] NICE analysis.

Table 24: GRADE profile – Quinolone vs penicillin plus beta-lactamase inhibitor for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone	Penicillin plus beta-lactamase inhibitor	Relative (95% CI)	Absolute		
Clinical success in complicated erysipelas (per protocol population) (follow-up 14 to 28 days; assessed with: fluoroquinolone vs. penicillin plus beta-lactamase inhibitor)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	91/101 (90.1%)[4]	90/95 (94.7%)[5]	RR 0.95 (0.88 to 1.03)[6]	47 fewer per 1000 (from 114 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
Clinical success in complicated erysipelas (ITT population) (follow-up 14 to 28 days; assessed with: fluoroquinolone vs. penicillin plus beta-lactamase inhibitor)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	102/114 (89.5%)[4]	100/111 (90.1%)[5]	RR 0.99 (0.91 to 1.08)[6]	9 fewer per 1000 (from 81 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
Clinical success in complicated cellulitis (per protocol population) (follow-up 14 to 28 days; assessed with: fluoroquinolone vs. penicillin plus beta-lactamase inhibitor)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[7]	none	8/9 (88.9%)[4]	15/17 (88.2%)[5]	RR 1.01 (0.75 to 1.34)[6]	9 more per 1000 (from 221 fewer to 300 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in complicated cellulitis (ITT population) (follow-up 14 to 28 days; assessed with: fluoroquinolone vs. penicillin plus beta-lactamase inhibitor)												

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1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[7]	none	11/12 (91.7%)[4]	16/19 (84.2%)[5]	RR 1.09 (0.84 to 1.41)[6]	76 more per 1000 (from 135 fewer to 345 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Vick-Fragaso et al 2009.
[2] Downgraded 1 level - the RCT was assessed as at risk of bias (see quality assessment tables).
[3] Downgraded 1 level - complicated erysipelas and cellulitis were subgroups of a larger cohort with complicated skin and soft tissue infection.
[4] IV then oral moxifloxacin.
[5] IV then oral co-amoxiclav.
[6] NICE analysis.
[7] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with moxifloxacin.

Table 25: GRADE profile – Lipopeptide vs penicillin for cellulitis in older adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Lipopeptide**	**Penicillin[1]**	**Relative (95% CI)**	**Absolute**		
Clinical success (follow-up 7 to 14 days[2]; assessed with: lipopeptide vs. penicillin[3])												
1[4]	randomised trials	serious[5]	not applicable	serious[6]	very serious[7]	none	14/18 (77.8%)[8]	10/12 (83.3%)[9]	RR 0.93 (0.66 to 1.33)[10]	58 fewer per 1000 (from 283 fewer to 275 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Small number may have received vancomycin.
[2] Post-treatment
[3] Defined as complete or partial resolution of clinically significant signs and symptoms at the pre-treatment infection site with no further antibacterial therapy required.
[4] Konychev et al 2013.
[5] Downgraded 1 level - RCT assessed as at risk of bias (see quality assessment tables).
[6] Downgraded 1 level - cellulitis as a subgroup of a larger cohort of skin and soft tissue infection.
[7] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with IV daptomycin.
[8] IV daptomycin.
[9] Semi synthetic penicillin (not further defined), some people may have received vancomycin (pooled comparator).
[10] NICE analysis.

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Table 26: GRADE profile – Glycylcycline vs penicillin plus beta-lactamase inhibitor for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glycylcycline	Penicillin + beta-lactamase inhibitor	Relative (95% CI)	Absolute		
Clinical success (cure) at test of cure visit (follow-up 8 to 50 days; assessed with: IV glycylcycline vs. IV penicillin plus beta-lactamase inhibitor in per protocol population)												
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	114/150 (76%)[4]	103/132 (78%)[5]	RR 0.97 (0.86 to 1.11)[6]	23 fewer per 1000 (from 109 fewer to 86 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; MRSA, Methicillin-resistant *Staphylococcus aureus.*												

[1] Matthews et al 2012.
[2] Downgraded 1 level - the RCT was open-label and therefore at risk of bias (see quality assessment tables).
[3] Downgraded 1 level - the cellulitis cohort made up 63% of the study population, and 92% of deep soft tissue infection subgroup (reported here) but was not reported separately.
[4] IV tigecycline.
[5] IV ampicillin-sulbactam or co-amoxiclav, with IV vancomycin if MRSA +ve.
[6] NICE analysis.

Table 27: GRADE profile – Cephalosporins (newer generation) vs. cephalosporins (older generation) for cellulitis in young people and adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Newer generation cephalosporin's	Older generation cephalosporin's	Relative (95% CI)	Absolute		
Symptom free or reduced at end of therapy (follow-up 0 to 16 days[1]; assessed with: Newer generation cephalosporin's vs. older generation cephalosporin's)												
6[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	248/284 (87.3%)[5]	220/254 (86.6%)[6]	RR 0.99 (0.93 to 1.06)[7]	9 fewer per 1000 (from 61 fewer to 52 more)	⊕⊕OO LOW	CRITICAL
Symptom free or reduce at end of therapy (assessed with: 2nd vs. 1st generation cephalosporin)												
1[2]	randomised trials[8]	serious[9]	not applicable	serious[4]	no serious imprecision	none	31/35 (88.6%)[10]	9/10 (90%)[11]	RR 0.98 (0.78 to 1.25)	18 fewer per 1000 (from 198 fewer to 225 more)	⊕⊕OO LOW	CRITICAL
Symptom free or reduced at end of therapy (follow-up 7 to 16 days; assessed with: 3rd vs. 1st generation cephalosporin)												
3[2]	randomised trials	serious[12]	no serious inconsistency	serious[4]	no serious imprecision	none	114/132 (86.4%)[13]	120/142 (84.5%)[14]	RR 1.02 (0.93 to 1.13)[7]	17 more per 1000 (from 59	⊕⊕OO LOW	CRITICAL

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										fewer to 110 more)		
Symptom free or reduced at end of therapy (follow-up 10 days; assessed with: 3rd vs. 2nd generation cephalosporin)												
1[2]	randomised trials	no serious risk of bias	not applicable	serious[4]	no serious imprecision	none	54/66 (81.8%)[15]	69/79 (87.3%)[16]	RR 0.94 (0.81 to 1.08)	52 fewer per 1000 (from 166 fewer to 70 more)	⊕⊕⊕O MODERATE	CRITICAL
Symptom free or reduced at end of therapy (follow-up 3 to 18 days; assessed with: 4th vs. 3rd generation cephalosporin)												
1[2]	randomised trials	serious[9]	not applicable	serious[4]	no serious imprecision	none	49/51 (96.1%)[17]	22/23 (95.7%)[18]	RR 1.00 (0.91 to 1.11)	0 fewer per 1000 (from 86 fewer to 105 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous; IM, Intramuscular.												

[1] Days overall and post therapy.
[2] Kilburn et al 2010.
[3] Downgraded 1 level - 3 out of 6 RCTs assessed by the Cochrane reviewers were not at low risk of bias.
[4] Downgraded 1 level - it is unclear for a number of studies if the population is people with cellulitis alone or skin and soft tissue infection.
[5] Newer agents were cefonicid (2nd generation), cefditoren (3rd generation in 2 RCTs), ceftriaxone (3rd generation), cefdinir (3rd generation) and cefepime (4th generation).
[6] Older agents were cefazolin (1st generation in 2 RCTs), cefadroxil (1st generation), cefalexin (1st generation), cefuroxime (2nd generation) and ceftazidime (3rd generation).
[7] NICE analysis (I^2<50%) fixed effect model used.
[8] Follow-up period not reported.
[9] Downgraded 1 level - RCT assessed by the Cochrane review as at risk of bias.
[10] 2nd generation cephalosporin, IV or IM cefonicid.
[11] 1st generation cephalosporin, IV or IM cefazolin.
[12] Downgraded 1 level - only 2 out of 3 RCTs assessed by the Cochrane reviewers were at low risk of bias.
[13] 3rd generation cephalosporins: oral cefditoren, IV ceftriaxone and oral cefdinir.
[14] 1st generation cephalosporins: oral cefadroxil, IV cefazolin and oral cephalexin.
[15] 3rd generation cephalosporin: Oral cefditoren.
[16] 2nd generation cephalosporin: cefuroxime.
[17] 4th generation cephalosporin: IV cefepime.
[18] 3rd generation cephalosporin: IV ceftazidime.

Table 28: GRADE profile – Cephalosporin vs. glycopeptide and monobactam for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cephalosporin**	**Glycopeptide + monobactam**	**Relative (95% CI)**	**Absolute**		
Cure rate (follow-up 8 to 15 days[1]; assessed with: cephalosporin vs. glycopeptide + monobactam)												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	213/229 (93%)[4]	222/243 (91.4%)[5]	RR 1.02 (0.97 to 1.07)[6]	18 more per 1000 (from 27 fewer to 64 more)	⊕⊕⊕O MODERATE	CRITICAL

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Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; IV, Intravenous; SR, Systematic review.

[1] Post therapy.
[2] Frampton et al 2013.
[3] Downgraded 1 level - the systematic review was at risk of bias (see quality assessment tables for SRs).
[4] Cephalosporin antibiotic, IV ceftaroline fosamil.
[5] Glycopeptide and monobactam antibiotic, IV vancomycin plus aztreonam.
[6] NICE analysis.

Table 29: GRADE profile – Macrolide vs. cephalosporin for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Cephalosporin	Relative (95% CI)	Absolute		
Cure rate (follow-up 11 days; assessed with: macrolide vs. cephalosporin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	23/24 (95.8%)[3]	22/23 (95.7%)[4]	RR 1.00 (0.89 to 1.13)[5]	0 fewer per 1000 (from 105 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Macrolide antibiotic, oral azithromycin.
[4] Cephalosporin antibiotic, oral cephalexin.
[5] NICE analysis.

Table 30: GRADE profile – Oxazolidinone vs. glycopeptide for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxazolidinone	Glycopeptide	Relative (95% CI)	Absolute		
Cure rate (follow-up 7 days; assessed with: oxazolidinone vs. glycopeptide)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	205/224 (91.5%)[4]	184/201 (91.5%)[5]	RR 1.00 (0.94 to 1.06)[6]	0 fewer per 1000 (from 55 fewer to 55 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - it is unclear if the population is people with cellulitis alone or skin and soft tissue infection.
[4] Oxazolidinone antibiotic, IV or oral linezolid.

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[5] Glycopeptide antibiotic, IV vancomycin.
[6] NICE analysis.

Table 31: GRADE profile – Cyclic lipopeptide vs glycopeptide for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cyclic lipopeptide	Glycopeptide	Relative (95% CI)	Absolute		
Cure or improvement (follow-up 7 to 14 days; assessed with: IV daptomycin vs. IV vancomycin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	47/50 (94%)	46/51 (90.2%)	RR 1.04 (0.93 to 1.17)[3]	36 more per 1000 (from 63 fewer to 153 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure or improvement (follow-up 6 to 20 days; assessed with: IV daptomycin vs. IV vancomycin)												
2[1]	randomised trials	very serious[4]	serious[5]	serious[6]	serious[7]	none	22/28 (78.6%)	16/22 (72.7%)	RR 1.08 (0.78 to 1.49)[3, 8]	58 more per 1000 (from 160 fewer to 356 more)	⊕OOO VERY LOW	CRITICAL
Secondary outcomes (follow-up 7 to 14 days; assessed with: IV daptomycin vs. IV vancomycin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	0/50 (0%)	0/51 (0%)	No significant differences reported for time to stabilisation of infection (p=0.875); time to abatement of fever (p=0.690); cessation of advancement of erythema (p=0.833); time to readiness for discharge (p=0.993); median time to 50% improvement (0.755); patient reported pain (p=0.632) or time to reduction in tightness or swelling score (p=0.307). Insufficient data presented for recalculation.		⊕⊕⊕O MODERATE	IMPORTANT
Microbiological eradication (follow-up not reported; assessed with: IV daptomycin vs. IV vancomycin)												
2[1]	randomised trials	very serious[4]	serious[5]	serious[6]	serious[7]	none	16/22 (72.7%)	7/14 (50%)	RR 1.45 (0.81 to 2.61)[3, 8]	225 more per 1000 (from 95 fewer to 805 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; p, P value; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Pertel et al 2009
[2] Downgraded 1 level - the RCT (Pertel et al 2009) was assessed as at risk of bias (see Appendix G: quality assessment of included studies).
[3] NICE analysis.
[4] Downgraded 2 levels - data from 2, phase 3, RCTs pooled for a cellulitis population, no quality assessment was undertaken or methods for study identification.
[5] Downgraded 1 level - pooled data from 2, phase 3, RCTs not data on pooling presented.
[6] Downgraded 1 level - cellulitis was a subgroup of larger cohort of complicated skin and soft tissue infection.
[7] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with IV daptomycin.
[8] Comparator was penicillin or vancomycin in the pooled data from the 2, phase 3, RCTs.

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Table 32: GRADE profile – Macrolide vs. macrolide for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Macrolide	Relative (95% CI)	Absolute		
Cure rate (follow-up 48 hours post treatment; assessed with: macrolide vs. macrolide)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	no serious imprecision	none	51/72 (70.8%)[4]	37/50 (74%)[5]	RR 0.96 (0.77 to 1.19)[6]	30 fewer per 1000 (from 170 fewer to 141 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - it is unclear if the population is people with cellulitis alone or skin and soft tissue infection.
[4] Oral azithromycin.
[5] Oral erythromycin.
[6] NICE analysis.

Table 33: GRADE profile – Carbapenem vs. carbapenem for cellulitis in young people and adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbapenem	Carbapenem	Relative (95% CI)	Absolute		
Cure rate (follow-up 7 to 14 days; assessed with: carbapenem vs. carbapenem)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[2]	serious[3]	none	27/39 (69.2%)[4]	33/42 (78.6%)[5]	RR 0.88 (0.68 to 1.15)[6]	94 fewer per 1000 (from 251 fewer to 118 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; IV, Intravenous.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - it is unclear if the population is people with cellulitis alone or skin and soft tissue infection.
[3] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with imipenem-silastatin.
[4] Carbapenem antibiotic, IV meropenem.
[5] Carbapenem antibiotic, IV Imipenem-silastatin.
[6] NICE analysis.

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Table 34: GRADE profile – Oxazolidinone vs glycopeptide for cellulitis in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oxazolidinone	Glycopeptide	Relative (95% CI)	Absolute		
Clinical cure rate for cellulitis (follow-up not reported[1]; assessed with: oxazolidinone vs. glycopeptide)												
1[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	19/20 (95%)[5]	15/16 (93.8%)[6]	RR 1.01 (0.86 to 1.19)[7]	9 more per 1000 (from 131 fewer to 178 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Follow-up was at 3, 10, 17 and 24 days; test of cure visit was at 7 to 35 days, however the data in the authors paper for clinical cure by diagnosis is unlabelled.
[2] Yogev et al 2003.
[3] Downgraded 1 level - the RCT was assessed as at risk of bias (see quality assessment tables).
[4] Downgraded 1 level - cellulitis was a subgroup of a larger cohort of skin and soft tissue infection.
[5] IV linezolid (oral switch possible after 3 days).
[6] IV vancomycin (oral switch possible after 3 days, oral antibiotic not defined).
[7] NICE analysis.

H.3 Dual antibiotic therapy in children and adults with cellulitis or erysipelas

Table 35: GRADE profile – Dual therapy with penicillin and penicillin vs. penicillin and placebo for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-treatment with penicillin	Penicillin + Placebo	Relative (95% CI)	Absolute		
Treatment failure (follow-up 1 to 2 days; assessed with: penicillin vs. placebo)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	3/41 (7.3%)[5]	2/40 (5%)[6]	RR 1.46 (0.26 to 8.30)[7]	23 more per 1000 (from 37 fewer to 365 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; IV, Intravenous.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - it is unclear if the population is people with cellulitis alone or skin and soft tissue infection.
[4] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with benzyl

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penicillin co-treatment, and no meaningful difference or appreciable benefit with placebo.
[5] IV flucloxacillin + IV benzyl penicillin, continue orally after discharge home.
[6] IV flucloxacillin + IV placebo, continue orally after discharge home.
[7] NICE analysis.

Table 36: GRADE profile – Dual therapy with penicillin and lincosamide vs. penicillin and placebo for people with cellulitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-treatment with clindamycin	Placebo	Relative (95% CI)	Absolute		
Improvement at day 5 in the evaluable population (follow-up 5 days; assessed with: co-treatment with penicillin and lincosamide vs. penicillin plus placebo)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	136/156 (87.2%)[2]	140/172 (81.4%)[3]	RR 1.07 (0.98 to 1.18)[4]	57 more per 1000 (from 16 fewer to 147 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Improvement at day 5 in the randomised population (follow-up 5 days; assessed with: co-treatment with penicillin and lincosamide vs. penicillin plus placebo)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	136/203 (67%)[2]	140/207 (67.6%)[3]	RR 0.99 (0.87 to 1.13)[4]	7 fewer per 1000 (from 88 fewer to 88 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Compliance with study medication (follow-up period not reported; assessed with: co-treatment with penicillin and lincosamide vs. penicillin plus placebo)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	148/159 (93.1%)[2]	159/176 (90.3%)[3]	RR 1.03 (0.97 to 1.10)[4]	27 more per 1000 (from 27 fewer to 90 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Secondary outcomes (follow-up 5 and 10 days; assessed with: co-treatment with penicillin and lincosamide vs. penicillin plus placebo)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	Unclear	Yes[5]	Evaluable: 160 at day 5 135 at day 10	Evaluable: 176 at day 5 151 at day 10	Secondary outcomes at days 5 and 10: No significant differences for body or limb temperature, pulse, affected skin area, limb circumference, laboratory values (neutrophils, urea, albumin or c-reactive protein) or pain score. The authors noted a slightly lower mean blood pressure (systolic, 3 mm Hg) in the clindamycin cohort at day 10 (p=0.02) and lower median lymphocyte counts in the clindamycin allocation at both days 5 and 10 (0.18 and 0.19×10^9/L, respectively, p=0.01).		⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; p, P value.												

[1] Brindle et al 2017.
[2] Antibiotics were flucloxacillin + clindamycin.
[3] Antibiotics were flucloxacillin plus placebo.
[4] NICE analysis.
[5] Data for secondary outcomes was mean or median with p value (no standard deviation or IQR) unable to recalculate.

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Table 37: GRADE profile – Dual therapy with cephalosporin and trimethoprim-sulfamethoxazole vs. cephalosporin plus placebo for cellulitis in children (aged ≥12 years) and adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin and trimethoprim-sulfamethoxazole	Cephalosporin plus placebo	Relative (95% CI)	Absolute		
Clinical cure (follow-up 12 to 21 days[1]; assessed with: oral cephalosporin plus trimethoprim-sulfamethoxazole vs. oral cephalosporin alone)												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	251/321 (78.2%)[4]	231/321 (72%)[5]	RR 1.09 (0.99 to 1.19)[6]	65 more per 1000 (from 7 fewer to 137 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (follow-up 14 to 21 days; assessed with: oral cephalosporin plus trimethoprim-sulfamethoxazole vs. oral cephalosporin alone[7])												
1[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182/218 (83.5%)[4]	165/193 (85.5%)[5]	RR 0.98 (0.9 to 1.06)[8]	17 fewer per 1000 (from 85 fewer to 51 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial; ITT, Intention-to-treat; mITT, modified intention-to-treat.												

[1] Follow-up varied by study.
[2] Bowen et al 2017.
[3] Downgraded 1 level - the systematic review (Bowen et al 2017) is at risk of bias (see Appendix G: quality assessment of included studies).
[4] Oral cephalexin with oral trimethoprim-sulfamethoxazole.
[5] Oral cephalexin plus placebo.
[6] NICE meta-analysis of an ITT population (Pallin et al 2013) and a modified ITT population (mITT-1; Moran et al 2017).
[7] Per protocol population. Although not reported by the Bowen et al 2017 systematic review, 1 other RCT (Pallin et al 2013) also had a per protocol analysis for clinical cure outcome (n=142, risk difference of 4.2% (95% CI, −7.4% to 16%; P = .45), no data reported so no re-analysis possible.
[8] NICE analysis.

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Table 38: GRADE profile – Dual therapy with cephalosporin and glycopeptide vs. cephalosporin plus placebo for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin plus glycopeptide	Cephalosporin plus placebo	Relative (95% CI)	Absolute		
Clinical cure rate (follow-up 6 to 17 days; assessed with: co-treatment with glycopeptide plus cephalosporin vs. cephalosporin plus placebo)												
1[1]	randomised trials	no serious risk of bias	not applicable	serious[2]	no serious imprecision	none	32/36 (88.9%)[3]	80/86 (93%)[4]	RR 1.05 (0.92 to 1.19)[5,6]	44 more per 1000 (from 71 fewer to 169 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; IV, Intravenous.												

[1] Noel et al 2008.
[2] Downgraded 1 level - the cellulitis cohort was a subgroup of a larger cohort of skin infection, people with cellulitis were limited to <20% of the cohort overall.
[3] IV vancomycin and IV ceftzidime
[4] IV ceftibiprole plus placebo
[5] NICE analysis.
[6] Microbiological eradication rate was 90.3% vs. 88.0% for cellulitis, no data reported so no re-nalysis possible.

H.4 Antibiotic dose in people with cellulitis or erysipelas

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

H.5 Antibiotic dose frequency in adults with cellulitis or erysipelas

Table 39: GRADE profile – Cephalosporin (4X daily) vs. cephalosporin (2X daily) for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin 4X daily	Cephalosporin 2X daily	Relative (95% CI)	Absolute		
Cure (number resolved) (follow-up end of therapy (not defined); assessed with: cephalosporin 4X daily vs. 2X daily (same daily dose)[1])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	no serious imprecision	none	7/7 (100%)	12/12 (100%)	RR 1.00 (0.81 to 1.23)	0 fewer per 1000 (from 190 fewer to 230 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; RCT, Randomised controlled trial.												

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[1] Cephalosporin was oral cefalexin in the same daily dose.
[2] Kilburn et al 2010.
[3] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[4] Downgraded 1 level - it is unclear if the population is people with cellulitis alone or skin and soft tissue infection.

H.6 Antibiotic course length in adults with cellulitis or erysipelas

Table 40: GRADE profile – Six days vs. 10 days of oxazolidinone for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6 days of oxazolidinone	10 days of oxazolidinone	Relative (95% CI)	Absolute		
Clinical response at 48 to 72 hours (follow-up 48 to 72 hours; assessed with: 6 vs. 10 days of oral oxazolidinone in ITT population[1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	no serious imprecision	none	235/301 (78.1%)[5]	235/307 (76.5%)[6]	RR 1.02 (0.94 to 1.11)[7]	15 more per 1000 (from 46 fewer to 84 more)	⊕⊕OO LOW	CRITICAL
Sustained clinical response at end of therapy (follow-up 11 days; assessed with: 6 vs. 10 days of oral oxazolidinone in ITT population[1])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	no serious imprecision	none	85/133 (63.9%)[5]	84/135 (62.2%)[6]	RR 1.03 (0.86 to 1.23)[7]	19 more per 1000 (from 87 fewer to 143 more)	⊕⊕OO LOW	CRITICAL
Clinically evaluable at end of therapy (follow-up 11 days; assessed with: 6 vs. 10 days of oral oxazolidinone in per protocol population[1])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	no serious imprecision	none	77/112 (68.8%)[5]	80/117 (68.4%)[6]	RR 1.01 (0.84 to 1.20)[7]	7 more per 1000 (from 109 fewer to 137 more)	⊕⊕OO LOW	CRITICAL
Investigators assessment at post-therapy evaluation (follow-up 7 to 14 days; assessed with: 6 vs. 10 days oral oxazolidinone in ITT population[1])												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	no serious imprecision	none	119/135 (88.1%)[5]	114/139 (82%)[6]	RR 1.07 (0.97 to 1.19)[7]	57 more per 1000 (from 25 fewer to 156 more)	⊕⊕OO LOW	CRITICAL
Investigators assessment at the post-therapy evaluation (follow-up 7 to 14 days; assessed with: 6 vs. 10 days of oral oxazolidinone in per protocol population)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	no serious imprecision	none	109/117 (93.2%)[5]	100/113 (88.5%)[6]	RR 1.05 (0.97 to 1.14)[7]	44 more per 1000 (from 27 fewer to 124 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk; ITT, Intention-to-treat.												

[1] Objective clinical criteria (afebrile, cessation of lesion spread, no further antibiotics required, no mortality)
[2] Hanretty et al 2018 (additional data from Moran et al 2014 and Prokocimer et al 2013).
[3] Downgraded 1 level - the systematic review (Hanretty et al 2018) was at risk of bias (see quality assessment tables).
[4] Downgraded 1 level - the cellulitis cohort was a subgroup of 2 larger cohorts of skin infection.

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[5] 6 days of oral tedizolid.
[6] 10 days of oral linezolid.
[7] NICE analysis.

Table 41: GRADE profile – Five days vs. 10 days of quinolone for uncomplicated cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone for 5 days	Quinolone for 10 days	Relative (95% CI)	Absolute		
Symptom free or reduced at end of treatment (follow-up 14 days; assessed with: 5 days vs. 10 days of treatment with 3rd generation quinolone)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	43/44 (97.7%)[2]	42/43 (97.7%)[2]	RR 1.00 (0.94 to 1.07)	0 fewer per 1000 (from 59 fewer to 68 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RR, Relative risk.												

[1] Kilburn et al 2010, also reported in Hanretty et al 2018.
[2] 3rd generation quinolone, oral levofloxacin.

H.7 Antibiotic prophylaxis for the prevention of recurrent cellulitis or erysipelas in adults

Table 42: GRADE profile – Antibiotics vs no treatment or placebo for cellulitis in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	No treatment or placebo	Relative (95% CI)	Absolute		
Recurrence of cellulitis (on prophylaxis) (assessed with: antibiotic prophylaxis vs. no treatment (3 RCTs) or placebo (2 RCTs))												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	34/250 (13.6%)[3]	83/263 (31.6%)[4]	RR 0.43 (0.30 to 0.61)[5]	180 fewer per 1000 (from 123 fewer to 221 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence rate of cellulitis recurrence (on prophylaxis) (assessed with: antibiotic recurrence vs. no treatment (2 RCTs) or placebo (2 RCTs) data is episodes per person-month)												
4[1]	randomised trials	serious[6]	serious[7]	no serious indirectness	serious[8]	Serious [28]	88/2176 (4%)[9]	168/2199 (7.6%)[10]	RR 0.44 (0.22 to 0.89)[11]	43 fewer per 1000 (from 8 fewer to 60 fewer)	⊕OOO VERY LOW	CRITICAL
Time to next episode of cellulitis (on prophylaxis) (assessed with: pooled hazard ratio; 2 RCTs reported and 1 RCT had data from a survival curve)												

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3[1]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	n=437[13, 27]	n=437[18, 27]	HR 0.51 (0.34 to 0.78)[14]	Not estimable	⊕⊕⊕O MODERATE	CRITICAL
Hospitalisation (on prophylaxis) (assessed with: antibiotic prophylaxis vs. no treatment (1 RCT) or placebo (2 RCTs))												
3[1]	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	very serious[16]	none	12/212 (5.7%)[17]	16/217 (7.4%)[18]	RR 0.77 (0.38 to 1.6)[5]	17 fewer per 1000 (from 46 fewer to 44 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (on prophylaxis) (assessed with: antibiotic prophylaxis (all antibiotics) vs. no treatment or placebo)												
4[1]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[19]	none	58/232 (25%)[20]	68/237 (28.7%)[21]	RR 0.88 (0.65 to 1.17)[5]	34 fewer per 1000 (from 100 fewer to 49 more)	⊕⊕OO LOW	CRITICAL
Adverse events (on prophylaxis) (assessed with: antibiotic prophylaxis (penicillin) vs. no treatment or placebo.)												
3[1]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[19]	none	55/216 (25.5%)	68/221 (30.8%)	RR 0.83 (0.62 to 1.12)[5]	52 fewer per 1000 (from 117 fewer to 37 more)	⊕⊕OO LOW	CRITICAL
Adverse events (on prophylaxis) (assessed with: antibiotic prophylaxis (erythromycin) vs. no treatment)												
1[1]	randomised trials	serious[22]	no serious inconsistency	no serious indirectness	very serious[23]	none	3/16 (18.8%)	0/16 (0%)	RR 7.00 (0.39 to 125.44)	Not estimable	⊕OOO VERY LOW	CRITICAL
Mortality (on prophylaxis) (assessed with: antibiotic prophylaxis vs. no treatment (1 RCT) or placebo (2 RCTs))												
3[1]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	very serious[24]	none	11/216 (5.1%)[13]	9/221 (4.1%)[18]	RR 1.24 (0.53 to 2.88)[5]	10 more per 1000 (from 19 fewer to 77 more)	⊕OOO VERY LOW	CRITICAL
Recurrence of cellulitis (post-prophylaxis) (assessed with: antibiotic prophylaxis (penicillin V) vs. placebo)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[25]	none	36/153 (23.5%)	36/134 (26.9%)	RR 0.87 (0.58 to 1.30)[5]	35 fewer per 1000 (from 113 fewer to 81 more)	⊕⊕OO LOW	CRITICAL
Incidence rate of cellulitis recurrence (post-prophylaxis) (assessed with: antibiotic prophylaxis (penicillin V) vs. placebo) data is episodes per person-month.												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[25]	Serious [28]	53/2297 (2.3%)	56/2269 (2.5%)	RR 0.94 (0.65 to 1.36)[5]	1 fewer per 1000 (from 9 fewer to 9 more)	⊕⊕OO VERY LOW	CRITICAL
Time to next episode of cellulitis (post-prophylaxis) (assessed with: antibiotic prophylaxis (penicillin V) vs. placebo; pooled hazard ratio)												
2[1]	randomised trials	no serious risk of bias	serious[11]	no serious indirectness	no serious imprecision	none	n=397[27]	n=397[27]	HR 0.78 (0.39 to 1.56)[14]	Not estimable	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of cellulitis (overall) (assessed with: antibiotic prophylaxis (penicillin V) vs. placebo)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[26]	none	68/196 (34.7%)	94/201 (46.8%)	RR 0.74 (0.58 to 0.94)[5]	122 fewer per 1000 (from 28 fewer to 196 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence rate of cellulitis recurrence (overall) (assessed with: antibiotic prophylaxis (penicillin V) vs. placebo) data is episodes per person-month.												

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2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[26]	none	141/3976 (3.5%)	199/3878 (5.1%)	RR 0.69 (0.56 to 0.85)[5]	16 fewer per 1000 (from 8 fewer to 23 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; RCT, Randomised controlled trial; RR, Relative risk; HR, Hazard ratio; IM, Intramuscular.												

[1] Dalal et al 2017.
[2] Downgraded 1 level - only 2 of 5 RCTs were assessed by the Cochrane reviewers as at low risk of bias.
[3] Antibiotics were (IM benzathine penicillin every 15 days, oral erythromycin, oral phenoxymethyl penicillin or penicillin V).
[4] Comparator was no treatment (3 open label RCTs) or placebo (2 double-blind RCTs).
[5] NICE analysis using fixed effects model (I^2<50%).
[6] Downgraded 1 level - only 2 of 4 RCTs were assessed by the Cochrane reviewers as at low risk of bias.
[7] Downgraded 1 level - I^2>50%.
[8] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis.
[9] Antibiotics were (IM benzathine penicillin every 15 days, oral erythromycin or penicillin V).
[10] Comparator was no treatment (2 open label RCTs) or placebo (2 double-blind RCTs).
[11] Random effects model (I2>50%).
[12] Downgraded 1 level - only 2 of 3 RCTs were assessed by the Cochrane reviewers as at low risk of bias.
[13] Antibiotics were oral phenoxymethyl penicillin or penicillin V.
[14] Estimate not re-calculable due to paucity of data.
[15] Downgraded 1 level - only 2 of 3 RCTs were assessed by the Cochrane reviewers as at low risk of bias.
[16] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis, and no meaningful difference or appreciable harm with no treatment or placebo.
[17] Antibiotics were (oral erythromycin or penicillin V).
[18] Comparator was no treatment (1 open label RCT) or placebo (2 double-blind RCTs).
[19] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotic prophylaxis.
[20] Antibiotics were (oral erythromycin, oral phenoxymethyl penicillin or penicillin V).
[21] Comparator was no treatment (2 open label RCTs) or placebo (2 double-blind RCTs).
[22] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[23] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with erythromycin, and no meaningful difference or appreciable benefit with no treatment.
[24] Downgraded 2 levels - at a minimal important difference of 0% relative risk increase (RRI), the effect estimate is consistent with appreciable benefit or harm; very wide 95% confidence intervals for absolute figures.
[25] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with penicillin V, and no meaningful difference or appreciable harm with placebo.
[26] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with penicillin V.
[27] combined n for intervention and comparator groups, not reported separately in Dalal et al. 2017
[28] Downgraded 1 level: The metric RR is inconsistent with the study methods section with respect to how the data were analysed (the method section stated incidence rate ratios (IRR). It is unclear what methods have been used, therefore leading to undertainty in the evidence.

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H.8 Adverse events with antibiotic treatment in people with cellulitis

Table 43: GRADE profile – Antibiotics vs. other antibiotics for adverse events of treatment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Other antibiotics	Relative (95% CI)	Absolute		
Any adverse event (assessed with: Oral roxithromycin vs. IV penicillin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	0/31 (0%)	2/38 (5.3%)	RR 0.24 (0.01 to 4.9)[4]	40 fewer per 1000 (from 52 fewer to 205 more)	⊕OOO VERY LOW	CRITICAL
Any adverse event (assessed with: Oral pristinamycin vs. IV penicillin[5])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[6]	none	39/138 (28.3%)	26/150 (17.3%)	RR 1.63 (1.05 to 2.53)[4]	109 more per 1000 (from 9 more to 265 more)	⊕⊕OO LOW	CRITICAL
Any adverse event (assessed with: Oral cefazolin vs. IV ceftriaxone[7])												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[8]	none	14/67 (20.9%)	7/67 (10.4%)	RR 2.00 (0.86 to 4.64)[4]	104 more per 1000 (from 15 fewer to 380 more)	⊕⊕⊕O MODERATE	CRITICAL
Any adverse event (assessed with: IV ceftriaxone vs. IV flucloxacillin[9])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[10]	none	3/24 (12.5%)	6/23 (26.1%)	RR 0.48 (0.14 to 1.69)[4]	136 fewer per 1000 (from 224 fewer to 180 more)	⊕OOO VERY LOW	CRITICAL
Any adverse event (assessed with: IV penicillin vs. IM penicillin[11])												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[12]	none	14/55 (25.5%)	0/57 (0%)	RR 30.04 (1.84 to 491.55)[4]	not estimable	⊕⊕OO LOW	CRITICAL
Any adverse event (assessed with: 5 days vs. 10 days of oral levofloxacin[9])												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[13]	none	1/44 (2.3%)	0/43 (0%)	RR 2.93 (0.12 to 70.08)[4]	not estimable	⊕⊕OO LOW	CRITICAL
Any adverse event (follow-up 30 days; assessed with: oral cefalexin plus trimethoprim-sulfamethoxazole vs. oral cefalexin plus placebo[14])												
1[15]	randomised trials	serious[16]	not applicable	no serious indirectness	no serious imprecision	none	62/73 (84.9%)	60/73 (82.2%)	RR 1.03 (0.89 to 1.19)[4,17]	25 more per 1000 (from 90 fewer to 156 more)	⊕⊕⊕O MODERATE	CRITICAL
Any adverse event (follow-up 5 days; assessed with: co-treatment with oral flucloxacillin plus clindamycin vs. oral flucloxacillin plus placebo)												

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1[22]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[23]	none	46/160 (28.8%)	27/176 (15.3%)	RR 1.87 (1.23 to 2.86)[4]	133 more per 1000 (from 35 more to 285 more)	⊕⊕⊕O MODERATE	CRITICAL
Any adverse event (follow-up 10 days; assessed with: co-treatment with oral flucloxacillin plus clindamycin vs. oral flucloxacillin plus placebo)												
1[22]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[24]	none	19/135 (14.1%)	19/151 (12.6%)	RR 1.12 (0.62 to 2.02)[4]	15 more per 1000 (from 48 fewer to 128 more)	⊕⊕OO LOW	CRITICAL
Any adverse event (assessed with: IV daptomycin vs. IV vancomycin)												
1[25]	randomised trials	serious[26]	not applicable	no serious indirectness	very serious[27]	none	8/50 (16%)	8/51 (15.7%)	RR 1.02 (0.42 to 2.51)[4]	3 more per 1000 (from 91 fewer to 237 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; IV, Intravenous; RR, Relative risk; IM, Intramuscular; RCT, Randomised controlled trial; N/A, Not applicable.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oral roxithromycin, and no meaningful difference or appreciable harm with IV penicillin.
[4] NICE analysis (n/N data provided).
[5] Mainly mild or moderate gastrointestinal adverse events.
[6] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with oral pristinamycin.
[7] Adverse events reported were mainly nausea and vomiting.
[8] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with cefazolin.
[9] Type of adverse event not reported.
[10] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone, and no meaningful difference or appreciable harm with flucloxacillin.
[11] Adverse events were mostly venitis (phlebitis) at the site of insertion of the needle.
[12] Downgraded 1 level - very wide confidence intervals.
[13] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with 5 days of levofloxacin, and no meaningful difference or appreciable benefit with 10 days of levofloxacin.
[14] Mostly nausea and diarrhoea.
[15] Bowen et al 2017.
[16] Downgraded 1 level - the systematic review (Bowen et al 2017) was at risk of bias (see Appendix G: quality of included studies).
[17] An RCT (Moran et al 2017) had the same comparator and intervention but reported treatment related (mostly mild gastrointestinal) adverse events (n=496, 41% vs. 36.2%, RR 1.13, 95% CI 0.91 to 1.42; NICE analysis n/N data).
[18] All participants in this study had incision and drainage of abscess, as well as cellulitis.
[19] Downgraded 1 level - all participants had abscess and cellulitis, rather than cellulitis alone.
[20] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with clindamycin.
[21] Downgraded 2 levels - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with trimethoprim-sulfamethoxazole, and no meaningful difference or appreciable harm with placebo.
[22] Brindle et al 2017.
[23] Downgraded 1 level - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with oral flucloxacillin plus clindamycin.
[24] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with

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flucloxacillin and clindamycin, and no meaningful difference or appreciable benefit with flucloxacillin and placebo.
[25] Pertel et al 2009
[26] Downgraded 1 level – the RCT (Pertel et al 2009) was at risk of bias (see Appendix G: quality of included studies).
[27] Downgraded 2 levels - at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with daptomycin, and no meaningful difference or appreciable benefit with vancomycin..

Table 44: GRADE profile – Antibiotics vs. other antibiotics for adverse events leading to study withdrawal.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Other antibiotics	Relative (95% CI)	Absolute		
Adverse event leading to study withdrawal (assessed with: Oral roxithromycin vs. IV penicillin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	0/31 (0%)	0/38 (0%)	Not estimable	-	⊕⊕OO LOW	CRITICAL
Adverse event leading to study withdrawal (assessed with: Oral pristinamycin vs. IV penicillin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	15/138 (10.9%)	25/150 (16.7%)	RR 0.65 (0.36 to 1.18)[5]	58 fewer per 1000 (from 107 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Adverse event leading to study withdrawal (assessed with: IV cefotaxime vs. IV flucloxacillin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	0/24 (0%)	0/23 (0%)	Not estimable	-	⊕⊕OO LOW	CRITICAL
Adverse event leading to study withdrawal (assessed with: IV penicillin vs. IM penicillin)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	0/55 (0%)	0/57 (0%)	Not estimable	-	⊕⊕OO LOW	CRITICAL
Abbreviations: 95% CI, 95% Confidence interval; IV, Intravenous; RR, Relative risk; IM, Intramuscular; RCT, Randomised controlled trial.												

[1] Kilburn et al 2010.
[2] Downgraded 1 level - the RCT was assessed by the Cochrane reviewers as at risk of bias.
[3] Downgraded 1 level - not estimable
[4] Downgraded 1 level - at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with pristinamycin.
[5] NICE analysis (n/N data provided).

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Appendix I: Studies not-prioritised

Mason James M, Thomas Kim S, Crook Angela M, Foster Katharine A, Chalmers Joanne R, Nunn Andrew J, and Williams Hywel C (2014) Prophylactic antibiotics to prevent cellulitis of the leg: economic analysis of the PATCH I & II trials. PloS one 9(2), e82694

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Appendix J: Excluded studies

Study reference	Reason for exclusion
Abbate LM (2013) Penicillin to prevent recurrent leg cellulitis: Thomas KS, Crook AM, Nunn AJ, et al. N Engl J Med 2013;368:1695-703. *Journal of Emergency Medicine* 45(2), 309-310	Incorrect study type*:* Conference abstract
Agarwal R, Bartsch SM, Kelly BJ et al (2018) Newer glycopeptide antibiotics for treatment of complicated skin and soft tissue infections: systematic review, network meta-analysis and cost analysis. *Clinical Microbiology and Infection* 24(4), 361-368	Incorrect population: Cellulitis data not reported separately
Aikawa N, Kusachi S, Mikamo H et al (2013) Efficacy and safety of intravenous daptomycin in Japanese patients with skin and soft tissue infections. *Journal of infection and chemotherapy: official journal of the Japan Society of Chemotherapy* 19(3), 447-55	Incorrect population: Cellulitis data not reported separately
Alimov V, Lovecchio F, Sinha M et al (2013) Use of a silver-containing hydrofiber dressing for filling abscess cavity following incision and drainage in the emergency department: a randomized controlled trial. *Advances in skin & wound care* 26(1), 20-25	Incorrect population: Abscess treatment predominantly, cellulitis data not reported separately
Allan K, Atkinson H, Agada F (2013) Posterior orbital cellulitis: Case report and literature review. *Journal of Laryngology and Otology* 127(11), 1148-1151	Incorrect study type: Not an SR or RCT
Amin AN, Cerceo EA, Deitelzweig SB et al (2014) Hospitalist perspective on the treatment of skin and soft tissue infections. *Mayo Clinic proceedings* 89(10), 1436-51	Incorrect study type: Narrative review
Anastasioua J, Williams R (2013) When to use antibiotics in the cirrhotic patient? The evidence base. *Annals of Gastroenterology* 26(2), 128-131	Incorrect study type: Narrative review
Anonymous (2003) Erysipelas: Treat the bacterial infection with penicillin and prevent recurrence by treating local factors. *Drugs and Therapy Perspectives* 19(12), 10-12	Incorrect study type: Not an SR or RCT
Anonymous (2016) Clindamycin versus trimethoprim-sulfamethoxazole for skin infections. *Journal of Paediatrics and Child Health* 52(1), 97	Incorrect study type: Not an SR or RCT
Ansari MA, Shukla VK (2005) Foot infections. *International Journal of Lower Extremity Wounds* 4(2), 74-87	Incorrect study type: Not an SR or RCT
Attwood RJ, LaPlante KL (2007) Telavancin: A novel lipoglycopeptide antimicrobial agent. *American Journal of Health-System Pharmacy* 64(22), 2335-2348	Incorrect study type: Narrative review
Auwaerter PG (2006) Cellulitis, skin abscesses, and community-acquired methicillin-resistant Staphylococcus aureus. *Advanced Studies in Medicine* 6(2), 62-70	Incorrect study type: Not an SR or RCT
Avdic E, Cosgrove SE (2008) Management and control strategies for community-associated methicillin-resistant Staphylococcus aureus. *Expert Opinion on Pharmacotherapy* 9(9), 1463-1479	Incorrect population: Cellulitis data not reported separately
Backus D (2015) Antimicrobial Therapy in Long-Term Care: Controversy, Colonization, and Criteria. *The Consultant pharmacist: the journal of the American Society of Consultant Pharmacists* 30(9), 513-22	Incorrect study type: Narrative review
Baculik T, Eckburg PB, Friedland HD et al (2011) CANVAS 1 and 2: analysis of clinical response at Day 3 from 2 phase III trials of ceftaroline fosamil vs vancomycin plus aztreonam in the treatment	Incorrect study type: Conference abstract

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Study reference	Reason for exclusion
of complicated skin and skin structure infections. *Pharmacotherapy* 31(10), 351e	
Bally M, Dendukuri N, Sinclair A et al (2012) A network meta-analysis of antibiotics for treatment of hospitalised patients with suspected or proven meticillin-resistant Staphylococcus aureus infection. *International journal of antimicrobial agents* 40(6), 479-95	Incorrect population: No included studies with a cellulitis population
Bassetti M, Eckmann C, Peghin M et al (2018) When to switch to an oral treatment and/or to discharge a patient with skin and soft tissue infections. *Current Opinion in Infectious Diseases* 31(2), 163-169	Incorrect study type: Not an SR or RCT
Bassetti M, Melica G, Di Biagio, A et al (2004) New antibiotics for treatment of serious infections due to antibiotic-resistant Gram-positive cocci. *Reviews in Medical Microbiology* 15(3), 109-117	Incorrect study type: Not an SR or RCT
Bedwell J, Bauman NM (2011) Management of pediatric orbital cellulitis and abscess. *Current opinion in otolaryngology & head and neck surgery* 19(6), 467-73	Incorrect study type: Not an SR or RCT
Beibei L, Yun C, Mengli C et al (2010) Linezolid versus vancomycin for the treatment of gram-positive bacterial infections: meta-analysis of randomised controlled trials. *International journal of antimicrobial agents* 35(1), 3-12	Incorrect population: Not a cellulitis population
Bennett JW, Lewis IJ. S, Ellis MW (2008) Dalbavancin in the treatment of complicated skin and soft-tissue infections: A review. *Therapeutics and Clinical Risk Management* 4(1), 31-40	Incorrect study type: Not an SR or RCT
Bernard P (2008) Management of common bacterial infections of the skin. *Current opinion in infectious diseases* 21(2), 122-8	Incorrect study type: Not an SR or RCT
Bernard P, Chosidow O, Vaillant L (2002) Oral pristinamycin vs standard penicillin regimen for treatment of erysipelas in adults. *Annales de dermatologie et de venereologie* 129, P0856	RCT included in a prioritised systematic review
Bernard P, Chosidow O, Vaillant L et al (2002) Oral pristinamycin versus standard penicillin regimen to treat erysipelas in adults: randomised, non-inferiority, open trial. *BMJ* (Clinical research ed.) 325(7369), 864	RCT included in a prioritised systematic review
Bertino Jr, Bertino JS (2009) Impact of antibiotic resistance in the management of ocular infections: The role of current and future antibiotics. *Clinical Ophthalmology* 3(1), 507-521	Incorrect study type: Narrative review
Biek Dd, Critchley IA, Riccobene TA et al (2010) Ceftaroline fosamil: a novel broad-spectrum cephalosporin with expanded anti-Gram-positive activity. *The Journal of antimicrobial chemotherapy* 65 Suppl 4, iv9-16	Incorrect study type: Narrative review
Bin A, Aref A, Zimmerman V et al (2009) Stenotrophomonas maltophilia infections of intact skin: a systematic review of the literature. *Diagnostic microbiology and infectious disease* 63(3), 330-3	Incorrect study type: Review of infection-causing agents
Bliziotis IA, Plessa E, Peppas G et al (2010) Daptomycin versus other antimicrobial agents for the treatment of skin and soft tissue infections: a meta-analysis. *The Annals of pharmacotherapy* 44(1), 97-106	Lower quality systematic review.
Bounthavong M, Hsu D I (2010) Efficacy and safety of linezolid in methicillin-resistant Staphylococcus aureus (MRSA) complicated skin and soft tissue infection (cSSTI): a meta-analysis. *Current medical research and opinion* 26(2), 407-21	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
Brade KD, Rybak JM, Rybak MJ (2016) Oritavancin: A New Lipoglycopeptide Antibiotic in the Treatment of Gram-Positive Infections. *Infectious Diseases and Therapy* 5(1),	Incorrect study type: Narrative review
Breilh D, Texier-Maugein J, Allaouchiche B et L (2013) Carbapenems. *Journal of Chemotherapy* 25(1), 1-17	Incorrect population: Cellulitis data not reported separately
Brindle R J, Ijaz A, Davies P (2018) Procalcitonin and cellulitis: correlation of procalcitonin blood levels with measurements of severity and outcome in patients with limb cellulitis. *Biomarkers*: biochemical indicators of exposure, response, and susceptibility to chemicals, 1-4	Incorrect intervention: Not antimicrobials
Britt JC, Josephson GD, Gross CW (2000) Ludwig's angina in the pediatric population: Report of a case and review of the literature. *International Journal of Pediatric Otorhinolaryngology* 52(1), 79-87	Incorrect study type: Not an SR or RCT
Brook I (2009) Role of methicillin-resistant Staphylococcus aureus in head and neck infections. *The Journal of laryngology and otology* 123(12), 1301-7	Incorrect study type: Narrative review
Buchanan MA, Muen W, Heinz P (2012) Management of periorbital and orbital cellulitis. *Paediatrics and Child Health* 22(2), 72-77	Incorrect study type: Not an SR or RCT
Bucko AD, Hunt BJ, Kidd SL et al (2002) Randomized, double-blind, multicenter comparison of oral cefditoren 200 or 400 mg BID with either cefuroxime 250 mg BID or cefadroxil 500 mg BID for the treatment of uncomplicated skin and skin-structure infections. *Clinical therapeutics* 24(7), 1134-47	RCT included in a prioritised systematic review
Burnham JP, Kirby JP, Kollef MH (2016) Diagnosis and management of skin and soft tissue infections in the intensive care unit: a review. *Intensive care medicine* 42(12), 1899-1911	Incorrect study type: Not an SR or RCT
Butson B, Kwa P (2015) Emergency department management of skin and soft tissue abscesses. *Emergency medicine Australasia: EMA* 27(5), 460-3	Incorrect study type: Not an SR or RCT
Cada D, Demaris K, Levien T et al (2013) Tofacitinib. *Hospital Pharmacy* 48(5), 413-424	Incorrect study type: Not an SR or RCT
Cada D, Ingram K, Baker D (2014) Formulary drug reviews: Dalbavancin. *Hospital Pharmacy* 49(9), 851-861	Incorrect study type: Not an SR or RCT
Cada D, Levien T, Baker D (2011) Formulary drug reviews-ceftaroline fosamil. *Hospital Pharmacy* 46(5), 349-355	Incorrect study type: Not an SR or RCT
Cardona AF, Wilson SE (2015) Skin and soft-tissue infections: a critical review and the role of telavancin in their treatment. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 61 Suppl 2, S69-78	Incorrect study type: Not an SR or RCT
Cenizal MJ, Skiest D, Luber S et al (2007) Prospective randomized trial of empiric therapy with trimethoprim-sulfamethoxazole or doxycycline for outpatient skin and soft tissue infections in an area of high prevalence of methicillin-resistant Staphylococcus aureus. *Antimicrobial agents and chemotherapy* 51(7), 2628-30	Incorrect population: Not a cellulitis population
Chahine EB, Sucher AJ, Knutsen SD (2015) Tedizolid: A New Oxazolidinone Antibiotic for Skin and Soft Tissue Infections. *The Consultant pharmacist: the journal of the American Society of Consultant Pharmacists* 30(7), 386-94	Incorrect population: Cellulitis data not reported separately
Chamberlin KW, Sahbani O (2017) Delafloxacin (Baxdela) for acute bacterial skin infections: The drug is indicated for the treatment of variety of skin and skin structure infections. *Drug Topics* 161(12),	Incorrect study type: Not an SR or RCT

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Study reference	Reason for exclusion
Charneski L, Patel PN, Sym D (2009) Telavancin: a novel lipoglycopeptide antibiotic. *The Annals of pharmacotherapy* 43(5), 928-38	Incorrect population: Cellulitis data not reported separately
Chaudhary M, Shrivastava SM, Sehgal R (2008) Efficacy and safety study of fixed-dose combination of ceftriaxone-vancomycin injection in patients with various infections. *Current Drug Safety* 3(1), 82-85	Incorrect population: Not cellulitis
Chen L, Silverman N, Wu A et al (2017) Intravenous Steroids with Antibiotics on Admission for Children with Orbital Cellulitis. *Ophthalmic Plastic and Reconstructive Surgery*,	Incorrect study type Not an SR or RCT
Chen YS, Lee SC, Kim WJ (2004) Efficacy and tolerability of linezolid in treating severe skin and soft tissue infections caused by gram-positive pathogens. *Journal of the Formosan Medical Association* 103(5), 349-354	Incorrect study type: Not an SR or RCT
Chin YC, Kumar C M (2013) Postoperative orbital swelling - Causes, diagnosis and management. *Trends in Anaesthesia and Critical Care* 3(2), 82-86	Incorrect study type: Narrative review
Chlebicki MP, Oh CC (2014) Recurrent cellulitis: Risk factors, etiology, pathogenesis and treatment. *Current Infectious Disease Reports* 16(9), 422	Incorrect study type: Not an SR or RCT
Chuang YC, Chang CM, Aradhya S et al (2011) Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. Jo*urnal of Microbiology, and Immunology and Infection* 44(2), 116-124	Incorrect population: Cellulitis data not reported separately
Colabella J, Chagan L (2008) Dalbavancin (Zeven), a novel glycopeptide for resistant gram-positive organisms. *P and T* 33(1), 42	Incorrect study type: Not an SR or RCT
Cooke FJ, Brown N M (2010) Community-associated methicillin-resistant Staphylococcus aureus infections. *British Medical Bulletin* 94(1), 215-227	Incorrect study type: Not an SR or RCT
Cope A, Francis N, Wood F et al (2014) Systemic antibiotics for symptomatic apical periodontitis and acute apical abscess in adults. *Cochrane Database of Systematic Reviews* (6),	Incorrect population: Cellulitis as an outcome of infection only, not total population with cellulitis
Corey GR, Kabler H, Mehra P et al (2014) Single-Dose oritavancin in the treatment of acute bacterial skin infections. *New England Journal of Medicine* 370(23), 2180-2190	Incorrect population: Cellulitis data not reported separately
Corey GR, Good S, Jiang H et al (2015) Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 60(2), 254-62	Incorrect population: Cellulitis data not reported separately
Corey GR, Wilcox M, Talbot GH et al (2010) Integrated analysis of CANVAS 1 and 2: Phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. *Clinical Infectious Diseases* 51(6), 641-650	RCT included in a prioritised systematic review.
Corey GR, Wilcox MH, Talbot GH et al (2010) CANVAS 1: the first Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *The Journal of antimicrobial chemotherapy* 65 Suppl 4, iv41-51	RCT included in a prioritised systematic review.

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Study reference	Reason for exclusion
Corrado ML (2010) Integrated safety summary of CANVAS 1 and 2 trials: Phase III, randomized, double-blind studies evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *The Journal of antimicrobial chemotherapy* 65 Suppl 4, iv67-iv71	Incorrect outcomes: No relevant outcomes reported
Corwin P, Toop L, McGeoch G et al (2005) Randomised controlled trial of intravenous antibiotic treatment for cellulitis at home compared with hospital. *BMJ* (Clinical research ed.) 330(7483), 129	Incorrect intervention: Not antimicrobials
Cox NH (2002) Management of lower leg cellulitis. *Clinical medicine* (London, and England) 2(1), 23-7	Incorrect study type: Not an SR or RCT
Cox VC, Zed PJ (2004) Once-daily cefazolin and probenecid for skin and soft tissue infections. *The Annals of pharmacotherapy* 38(3), 458-63	Lower quality systematic review
Craft JC, Moriarty SR, Clark K et al (2011) A randomized, double-blind phase 2 study comparing the efficacy and safety of an oral fusidic acid loading-dose regimen to oral linezolid for the treatment of acute bacterial skin and skin structure infections. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 52 Suppl 7, S520-6	Incorrect population: Cellulitis data not reported separately
Dar-Odeh N, Fadel HT, Abu-Hammad S et al (2018) Antibiotic prescribing for Oro-facial infections in the paediatric outpatient: A review. *Antibiotics* 7(2), 38	Incorrect study type: Narrative review
Davies BW, Smith JM, Hink EM et al (2015) C-Reactive Protein as a Marker for Initiating Steroid Treatment in Children with Orbital Cellulitis. *Ophthalmic Plastic and Reconstructive Surgery* 31(5), 364-368	Incorrect study type: Not an SR or RCT
Davis JS, Mackrow C, Binks P et al (2017) A double-blind randomized controlled trial of ibuprofen compared to placebo for uncomplicated cellulitis of the upper or lower limb. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases* 23(4), 242-246	Incorrect intervention: Not antimicrobials
Daum RS, Miller LG, Immergluck L et al (2017) A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses. *The New England journal of medicine* 376(26), 2545-2555	Incorrect population: Not a cellulitis population
De Anda C, Anuskiewicz S, Prokocimer P et al (2017) Outpatient treatment of acute bacterial skin and skin structure infections (ABSSSI) with tedizolid phosphate and linezolid in patients in the United States. *Medicine* (United States) 96(52)	Incorrect population: Cellulitis not reported separately
De Anda C, Fang E, Mehra P et al (2012) Efficacy and safety of tedizolid phosphate for 6 days versus linezolid for 10 days in a phase 3 study in patients with ABSSSI using the new FDA primary outcome measure. *Pharmacotherapy*. 32(10), e212	Incorrect population: Cellulitis not reported separately
Deshpande AV (2001) Do as you would be done by. *Journal of Postgraduate Medicine* 47(4), 286	Incorrect study type: Not an SR or RCT
Diaz JH (2014) Skin and soft tissue infections following marine injuries and exposures in travelers. *Journal of travel medicine* 21(3), 207-13	Incorrect study type: Narrative review
Doan TL, Fung HB, Mehta D et al (2006) Tigecycline: a glycylcycline antimicrobial agent. *Clinical therapeutics* 28(8), 1079-1106	Incorrect population: Cellulitis data not reported separately

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Study reference	Reason for exclusion
Dodds TJ, Hawke CI (2009) Linezolid versus vancomycin for MRSA skin and soft tissue infections (systematic review and meta-analysis). *ANZ journal of surgery* 79(9), 629-35	Incorrect population: Not a cellulitis population
Dotis J, Iosifidis E, Ioannidou M et al (2010) Use of linezolid in pediatrics: A critical review. *International Journal of Infectious Diseases* 14(8), e638-e648	Incorrect population: Cellulitis data not reported separately
Dunbar LM, Milata J, McClure T et al (2011) Comparison of the efficacy and safety of oritavancin front-loaded dosing regimens to daily dosing: an analysis of the SIMPLIFI trial. *Antimicrobial agents and chemotherapy* 55(7), 3476-84	Incorrect study type: Dose finding study
Duncan CJA, Barr DA, Seaton RA (2012) Outpatient parenteral antimicrobial therapy with ceftriaxone, a review. *International journal of clinical pharmacy* 34(3), 410-7	Incorrect population: Cellulitis data not reported separately
Dunn CJ, Peter D (2006) Tigecycline: An evidence-based review of its antibacterial activity and effectiveness in complicated skin and soft tissue and intraabdominal infections. *Core Evidence* 1(3), 181-194	Incorrect population: Cellulitis data not reported separately
Dunne MW, Puttagunta S, Giordano P et al (2016) A Randomized Clinical Trial of Single-Dose Versus Weekly Dalbavancin for Treatment of Acute Bacterial Skin and Skin Structure Infection. *Clinical Infectious Diseases* 62(5), 545-551	Incorrect population: Cellulitis data not reported separately
Durnovo EA, Furman IV, Pushkin SY et al (2008) Clinical results of the application of perftoran for the treatment of odontogenous abcesses and phlegmons in the maxillofacial region. *Journal of cranio-maxillo-facial surgery: official publication of the European Association for Cranio-Maxillo-Facial Surgery* 36(3), 161-172	Incorrect study type: Not an SR or RCT
Ebell MH (2013) Low-dose penicillin prevents recurrent cellulitis. *American Family Physician* 88(9), 608-609	Incorrect study type: Short report of another trial
Edwards SJ, Clarke MJ, Wordsworth S et al (2008) Carbapenems versus other beta-lactams in treating severe infections in intensive care: A systematic review of randomised controlled trials. *European Journal of Clinical Microbiology and Infectious Diseases* 27(7), 531-543	Incorrect population: Not a cellulitis population, cellulitis data not reported separately
Embil JM, Soto NE, Melnick DA (2006) A post hoc subgroup analysis of meropenem versus imipenem/cilastatin in a multicenter, double-blind, randomized study of complicated skin and skin-structure infections in patients with diabetes mellitus. *Clinical therapeutics* 28(8), 1164-1174	Incorrect population: Cellulitis data not reported separately
Enoch DA, Karas JA, Aliyu SH (2009) Oral antimicrobial options for the treatment of skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus (MRSA) in the UK. *International journal of antimicrobial agents* 33(6), 497-502	Incorrect study type: Narrative review
Esposito S, Bianchini S (2016) Dalbavancin for the treatment of paediatric infectious diseases. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology* 35(12), 1895-1901	Incorrect population: Cellulitis data not reported separately
Esposito S, Bassetti M, Borre S et al (2011) Diagnosis and management of skin and soft-tissue infections (SSTI): a literature review and consensus statement on behalf of the Italian Society of Infectious Diseases and International Society of Chemotherapy. *Journal of chemotherapy* (Florence, and Italy) 23(5), 251-62	Incorrect study type: Narrative review
Fahimi J, Singh A, Frazee BW (2015) The role of adjunctive antibiotics in the treatment of skin and soft tissue abscesses: a systematic review and meta-analysis. *CJEM* 17(4), 420-32	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
Falagas ME, Bliziotis IA, Rafailidis PI (2007) Do high doses of quinolones decrease the emergence of antibacterial resistance? A systematic review of data from comparative clinical trials. *Journal of Infection* 55(2), 97-105	Incorrect population: Cellulitis data not reported separately
Falagas ME, Karageorgopoulos DE, Georgantzi GG et al (2012) Susceptibility of Gram-negative bacteria to isepamicin: A systematic review. *Expert Review of Anti-Infective Therapy* 10(2), 207-218	Lower quality systematic review
Falagas ME, Kasiakou SK, Tsiodras S et al (2006) The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: A review of the recent literature. *Clinical Medicine and Research* 4(2), 138-146	Incorrect study type: Not an SR or RCT
Falagas ME, Lourida P, Poulikakos P et al (2014) Antibiotic treatment of infections due to carbapenem-resistant enterobacteriaceae: Systematic evaluation of the available evidence. *Antimicrobial Agents and Chemotherapy* 58(2), 654-663	Incorrect population: Cellulitis data not reported separately
Falagas ME, Matthaiou DK, Vardakas KZ (2006) Fluoroquinolones vs beta-lactams for empirical treatment of immunocompetent patients with skin and soft tissue infections: a meta-analysis of randomized controlled trials. *Mayo Clinic proceedings* 81(12), 1553-66	Lower quality systematic review
Falagas ME, Siempos II, Vardakas KZ (2008) Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. *The Lancet Infectious Diseases* 8(1), 53-66	Incorrect population: Cellulitis data not reported separately
Falagas M E, Vouloumanou E K, and Rafailidis P I (2009) Systemic colistin use in children without cystic fibrosis: a systematic review of the literature. *International Journal of Antimicrobial Agents* 33(6), 503	Incorrect study type: Not an SR or RCT
Fekete T (2015) Clindamycin did not differ from trimethoprim-sulfamethoxazole for curing uncomplicated skin infections. *Annals of Internal Medicine* 163(2), JC9	Incorrect study type: Not an SR or RCT
Forcade NA, Wiederhold NP, Ryan L et al (2012) Antibacterials as adjuncts to incision and drainage for adults with purulent methicillin-resistant Staphylococcus aureus (MRSA) skin infections. *Drugs* 72(3), 339-51	Incorrect study type: Not an SR or RCT
Friedland HD, O'Neal T, Biek D et al (2012) CANVAS 1 and 2: analysis of clinical response at day 3 in two phase 3 trials of ceftaroline fosamil versus vancomycin plus aztreonam in treatment of acute bacterial skin and skin structure infections. *Antimicrobial agents and chemotherapy* 56(5), 2231-6	Incorrect population: Cellulitis data not reported separately
Fu J, Ye X, Chen C et al (2013) The Efficacy and Safety of Linezolid and Glycopeptides in the Treatment of Staphylococcus aureus Infections. *PLoS ONE* 8(3), e58240	Incorrect population: Cellulitis data not reported separately
Fulton B, Perry CM (2001) Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. *Paediatric drugs* 3(2), 137-58	Incorrect intervention: Intervention not available in UK
Fung HB, Kirschenbaum HL, Ojofeitimi BO (2001) Linezolid: an oxazolidinone antimicrobial agent. *Clinical therapeutics* 23(3), 356-91	Incorrect population: Cellulitis data not reported separately
Gabillot-Carre M, Roujeau J-C (2007) Acute bacterial skin infections and cellulitis. *Current opinion in infectious diseases* 20(2), 118-23	incorrect study type: Not an SR or RCT

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Study reference	Reason for exclusion
Garau J (2006) Management of cSSTIs: the role of daptomycin. *Current medical research and opinion* 22(11), 2079-87	Incorrect study type: Not an SR or RCT
Garcia-Arguello LY, O'Horo JC, Farrell A et al (2017) Infections in the spinal cord-injured population: A systematic review. *Spinal Cord* 55(6), 526-534	Incorrect population: Not a cellulitis population
Garrett T, Harbort Y, Trebble M et al (2012) Once or twice-daily, algorithm-based intravenous cephazolin for home-based cellulitis treatment. *EMA - Emergency Medicine Australasia* 24(4), 383-392	Incorrect study type: Not an SR or RCT
Gemmell CG, Edwards DI, Fraise AP et al (2006) Guidelines for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the UK. *Journal of Antimicrobial Chemotherapy* 57(4), 589-608	Incorrect study type: Not an SR or RCT
Giordano P, Weber K, Gesin G et al (2007) Skin and skin structure infections: Treatment with newer generation fluoroquinolones. *Therapeutics and Clinical Risk Management* 3(2), 309-317	Incorrect study type: Not an SR or RCT
Giordano PA, Elston D, Akinlade BK et al (2006) Cefdinir vs. cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. *Current medical research and opinion* 22(12), 2419-28	Incorrect intervention: Intervention not available in UK
Glasmacher A, von Lilienfeld-Toal M, Schulte S et al (2005) An evidence-based evaluation of important aspects of empirical antibiotic therapy in febrile neutropenic patients. *Clinical Microbiology and Infection*, Supplement 11(5), 17-23	Incorrect population: Not a cellulitis population
Goldstein EJC, Citron DM, Merriam CV et al (2002) General microbiology and in vitro susceptibility of anaerobes isolated from complicated skin and skin-structure infections in patients enrolled in a comparative trial of ertapenem versus piperacillin-tazobactam. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 35(Suppl 1), S119-25	Incorrect population: Cellulitis data not reported separately
Gomez-Arambula H, Hidalgo-Hurtado A, Rodriguez-Flores R et al (2015) Moxifloxacin versus Clindamycin/Ceftriaxone in the management of odontogenic maxillofacial infectious processes: A preliminary, intrahospital, controlled clinical trial. *Journal of clinical and experimental dentistry* 7(5), e634-9	Incorrect population: Not an included cellulitis population
Gould FK, Brindle R, Chadwick PR et al (2009) Guidelines (2008) for the prophylaxis and treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections in the United Kingdom. *Journal of Antimicrobial Chemotherapy* 63(5), 849-861	Incorrect study type: Not an SR or RCT
Gould IM, Miro JM, Rybak MJ (2013) Daptomycin: the role of high-dose and combination therapy for Gram-positive infections. *International journal of antimicrobial agents* 42(3), 202-10	Incorrect study type: Not an SR or RCT
Grayson ML, McDonald M, Gibson K et al (2002) Once-daily intravenous cefazolin plus oral probenecid is equivalent to once-daily intravenous ceftriaxone plus oral placebo for the treatment of moderate-to-severe cellulitis in adults. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 34(11), 1440-8	RCT included in a prioritised systematic review
Grupper M, Nicolau DP (2017) Obesity and skin and soft tissue infections: how to optimize antimicrobial usage for prevention and treatment? *Current opinion in infectious diseases* 30(2), 180-191	Incorrect study type: Not an SR or RCT
Guirao X, Garcia MS, Bassetti M et al (2013) Safety and tolerability of tigecycline for the treatment of complicated skin and soft-tissue and intra-abdominal infections: An analysis based on	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
five European observational studies. *Journal of Antimicrobial Chemotherapy* 68(SUPPL.2),	
Guo Z, Lin Z, Huang P et al (2011) Linezolid versus glycopeptides in the treatment of complicated skin and soft tissue infections: A meta-analysis of randomized controlled trials. *Chinese Journal of Infection and Chemotherapy* 11(4), 268	Not an English language paper
Gupta K, Kaushal S, Chopra S (2006) Tigecycline: A novel glycylcycline antibiotic. *Indian Journal of Pharmacology* 38(3), 217-219	Incorrect study type: Not an SR or RCT
Gustafson LW, Blaakaer J, Helmig RB (2017) Group A streptococci infection. A systematic clinical review exemplified by cases from an obstetric department. *European Journal of Obstetrics Gynecology and Reproductive Biology* 215, 33-40	Incorrect population: Not a cellulitis population
Hahn AW, Jain R, Spach DH (2016) New Approaches to Antibiotic Use and Review of Recently Approved Antimicrobial Agents. *The Medical clinics of North America* 100(4), 911-26	Incorrect study type: Not an SR or RCT
Hair PI, Keam SJ (2007) Daptomycin: a review of its use in the management of complicated skin and soft-tissue infections and Staphylococcus aureus bacteraemia. *Drugs* 67(10), 1483-512	Incorrect population: Not a cellulitis population
Hardalo C, Lodise TP, Bidell M et al (2018) Clinical safety and tolerability of tedizolid phosphate in the treatment of acute bacterial skin and skin structure infections. *Expert Opinion on Drug Safety* 17(4), 359-367	Incorrect population: Not a cellulitis population
Harrison B, Ben-Amotz O, Sammer DM (2015) Methicillin-resistant Staphylococcus aureus infection in the hand. *Plastic and reconstructive surgery* 135(3), 826-30	Incorrect population: Not a cellulitis population
Havey TC, Fowler RA, Daneman N (2011) Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Critical care* (London, and England) 15(6), R267	Lower quality systematic review
Hayashi Y, Roberts JA, Paterson DL et al (2010) Pharmacokinetic evaluation of piperacillin-tazobactam. *Expert Opinion on Drug Metabolism and Toxicology* 6(8), 1017-1031	Incorrect study type: Not an SR or RCT
Heintz B, Halilovic J (2010) Clinical experience with linezolid at a large academic medical center: A case series and review of the literature. *Hospital Pharmacy* 45(12), 916-926	Incorrect study type: Not an SR or RCT
Heldt M, Lucas A, Cohen PR (2017) Staphylococcus lugdunensis Infections of the Skin and Soft Tissue: A Case Series and Review. *Dermatology and therapy* 7(4), 555-562	Incorrect study type: Not an SR or RCT
Hennemann S, Crawford P, Nguyen L et al (2007) Clinical inquiries. What is the best initial treatment for orbital cellulitis in children? *The Journal of family practice* 56(8), 662-4	Incorrect study type: Not an SR or RCT
Hepburn MJ, Dooley DP, Skidmore PJ et al (2004) Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. Archives of internal medicine 164(15), 1669-74	RCT included in a prioritised systematic review
Heydemann J, Heydemann JS, Antony S (2010) Acute infection of a total knee arthroplasty caused by Pasteurella multocida: A case report and a comprehensive review of the literature in the last 10 years. *International Journal of Infectious Diseases* 14(SUPPL. 3), e242-e245	Incorrect study type: Not an SR or RCT
Holmes L, Ma C, Qiao H et al (2016) Trimethoprim-Sulfamethoxazole Therapy Reduces Failure and Recurrence in Methicillin-Resistant Staphylococcus aureus Skin Abscesses after Surgical Drainage Portions of the study were presented at	Incorrect population: Cellulitis data not reported separately

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Study reference	Reason for exclusion
meetings of the Pediatric Academic Societies, Boston, MA, April 28-May 1, 2012, and Washington, DC, May 4-7, 2013. *Journal of pediatrics* 169, 128-134e1	
Homer-Vanniasinkam S (2006) Treatment of intra-abdominal and skin and soft tissue infections: The role of the glycylcyclines. *International Journal of Surgery* 4(1), 45-52	Incorrect study type: Not an SR or RCT
Hood R, Shermock KM, Emerman C (2004) A Prospective, Randomized Pilot Evaluation of Topical Triple Antibiotic Versus Mupirocin for the Prevention of Uncomplicated Soft Tissue Wound Infection. *American Journal of Emergency Medicine* 22(1), 1-3	Incorrect population: Not a cellulitis population
Horseman M, Bowman JD (2013) Is Community-Acquired Methicillin-Resistant Staphylococcus aureus Coverage Needed for Cellulitis? *Infectious Diseases and Therapy* 2(2), 175-185	Incorrect study type: Not an SR or RCT
Howe L, Jones NS (2004) Guidelines for the management of periorbital cellulitis/abscess. *Clinical otolaryngology and allied sciences* 29(6), 725-8	Incorrect study type: Not an SR or RCT
Hsu Andrew R, Hsu Jessica W (2012) Topical review: skin infections in the foot and ankle patient. *Foot & ankle international* 33(7), 612-9	Incorrect study type: Not an SR or RCT
Ibrahim F, Khan T, Pujalte GGA (2015) Bacterial Skin Infections. *Primary care* 42(4), 485-99	Incorrect study type: Not an SR or RCT
Ioannidou M, Apostolidou-Kiouti F, Haidich AB et al (2014) Efficacy and safety of linezolid for the treatment of infections in children: A meta-analysis. *European Journal of Pediatrics* 173(9), 1179-1186	Incorrect population: Not a cellulitis population
Itani KMF, Dryden MS, Bhattacharyya H et al (2010) Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant Staphylococcus aureus. *American journal of surgery* 199(6), 804-16	Incorrect population: Not a cellulitis population
Itani KMF, Weigelt J, Li JZ et al (2005) Linezolid reduces length of stay and duration of intravenous treatment compared with vancomycin for complicated skin and soft tissue infections due to suspected or proven methicillin-resistant Staphylococcus aureus (MRSA). *International journal of antimicrobial agents* 26(6), 442-8	Incorrect population: Cellulitis data not reported separately
Janis JE, Hatef DA, Reece EM et al (2014) Does empiric antibiotic therapy change MRSA [corrected] hand infection outcomes? Cost analysis of a randomized prospective trial in a county hospital. *Plastic and reconstructive surgery* 133(4), 511e-8e	Incorrect population: Cellulitis data not reported separately
Jauregui LE, Babazadeh S, Seltzer E et al (2005) Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clinical Infectious Diseases* 41(10), 1407-1415	Incorrect population: Cellulitis data not reported separately
John CC, Schreiber JR (2006) Therapies and Vaccines for Emerging Bacterial Infections: Learning from Methicillin-resistant Staphylococcus aureus. *Pediatric Clinics of North America* 53(4), 699-713	Incorrect study type: Narrative review
Johnson S, Leak K, Singh S et al (2007) Can cycloidal vibration plus standard treatment reduce lower limb cellulitis treatment times? *Journal of wound care* 16(4), 166-169	incorrect intervention- not antibiotics
Jones P, Lamdin R (2010) Oral cyclo-oxygenase 2 inhibitors versus other oral analgesics for acute soft tissue injury:	Incorrect intervention: Not antimicrobials

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Study reference	Reason for exclusion
Systematic review and meta-analysis. *Clinical Drug Investigation* 30(7), 419-437	
Jump RLP, Crnich CJ, Mody L et al (2018) Infectious Diseases in Older Adults of Long-Term Care Facilities: Update on Approach to Diagnosis and Management. *Journal of the American Geriatrics Society* 66(4), 789-803	Incorrect study type: Not an SR or RCT
Kasiakou SK, Sermaides GJ, Michalopoulos A et al (2005) Continuous versus intermittent intravenous administration of antibiotics: A meta-analysis of randomised controlled trials. *Lancet Infectious Diseases* 5(9), 581-589	Incorrect population: Not a cellulitis population
Kasten MJ, Litin SC, Bundrick JB (2015) Clinical pearls in infectious diseases. *Disease-a-Month* 61(8), 319-328	Incorrect study type: Not an SR or RCT
Kaushik D, Rathi S, Jain A (2011) Ceftaroline: a comprehensive update. *International journal of antimicrobial agents* 37(5), 389-95	Incorrect study type: Not an SR or RCT
Khalil PN, Huber-Wagner S, Altheim S et al (2008) Diagnostic and treatment options for skin and soft tissue abscesses in injecting drug users with consideration of the natural history and concomitant risk factors. *European journal of medical research* 13(9), 415-24	Incorrect population: Not a cellulitis population
Khawcharoenporn T, Alan T (2006) Oral antibiotic treatment for methicillin-resistant Staphylococcus aureus skin and soft tissue infections: review of the literature. *Hawaii medical journal* 65(10), 290-3	Incorrect study type: Not an SR or RCT
Ki V, Rotstein C (2008) Bacterial skin and soft tissue infections in adults: A review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. *Canadian Journal of Infectious Diseases and Medical Microbiology* 19(2), 173-184	Incorrect study type: Not an SR or RCT
Kish TD, Chang MH, Fung HB (2010) Treatment of skin and soft tissue infections in the elderly: A review. *The American journal of geriatric pharmacotherapy* 8(6), 485-513	Incorrect study type: Not an SR or RCT
Kluytmans J, Struelens M (2009) Meticillin resistant Staphylococcus aureus in the hospital. *BMJ* (Online) 338(7693),	Incorrect study type: Narrative review
Kmeid J, Kanafani ZA (2015) Oritavancin for the treatment of acute bacterial skin and skin structure infections: An evidence-based review. *Core Evidence* 10, 39-47	Incorrect intervention: Intervention not available in UK
Ko LN, Garza-Mayers AC, St John J et al (2018) Effect of Dermatology Consultation on Outcomes for Patients with Presumed Cellulitis: A Randomized Clinical Trial. *JAMA dermatology* 154(5), 529-536	Incorrect intervention: Intervention not available in UK
Konychev A, Heep M, Moritz R et al (2012) A comparative randomised clinical trial against semisynthetic penicillins and glycopeptides supports the use of daptomycin as first-line treatment of complicated skin and soft-tissue infections in the elderly. *Clinical microbiology and infection*. Conference: 22nd European congress of clinical microbiology and infectious diseases London United Kingdom. Conference start: 20120331 conference end: 20120403. Conference publication: (var.pagings) 18, 838-839	Incorrect study type: Conference abstract
Ladhani S, Garbash M (2005) Staphylococcal skin infections in children: rational drug therapy recommendations. *Paediatric drugs* 7(2), 77-102	Incorrect study type: Not an SR or RCT
Lagace-Wiens P, Walkty A, Karlowsky JA (2014) Ceftazidime-avibactam: An evidence-based review of its pharmacology and	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
potential use in the treatment of Gram-negative bacterial infections. *Core Evidence* 9, 13-25	
Langlois DM, Andreae M (2011) Group A streptococcal infections. *Pediatrics in Review* 32(10), 423-429	Incorrect study type: Not an SR or RCT
Larsen JW, Hager WD, Livengood C et al (2003) Guidelines for the diagnosis, treatment and prevention of postoperative infections. *Infectious diseases in obstetrics and gynecology* 11(1), 65-70	Incorrect study type: Narrative review
Lee S, Yen MT (2011) Management of preseptal and orbital cellulitis. *Saudi Journal of Ophthalmology* 25(1), 21-29	Incorrect study type: Not an SR or RCT
Lee SY, Kuti JL, Nicolau DP (2005) Antimicrobial management of complicated skin and skin structure infections in the era of emerging resistance. *Surgical infections* 6(3), 283-95	Incorrect population: Not a cellulitis population
Leman P, Mukherjee D (2005) Flucloxacillin alone or combined with benzylpenicillin to treat lower limb cellulitis: a randomised controlled trial. *Emergency medicine journal*: EMJ 22(5), 342-6	RCT included in a prioritised systematic review
Lentino JR, Narita M, Yu VL (2008) New antimicrobial agents as therapy for resistant gram-positive cocci. *European Journal of Clinical Microbiology and Infectious Diseases* 27(1), 3-15	Incorrect study type: Not an SR or RCT
Li Y, Xu W (2018) Efficacy and safety of linezolid compared with other treatments for skin and soft tissue infections: a meta-analysis. *Bioscience reports* 38(1),	Incorrect population: Not a cellulitis population
Lin SW, Carver PL, DePestel DD (2006) Dalbavancin: A new option for the treatment of gram-positive infections. *Annals of Pharmacotherapy* 40(3), 449-460	Incorrect population: Not a cellulitis population
Liu HH (2010) Safety profile of the fluoroquinolones: Focus on levofloxacin. *Drug Safety* 33(5), 353-369	Incorrect study type: Not an SR or RCT
Liu Y, Ma Y, Xiang LH (2013) Successful treatment of recalcitrant dissecting cellulitis of the scalp with ALA-PDT: Case report and literature review. *Photodiagnosis and Photodynamic Therapy* 10(4), 410-413	Incorrect study type: Not an SR or RCT
Loewen K, Schreiber Y, Kirlew M et al (2017) Community-associated methicillin-resistant Staphylococcus aureus infection: Literature review and clinical update. *Canadian family physician Medecin de famille canadien* 63(7), 512-520	Incorrect study type: narrative review
Logman J, Floris S, Stephens J et al (2010) Comparative effectiveness of antibiotics for the treatment of MRSA complicated skin and soft tissue infections. *Current medical research and opinion* 26(7), 1565-78	Incorrect population: Not a cellulitis population
Lopez F A, Lartchenko S (2006) Skin and Soft Tissue Infections. *Infectious Disease Clinics of North America* 20(4), 759-772	Incorrect study type: Not an SR or RCT
Love BL, Kehr H (2007) Management of complicated skin and soft tissue infections in hospitalized patients. *U.S. Pharmacist* 32(4), HS5-HS12	Incorrect study type: Not an SR or RCT
Lv X, O'Riordan W, Zhu X et al (2017) Tedizolid versus linezolid in acute bacterial skin and skin structure infections (ABSSSI): results of a phase 3 clinical trial. *International journal of antimicrobial agents*. Conference: 30th international congress of chemotherapy and infection, and ICC 2017. Taiwan (republic of china) 50(Supplement 2), S191-s192	Incorrect study type: Conference abstract only
Mah GT, Mabasa VH, Chow I et al (2012) Evaluating outcomes associated with alternative dosing strategies for	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
piperacillin/tazobactam: A qualitative systematic review. *Annals of Pharmacotherapy* 46(2), 265-275	
Manaktala C, Singh AK, Verma M et al (2009) Efficacy and tolerability of cefditoren pivoxil in uncomplicated skin and skin structure infections in Indian patients. *Indian Journal of Dermatology* 54(4), 350-356	Incorrect study type: Not an SR or RCT
Manfredi R (2006) Update on the appropriate use of linezolid in clinical practice. *Therapeutics and Clinical Risk Management* 2(4), 455-464	Incorrect study type: Not an SR or RCT
Manfredi R, Calza L (2008) Novel therapeutic agents for resistant gram-positive infections. *Current Drug Therapy* 3(2), 98-110	Incorrect study type: Not an SR or RCT
Manfredi R, Sabbatani S (2010) Novel pharmaceutical molecules against emerging resistant gram-positive cocci. *Brazilian Journal of Infectious Diseases* 14(1), 96-108	Incorrect study type: Not an SR or RCT
Maraki S, Sarchianaki E, Barbagadakis S (2012) Myroides odoratimimus soft tissue infection in an immunocompetent child following a pig bite: Case report and literature review. *Brazilian Journal of Infectious Diseases* 16(4), 390-392	Incorrect study type: Not an SR or RCT
May AK (2011) Skin and soft tissue infections: the new surgical infection society guidelines. *Surgical infections* 12(3), 179-84	Incorrect study type: Not an SR or RCT
May AK, Stafford RE, Bulger EM et al (2009) Treatment of complicated skin and soft tissue infections. Surgical infections 10(5), 467-99	Lower quality systematic review
McClain SL, Bohan JG, Stevens DL (2016) Advances in the medical management of skin and soft tissue infections. *BMJ* (Clinical research ed.) 355, i6004	Incorrect population: Cellulitis data not reported separately
McClaine RJ, Husted TL, Hebbeler-Clark RS et al (2010) Meta-analysis of trials evaluating parenteral antimicrobial therapy for skin and soft tissue infections. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 50(8), 1120-6	Incorrect population: Cellulitis data not reported separately
McConeghy KW, Bleasdale SC, Rodvold KA (2013) The empirical combination of vancomycin and a beta-lactam for staphylococcal bacteremia. *Clinical Infectious Diseases* 57(12), 1760-1765	Incorrect population: Not a cellulitis population
Meals C, Hattwick E (2011) Mycobacterial infections of the hand and wrist: A review of current literature. *Current Orthopaedic Practice* 22(2), 198-203	Incorrect study type: Not an SR or RCT
Michalek K, Lechowicz M, Pastuszczak M et al (2015) The use of trimethoprim and sulfamethoxazole (TMP-SMX) in dermatology. *Folia medica Cracoviensia* 55(1), 35-41	Incorrect study type: Not an SR or RCT
Michalopoulos A, Falagas ME (2010) Treatment of Acinetobacter infections. *Expert Opinion on Pharmacotherapy* 11(5), 779-788	Incorrect study type: Not an SR or RCT
Mikamo H, Takesue Y, Iwamoto Y et al (2018) Efficacy, safety and pharmacokinetics of tedizolid versus linezolid in patients with skin and soft tissue infections in Japan - Results of a randomised, multicentre phase 3 study. *Journal of Infection and Chemotherapy* 24(6), 434-442	Incorrect population: Cellulitis data not reported separately
Miller LG (2017) Cephalexin plus trimethoprim-sulfamethoxazole was not superior to cephalexin alone for the treatment of outpatient non-purulent cellulitis. *Evidence-Based Medicine* 22(6), 213	Incorrect study type: Not an SR or RCT

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Study reference	Reason for exclusion
Miller LG, Daum RS, Creech CB et al (2015) Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. The New England journal of medicine 372(12), 1093-103	RCT included in a prioritised systematic review.
Mishra AK, Yadav P, Mishra A (2016) A Systemic Review on Staphylococcal Scalded Skin Syndrome (SSSS): A Rare and Critical Disease of Neonates. *The open microbiology journal* 10, 150-9	Incorrect study type: Not an SR or RCT
Mongkolrattanothai K, Daum RS (2005) Impact of community-associated, methicillin-resistant Staphylococcus aureus on management of the skin and soft tissue infections in children. *Current Infectious Disease Reports* 7(5), 381-389	Incorrect study type: Not an SR or RCT
Moran GJ, Abrahamian FM, Lovecchio F et al (2013) Acute bacterial skin infections: developments since the 2005 Infectious Diseases Society of America (IDSA) guidelines. *The Journal of emergency medicine* 44(6), e397-412	Incorrect study type: Not an SR or RCT
Moran GJ, Fang E, Corey GR et al (2014) Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. *The Lancet. Infectious diseases* 14(8), 696-705	RCT included in a prioritised systematic review
Moran GJ, Krishnadasan A, Mower WR et al (2017) Effect of Cephalexin Plus Trimethoprim-Sulfamethoxazole vs Cephalexin Alone on Clinical Cure of Uncomplicated Cellulitis: A Randomized Clinical Trial. *JAMA* 317(20), 2088-2096 .	RCT included in a prioritised systematic review
Morgan A, Cofer C, Stevens DL (2009) Iclaprim: a novel dihydrofolate reductase inhibitor for skin and soft tissue infections. *Future microbiology* 4(2), 131-44	Incorrect study type: Not an SR or RCT
Morris AD (2008) Cellulitis and erysipelas. *BMJ clinical evidence* 2008	Older systematic review with fewer relevant studies
Mukherjee S, Coha T, Torres Z (2010) Common skin problems in children with special healthcare needs. *Pediatric Annals* 39(4), 206-215	Incorrect population: Not a cellulitis population
Nageswaran S, Woods CR, Benjamin DK Jr et al (2006) Orbital cellulitis in children. *The Pediatric infectious disease journal* 25(8), 695-9	Incorrect study type: Not an SR or RCT
Nagoba BS, Selkar SP, Wadher BJ et al (2013) Acetic acid treatment of pseudomonal wound infections - A review. *Journal of Infection and Public Health* 6(6), 410-415	Incorrect study type: Not an SR or RCT
Nall M, Bridges C, Ramakrishnan K et al (2012) Question: in non-diabetic patients over 12 years of age with cellulitis being treated in an outpatient setting, does antibiotic therapy with clindamycin or trimethoprim-sulfamethoxazole better prevent hospitalization due to failed outpatient therapy? *The Journal of the Oklahoma State Medical Association* 105(12), 461-2	Incorrect study type: Not an SR or RCT
Namias N (2003) Honey in the management of infections. *Surgical infections* 4(2), 219-26	Incorrect study type: Not an SR or RCT
Napolitano LM (2005) Emerging issues in the diagnosis and management of infections caused by multi-drug-resistant, gram-positive cocci. *Surgical infections* 6 Suppl 2, S-22	Incorrect population: Cellulitis data not reported separately
Napolitano LM (2008) Early appropriate parenteral antimicrobial treatment of complicated skin and soft tissue infections caused by methicillin-resistant Staphylococcus aureus. *Surgical infections* 9 Suppl 1, s17-27	Incorrect study type: Not an SR or RCT

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Study reference	Reason for exclusion
Nathwani D, Morgan M, Masterton RG et al (2008) Guidelines for UK practice for the diagnosis and management of methicillin-resistant Staphylococcus aureus (MRSA) infections presenting in the community. *Journal of Antimicrobial Chemotherapy* 61(5), 976-994	Incorrect study type: Not an SR or RCT
Nathwani D, Dryden M, Garau J (2016) Early clinical assessment of response to treatment of skin and soft-tissue infections: how can it help clinicians? Perspectives from Europe. *International journal of antimicrobial agents* 48(2), 127-36	Incorrect study type: Not an SR or RCT
Natsis NE, Cohen PR (2018) Coagulase-Negative Staphylococcus Skin and Soft Tissue Infections. *American journal of clinical dermatology*,	Incorrect study type: narrative review
Nazarko L (2012) An evidence-based approach to diagnosis and management of cellulitis. *British journal of community nursing* 17(1), 6-2	Incorrect study type: Not an SR or RCT
Nemeth J, Oesch G, Kuster SP (2015) Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: Systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy* 70(2), 382-395	Incorrect population: Cellulitis data not reported separately
Nguyen H M, Graber C J (2010) Limitations of antibiotic options for invasive infections caused by methicillin-resistant Staphylococcus aureus: Is combination therapy the answer? *Journal of Antimicrobial Chemotherapy* 65(1), 24-36	Incorrect study type: Not an SR or RCT
Nguyen L, Rowland K (2014) Low-dose penicillin for recurrent cellulitis. *Journal of Family Practice* 63(1), E10-E12	Incorrect study type: Not an SR or RCT
Obaitan I, Dwyer R, Lipworth AD et al (2016) Failure of antibiotics in cellulitis trials: a systematic review and meta-analysis. *The American journal of emergency medicine* 34(8), 1645-52	Incorrect study type: narrative review
Oh CCh (2015) Cellulitis and erysipelas: prevention. BMJ clinical evidence 2015	Lower quality systematic review
Oh CCh, Ko HCH, Lee HY et al (2014) Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. The Journal of infection 69(1), 26-34	Lower quality systematic review
O'Brien DJ, Gould IM (2014) Does vancomycin have a future in the treatment of skin infections? *Current opinion in infectious diseases* 27(2), 146-54	Incorrect study type: Not an SR or RCT
O'Riordan W, Mehra P, Manos P et al (2015) A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. International journal of infectious diseases: *IJID: official publication of the International Society for Infectious Diseases* 30, 67-73	Incorrect intervention: Intervention not available in UK
Oumeish I, Oumeish OY, Bataineh O (2000) Acute bacterial skin infections in children. *Clinics in Dermatology* 18(6), 667-678	Incorrect study type: Not an SR or RCT
Pacifico L, Chiesa C (2002) Azithromycin in children: A critical review of the evidence. *Current Therapeutic Research - Clinical and Experimental* 63(1), 54-76	Incorrect population: Not a cellulitis population
Pallin DJ, Binder WD, Allen MB et al (2013) Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 56(12), 1754-62	RCT included in a prioritised systematic review
Pan A, Cauda R, Concia E et al (2010) Consensus document on controversial issues in the treatment of complicated skin and skin-	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
structure infections. *International Journal of Infectious Diseases* 14(SUPPL. 4), S39-S53	
Pangilinan R, Tice A, Tillotson G (2009) Topical antibiotic treatment for uncomplicated skin and skin structure infections: review of the literature. *Expert review of anti-infective therapy* 7(8), 957-65	Incorrect intervention: Article states topical antibiotics are not indicated for cellulitis
Pappa G, Athanasoulia AP, Matthaiou DK et al (2009) Trimethoprim-sulfamethoxazole for methicillin-resistant staphylococcus aureus: a forgotten alternative? *Journal of Chemotherapy* 21(2), 115-126	Incorrect population: Not a cellulitis population
Paul JC, Pieper BA (2008) Topical metronidazole for the treatment of wound odor: a review of the literature. *Ostomy/wound management* 54(3), 18-9	Incorrect study type: Not an SR or RCT
Perlroth J, Kuo M, Tan J et al (2008) Adjunctive use of rifampin for the treatment of Staphylococcus aureus infections: A systematic review of the literature. *Archives of Internal Medicine* 168(8), 805-819	Incorrect population: Not a cellulitis population
Peters EJ, Lipsky BA, Aragon-Sanchez J et al (2016) Interventions in the management of infection in the foot in diabetes: A systematic review. *Diabetes/Metabolism Research and Reviews* 32(Supplement 1), 145-153	Incorrect population: Not a cellulitis population
Peters EJG, Lipsky BA, Berendt AR et al (2012) A systematic review of the effectiveness of interventions in the management of infection in the diabetic foot. *Diabetes/Metabolism Research and Reviews* 28(SUPPL. 1), 142-162	Incorrect population: Not a cellulitis population
Phoenix G, Das S, Joshi M (2012) Diagnosis and management of cellulitis. *BMJ* (Clinical research ed.) 345, e4955	Incorrect study type: Not an SR or RCT
Pichon RA , Augustovski F, Alcaraz A et al (2006) Linezolid for the management of severe cocci gram-positive infections. *Ciudad de Buenos Aires: Institute for Clinical Effectiveness and Health Policy* (IECS),	Not an English language paper
Plosker GL, Figgitt DP (2005) Linezolid: a pharmacoeconomic review of its use in serious Gram-positive infections. *PharmacoEconomics* 23(9), 945-64	Incorrect study type: narrative review
Pollack Jr C, Corey G, Good S et al (2014) A single dose of oritavancin compared to 7 to 10 days of vancomycin: lesion size reduction in phase 3 studies of acute bacterial skin and skin infections. *Annals of emergency medicine*. 64(4 suppl. 1), S36	Incorrect study type: Conference abstract only
Pollack Jr C, Corey G, Good S et al (2014) Efficacy outcomes by lesion type in studies of a single dose of oritavancin compared to 7 to 10 days of vancomycin. *Annals of emergency medicine*. 64(4 suppl. 1), S90	Incorrect study type: Conference abstract only
Polyzos KA, Mavros MN, Vardakas KZ et al (2012) Efficacy and safety of telavancin in clinical trials: A systematic review and meta-analysis. *PLoS ONE* 7(8), e41870	Incorrect population: Cellulitis data not reported separately
Poon H, Chang MH, Fung HB (2012) Ceftaroline Fosamil: A Cephalosporin with Activity Against Methicillin-Resistant Staphylococcus Aureus. *Clinical Therapeutics* 34(4), 743-765	Incorrect population: Cellulitis data not reported separately
Powers JH, 3rd , Das AF, De Anda C et al (2016) Clinician-reported lesion measurements in skin infection trials: Definitions, reliability, and association with patient-reported pain. *Contemporary clinical trials* 50, 265-72	Incorrect outcomes: Outcomes not of interest
Prokocimer P, De Anda C, Fang E et al (2013) Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and	Included in a prioritised systematic review

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Study reference	Reason for exclusion
skin structure infections: the ESTABLISH-1 randomized trial. *JAMA* 309(6), 559-69	
Pushker N, Tejwani LK, Bajaj MS et al (2013) Role of oral corticosteroids in orbital cellulitis. *American journal of ophthalmology* 156(1), 178-183.e1	Incorrect intervention: Not antimicrobials
Puzniak LA, Quintana A, Wible M et al (2014) Methicillin-resistant Staphylococcus aureus infection epidemiology and clinical response from tigecycline soft tissue infection trials. *Diagnostic microbiology and infectious disease* 79(2), 261-5	Incorrect population: Cellulitis data not reported separately
Quirke M, O'Sullivan R, McCabe A et al (2014) Are two penicillins better than one? A systematic review of oral flucloxacillin and penicillin V versus oral flucloxacillin alone for the emergency department treatment of cellulitis. *European journal of emergency medicine: official journal of the European Society for Emergency Medicine* 21(3), 170-4	Incorrect study type: narrative review
Quist S, Fierlbeck G, Seaton R et al (2012) Comparative randomised clinical trial against glycopeptides supports the use of daptomycin as first-line treatment of complicated skin and soft-tissue infections. *International journal of antimicrobial agents* 39(1), 90-91	Incorrect study type: Not an SR or RCT
Rafailidis PI, Polyzos KA, Sgouros K et al (2011) Prulifloxacin: A review focusing on its use beyond respiratory and urinary tract infections. *International Journal of Antimicrobial Agents* 37(4), 283-290	Incorrect intervention: Intervention not available in UK
Rajendran PM, Young D, Maurer T et al (2007) Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant Staphylococcus aureus infection. *Antimicrobial Agents and Chemotherapy* 51(11), 4044-4048	Incorrect population: Not a cellulitis population
Rasler F, Lukacs J, Elsner P (2016) Treatment of eosinophilic cellulitis (Wells syndrome) - a systematic review. *Journal of the European Academy of Dermatology and Venereology: JEADV* 30(9), 1465-79	Incorrect population: Not an included cellulitis population
Roberts SA, Lang SDR (2000) Skin and soft tissue infections. *New Zealand Medical Journal* 113(1109), 164-167	Incorrect study type: Not an SR or RCT
Roberts SA, Lang SDR (2000) Skin and soft tissue infections. *New Zealand Medical Journal* 113(1109), 164-167	Incorrect study type: Not an SR or RCT
Robinson AHN, Pasapula C, Brodsky JW (2009) Surgical aspects of the diabetic foot. *Journal of Bone and Joint Surgery* - Series B 91(1), 1-7	Incorrect study type: Not an SR or RCT
Rush DE, Abdel-Haq N, Zhu J-F et al (2007) Clindamycin versus Unasyn in the treatment of facial cellulitis of odontogenic origin in children. *Clinical pediatrics* 46(2), 154-9	Incorrect population: Not an included cellulitis population
Scheinfeld N (2006) Dalbavancin: A review for dermatologists. *Dermatology Online Journal* 12(4), 6	Incorrect study type: Not an SR or RCT
Scheinfeld N (2014) Dissecting cellulitis (perifolliculitis capitis abscedens et suffodiens): A comprehensive review focusing on new treatments and findings of the last decade with commentary comparing the therapies and causes of dissecting cellulitis to hidradenitis suppurativa. *Dermatology Online Journal* 20(5), 2	Incorrect study type: Not an SR or RCT
Scheinfeld NS, Tutrone WD, Torres O et al (2003) Macrolides in dermatology. *Clinics in Dermatology* 21(1), 40-49	Incorrect study type: Not an SR or RCT

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Study reference	Reason for exclusion
Schofer H, Simonsen L (2010) Fusidic acid in dermatology: An updated review. *European Journal of Dermatology* 20(1), 6-15	Incorrect study type: Not an SR or RCT
Schriever CA, Fernandez C, Rodvold KA et al (2005) Daptomycin: A novel cyclic lipopeptide antimicrobial. *American Journal of Health-System Pharmacy* 62(11), 1145-1158	Incorrect study type: Not an SR or RCT
Scott LJ (2016) Ceftaroline Fosamil: A Review in Complicated Skin and Soft Tissue Infections and Community-Acquired Pneumonia. *Drugs* 76(17), 1659-1674	Incorrect study type: Not an SR or RCT
Shaw G, Meunier J, Wayne B et al (2014) Evaluation of daptomycin for the emergency department treatment of cellulitis. *Academic emergency medicine*. 21(5 suppl. 1), S50	Incorrect study type: Conference abstract only
Shoemaker DM, Simou J, Roland WE (2006) A review of daptomycin for injection (Cubicin) in the treatment of complicated skin and skin structure infections. *Therapeutics and Clinical Risk Management* 2(2), 169-174	Incorrect study type: Not an SR or RCT
Shorr AF, Kunkel MJ, Kollef M (2005) Linezolid versus vancomycin for Staphylococcus aureus bacteraemia: pooled analysis of randomized studies. *Journal of Antimicrobial Chemotherapy* 56(5), 923-929	Incorrect population: Not a cellulitis population
Shorr AF, Lodise TP, Corey GR et al (2015) Analysis of the phase 3 ESTABLISH trials of tedizolid versus linezolid in acute bacterial skin and skin structure infections. *Antimicrobial Agents and Chemotherapy* 59(2), 864-871	Incorrect population: Not a cellulitis population
Siami G, Christou N, Eiseman I et al (2001) Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections. *Antimicrobial agents and chemotherapy* 45(2), 525-31	Incorrect population: Cellulitis data not reported separately
Sinno H, Lacroix J-P, Lee J et al (2012) Diagnosis and management of eosinophilic cellulitis (Wells' syndrome): A case series and literature review. *The Canadian journal of plastic surgery = Journal canadien de chirurgie plastique* 20(2), 91-7	Incorrect study type: Not an SR or RCT
Slover CM, Rodvold KA, Danziger LH (2007) Tigecycline: A novel broad-spectrum antimicrobial. *Annals of Pharmacotherapy* 41(6), 965-972	Incorrect study type: Not an SR or RCT
Spellberg B, Talbot GH, Boucher H et al (2009) Antimicrobial agents for complicated skin and skin-structure infections: justification of noninferiority margins in the absence of placebo-controlled trials. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 49(3), 383-91	Incorrect study type: Not an SR or RCT
Stein GE, Wells EM (2010) The importance of tissue penetration in achieving successful antimicrobial treatment of nosocomial pneumonia and complicated skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus: vancomycin and linezolid. *Current medical research and opinion* 26(3), 571-88	Incorrect study type: Not an SR or RCT
Steurer J (2015) Clindamycin vs. trimethoprim-sulfamethoxazole: equally effective in skin infections. *Praxis* 104(12), 645-646	Not an English language paper
Stevens DL, Bisno AL, Chambers HF et al (2014) Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clinical Infectious Diseases* 59(2), e10-e52	Incorrect study type: Not an SR or RCT
Stevens DL, Bisno AL, Chambers HF et al (2005) Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clinical Infectious Diseases* 41(10), 1373-1406	Incorrect study type: Narrative review

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Study reference	Reason for exclusion
Stryjewski ME, Potgieter PD, Li YP et al (2012) TD-1792 versus vancomycin for treatment of complicated skin and skin structure infections. *Antimicrobial Agents and Chemotherapy* 56(11), 5476-5483	Incorrect population: Cellulitis data not reported separately
Stryjewski ME, Barriere SL, O'Riordan W et al (2012) Efficacy of telavancin in patients with specific types of complicated skin and skin structure infections. *The Journal of antimicrobial chemotherapy* 67(6), 1496-502	Incorrect study type: Not an SR or RCT
Sunderkotter C, Herrmann M, Jappe U (2006) Antimicrobial therapy in dermatology. *JDDG - Journal of the German Society of Dermatology* 4(1), 10-27	Incorrect study type: Not an SR or RCT
Sutherland M, Parent A (2017) Diagnosis and management of cellulitis: a dermatology perspective. *British journal of community nursing* 22(6), 272-275	Incorrect study type: Not an SR or RCT
Swartz M N (2004) Cellulitis. *New England Journal of Medicine* 350(9), 904-912	Incorrect study type: Not an SR or RCT
Tamma PD, Putcha N, Suh YD et al (2011) Does prolonged beta-lactam infusions improve clinical outcomes compared to intermittent infusions? A meta-analysis and systematic review of randomized, controlled trials. *BMC Infectious Diseases* 11, 181	Incorrect population: Not a cellulitis population
Thomas K, Crook A, Foster K et al (2012) Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the UK Dermatology Clinical Trials Network's PATCH II trial. *The British journal of dermatology* 166(1), 169-78	Incorrect study type: Conference abstract only
Thielen TL, Castle SS, Terry JE (2000) Anterior ocular infections: An overview of pathophysiology and treatment. Annals of *Pharmacotherapy* 34(2), 235-246	Incorrect study type: narrative review
Thomas K, Patchi U (2013) Results of the UK dermatology clinical trials network's PATCH I trial: an RCT of prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg in patients with recurrent disease. *Journal of investigative dermatology* 133, S166	Incorrect study type: Conference abstract only
Thomas K, Williams H, Foster K et al (2012) Prophylactic antibiotics for prevention of cellulitis (erysipelas) of the leg. *British journal of dermatology*. 167(2), e8-e9	RCT included in a prioritised systematic review
Thomas KS, Crook AM, Nunn AJ et al (2013) Penicillin to prevent recurrent leg cellulitis. *The New England journal of medicine* 368(18), 1695-703	RCT included in a prioritised systematic review
Thomas M (2014) Oral clindamycin compared with sequential intravenous and oral flucloxacillin in the treatment of cellulitis in adults a randomized, double-blind trial. *Infectious diseases in clinical practice* (baltimore, and md.) 22(6), 330-334	RCT included in a prioritised systematic review
Torok E, Somogyi T, Rutkai K et al (2004) Fusidic acid suspension twice daily: A new treatment schedule for skin and soft tissue infection in children, with improved tolerability. *Journal of Dermatological Treatment* 15(3), 158-163	Incorrect population: Not a cellulitis population
Tremblay S, Lau TTY, Ensom MHH (2013) Addition of rifampin to vancomycin for methicillin- resistant Staphylococcus aureus infections: What Is the evidence? *Annals of Pharmacotherapy* 47(7-8), 1045-1054	Incorrect population: Not a cellulitis population
Tsoulas C, Nathwani D (2015) Review of meta-analyses of vancomycin compared with new treatments for Gram-positive skin and soft-tissue infections: Are we any clearer? *International journal of antimicrobial agents* 46(1), 1-7	Incorrect population: Not a cellulitis population

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Study reference	Reason for exclusion
Tuon FF, Rocha JL, Formigoni-Pinto MR (2018) Pharmacological aspects and spectrum of action of ceftazidime-avibactam: a systematic review. *Infection* 46(2), 165-181	Incorrect population: Not a cellulitis population
Tuon FF, Rocha JL, Morales HM et al (2015) Modulation of inflammatory mediators during treatment of cellulitis with daptomycin or vancomycin/ oxacillin. *International journal of antimicrobial agents* 46(4), 476-478	Incorrect study type: Not an SR or RCT
Van HO, Wang K, Lee JJ et al (2017) Implications of Antibiotic Resistance for Patients' Recovery from Common Infections in the Community: A Systematic Review and Meta-analysis. *Clinical Infectious Diseases* 65(3), 371-382	Incorrect population: Cellulitis data not reported separately
Van Zuuren EJ, Fedorowicz Z, Alper B et al (2014) Penicillin to prevent recurrent leg cellulitis: A critical appraisal. *British Journal of Dermatology* 171(6), 1300-1303	Incorrect study type: Not an SR or RCT
Vardakas KZ, Mavros MN, Roussos N et al (2012) Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: Focus on the study design. *Mayo Clinic Proceedings* 87(4), 349-363	Incorrect population: Not a cellulitis population
Vidal L, Borok S, Gafter-Gvili A et al (2007) Aminoglycosides as a single antibiotic versus other (non-aminoglycosides) antibiotics for the treatment of patients with infection. *Cochrane Database of Systematic Reviews* (2), CD006485	Incorrect population: Not a cellulitis population
Vidal L, Gafter-Gvili A, Borok S et al (2007) Efficacy and safety of aminoglycoside monotherapy: Systematic review and meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy* 60(2), 247-257	Incorrect population: Not a cellulitis population
Wacha H, Forster H (2000) Comparison of quinupristin/dalfopristin with standard therapies for the treatment of complicated skin and soft tissue infections due to gram-positive pathogens: results of two open, randomized multicenter studies. Che*motherapie journal, and supplement* 9(19), 63-68	Incorrect study type: Study unobtainable
Wang Shou Zhen, Hu Jun Tao, Zhang Chi et al (2014) The safety and efficacy of daptomycin versus other antibiotics for skin and soft-tissue infections: a meta-analysis of randomised controlled trials. *BMJ open* 4(6), e004744	Incorrect population: Not a cellulitis population
Watkins RR, Lemonovich TL, File Jr (2012) An evidence-based review of linezolid for the treatment of methicillin-resistant Staphylococcus aureus (MRSA): Place in therapy. *Core Evidence* 7, 131-143	Incorrect study type: Not an SR or RCT
Watts P (2012) Preseptal and orbital cellulitis in children: A review. *Paediatrics and Child Health* 22(1), 1-8	Incorrect study type: Not an SR or RCT
Weigelt J, Itani K, Stevens D et al (2005) Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrobial agents and chemotherapy* 49(6), 2260-6	RCT included in a prioritised systematic review
Wesner AR, Brackbill ML, Coyle LL et al (2013) Prospective trial of a novel nomogram to achieve updated vancomycin trough concentrations. *Interdisciplinary Perspectives on Infectious Diseases* 2013, 839456	Incorrect population: Cellulitis data not reported separately
White B, Seaton RA (2011) Complicated skin and soft tissue infections: Literature review of evidence for and experience with daptomycin. *Infection and Drug Resistance* 4(1), 115-127	Incorrect study type: Not an SR or RCT
Williams H, Crook A, Mason J (2013) Penicillin to prevent recurrent leg cellulitis. *New England journal of medicine* 369(9), 881-882	Incorrect study type: Not an SR or RCT

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Study reference	Reason for exclusion
Wilcox MH, Corey GR, and Talbot GH et al (2010) CANVAS 2: the second Phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. *The Journal of antimicrobial chemotherapy* 65 Suppl 4, iv53-iv65	RCT included in a prioritised systematic review
Wilson SE (2001) Clinical trial results with linezolid, an oxazolidinone, in the treatment of soft tissue and postoperative gram-positive infections. *Surgical infections* 2(1), 25-35	Incorrect population: Not a cellulitis population
Wu G, Abraham T, Rapp J et al (2011) Daptomycin: evaluation of a high-dose treatment strategy. *International journal of antimicrobial agents* 38(3), 192-6	Incorrect population: Not a cellulitis population
Yang BH, Peng MY, Hou SJ et al (2009) Fluconazole-resistant Kodamaea ohmeri fungemia associated with cellulitis: Case report and review of the literature. *International Journal of Infectious Diseases* 13(6), e493-e497	Incorrect study type: Not an SR or RCT
Young M, Plosker GL (2001) Piperacillin/tazobactam: A pharmacoeconomic review of its use in moderate to severe bacterial infections. *PharmacoEconomics* 19(11), 1135-1175	Incorrect population: Not a cellulitis population
Yu T, Stockmann C, Balch AH et al (2014) Evolution of interventional vancomycin trials in light of new antibiotic development in the USA, 1999-2012. *International Journal of Antimicrobial Agents* 43(3), 215-222	Incorrect population: Not a cellulitis population
Yue J, Dong BR, Yang M et al (2016) Linezolid versus vancomycin for skin and soft tissue infections. *Cochrane Database of Systematic Reviews* (1),	Incorrect population: Cellulitis data not reported separately
Zar FA (2017) Adding trimethoprim-sulfamethoxazole to cephalexin did not increase clinical cure in uncomplicated cellulitis. *Annals of Internal Medicine* 167(8), JC40	Incorrect study type: Not an SR or RCT
Zavascki AP, Goldani LZ, Li J et al (2007) Polymyxin B for the treatment of multidrug-resistant pathogens: A critical review. *Journal of Antimicrobial Chemotherapy* 60(6), 1206-1215	Incorrect study type: Not an SR or RCT
Zeglaoui F, Dziri C, Mokhtar I et al (2004) Intramuscular bipenicillin vs. intravenous penicillin in the treatment of erysipelas in adults: randomized controlled study. Journal of the European Academy of Dermatology and Venereology: *JEADV* 18(4), 426-8	RCT included in a prioritised systematic review
Zervos M (2008) Treatment options for uncomplicated community-acquired skin and soft tissue infections caused by methicillin-resistant Staphylococcus aureus: oral antimicrobial agents. *Surgical infections* 9 Suppl 1, s29-34	Incorrect study type: narrative review
Zhanel GG, Schroeder C, Vercaigne L et al (2001) A critical review of oxazolidinones: An alternative or replacement for glycopeptides and streptogramins? *Canadian Journal of Infectious Diseases* 12(6), 379-390	Incorrect population: Cellulitis data not reported separately

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