ClinicalEvidence

Cellulitis and erysipelas

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ABSTRACT

INTRODUCTION: Cellulitis is a common problem, caused by spreading bacterial inflammation of the skin, with redness, pain, and lymphangitis. Up to 40% of affected people have systemic illness. Erysipelas is a form of cellulitis with marked superficial inflammation, typically affecting the lower limbs and the face. The most common pathogens in adults are streptococci and Staphylococcus aureus. Cellulitis and erysipelas can result in local necrosis and abscess formation. Around a quarter of affected people have more than one episode of cellulitis within 3 years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for cellulitis and erysipelas? What are the effects of treatments to prevent recurrence of cellulitis and erysipelas? We searched: Medline, Embase, The Cochrane Library and other important databases up to May 2007 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 14 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antibiotics, comparative effects of different antibiotic regimens, duration of antibiotics, and treatment of predisposing factors.

QUESTIONS

INTERVENTIONS

Key points

- Cellulitis is a common problem caused by spreading bacterial inflammation of the skin, with redness, pain, and lymphangitis. Up to 40% of people have systemic illness.

  Erysipelas is a form of cellulitis with marked superficial inflammation, typically affecting the lower limbs and the face.

  Risk factors include lymphoedema, leg ulcer, toe web intertrigo, and traumatic wounds.

  The most common pathogens in adults are streptococci and *Staphylococcus aureus*.

  Cellulitis and erysipelas can result in local necrosis and abscess formation. Around a quarter of people have more than one episode of cellulitis within 3 years.

- Antibiotics cure 50−100% of infections, but we don't know which antibiotic regimen is most successful.

  We don't know whether antibiotics are as effective when given orally as when given intravenously, or whether intramuscular administration is more effective than intravenous.

  A 5-day course of antibiotics may be as effective as a 10-day course at curing the infection and preventing early recurrence.

- Although there is consensus that treatment of predisposing factors can prevent recurrence of cellulitis or erysipelas, we found no studies that assessed the benefits of this approach.

DEFINITION

Cellulitis is a spreading bacterial infection of the dermis and subcutaneous tissues. It causes local signs of inflammation, such as warmth, erythema, pain, lymphangitis, and frequently systemic upset with fever and raised white blood cell count. **Erysipelas** is a form of cellulitis and is characterised by pronounced superficial inflammation. The term erysipelas is commonly used when the face is affected. The lower limbs are by far the most common sites affected by cellulitis and erysipelas, but any area, such as the ears, trunk, fingers, and toes, can be affected.

INCIDENCE/ PREVALENCE We found no validated recent data on the incidence of cellulitis or erysipelas worldwide. UK hospital incidence data reported 69,576 episodes of cellulitis and 516 episodes of erysipelas in 2004–2005. Cellulitis infections of the limb accounted for most of these infections (58,824 episodes). [1]

AETIOLOGY/ RISK FACTORS The most common infective organisms for cellulitis and erysipelas in adults are streptococci (particularly *Streptococcus pyogenes*) and *Staphylococcus aureus*. [2] In children, *Haemophilus influenzae* was a frequent cause before the introduction of the *Haemophilus influenzae* type B vaccination. Several risk factors for cellulitis and erysipelas have been identified in a case-control study (167 cases and 294 controls): lymphoedema (OR 71.2, 95% CI 5.6 to 908.0), leg ulcer (OR 62.5, 95% CI 7.0 to 556.0), toe web intertrigo (OR 13.9, 95% CI 7.2 to 27.0), and traumatic wounds (OR 10.7, 95% CI 4.8 to 23.8). [3]

PROGNOSIS Cellulitis can spread through the bloodstream and lymphatic system. A retrospective case study of people admitted to hospital with cellulitis found that systemic symptoms, such as fever and raised white blood cell count, were present in up to 42% of cases at presentation. [4] Lymphatic involvement can lead to obstruction and damage of the lymphatic system that predisposes to recurrent cellulitis. [5] Recurrence can occur rapidly, or after months or years. One prospective cohort study found that 29% of people with erysipelas had a recurrent episode within 3 years. [6] Local necrosis and abscess formation can also occur. [5] It is not known whether the prognosis of erysipelas differs from cellulitis. We found no evidence about factors that predict recurrence, or a better or worse outcome. We found no good evidence on the prognosis of untreated cellulitis.

AIMS OF INTERVENTION To reduce the severity and duration of infection; to relieve pain and systemic symptoms; to restore the skin to its premorbid state; to prevent recurrence; to minimise adverse effects of treatment.

OUTCOMES Duration and severity of symptoms (pain, swelling, erythema, and fever); clinical cure (defined as the absence of pain, swelling, and erythema); recurrence; adverse effects of treatment. We found no standard scales of severity in cellulitis or erysipelas.

METHODS *BMJ Clinical Evidence* search and appraisal May 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2007, Embase 1980 to May 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and National Institute for Health and Clinical Excellence (NICE). We also searched for retractions of studies included in this review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 8).

QUESTION What are the effects of treatments for cellulitis and erysipelas?

OPTION ANTIBIOTICS VERSUS PLACEBO OR VERSUS EACH OTHER

Cure rates

Ceftriaxone compared with flucloxacillin Intravenous ceftriaxone may be more effective at 4–30 days than intravenous flucloxacillin at increasing cure rates in people with moderate to severe cellulitis (very low-quality evidence).

Intravenous benzylpenicillin compared with intramuscular bipenicillin (a mixture of benzylpenicillin and procaine penicillin) Intravenous benzylpenicillin may be no more effective at 10 days than intramuscular bipenicillin at increasing treatment success rates (absence of erythema, oedema, and pain) or at reducing time to recovery (low-quality evidence).

Cefazolin plus oral probenecid compared with ceftriazone Intravenous cefazolin plus oral probenecid is no more effective at 6–7 days than ceftriazone at increasing clinical cure rates in people with cellulitis (moderate-quality evidence).

Penicillin compared with oral roxithromycin Intravenous and oral penicillin is no more effective at 30 days than oral roxithromycin at increasing clinical cure rates in people with erysipelas (moderate-quality evidence).

Oral azithromycin compared with oral erythromycin, or oral cloxacillin, or cefalexin Oral azithromycin is no more effective at at 4–11 days than oral erythromycin, oral cloxacillin, or cefalexin at increasing clinical cure rates in people with cellulitis (moderate-quality evidence).

Cefdinir compared with cefalexin Cefdinir may be no more effective at 7–16 days than cefalexin at increasing clinical cure rates in people with cellulitis (low-quality evidence).

Oral amoxicillin–clavulanate potassium compared with oral fleroxacin Oral amoxicillin–clavulanate potassium may be no more effective at 3–9 days than oral fleroxacin at increasing clinical cure rates in people with cellulitis or erysipelas (low-quality evidence).

Intravenous fleroxacin compared with intravenous ceftazidime Intravenous fleroxacin may be no more effective at 21 days than intravenous ceftazidime at increasing clinical cure rates in people with cellulitis (low-quality evidence).

Ampicillin/sulbactam compared with cefazolin Intravenous ampicillin/sulbactam may be no more effective at 10 days than intravenous cefazolin at increasing clinical cure rates in people with cellulitis (low-quality evidence).

Symptom severity
Intravenous flucloxacillin plus intravenous benzylpenicillin compared with intravenous flucloxacillin Intravenous flucloxacillin plus intravenous benzylpenicillin may be no more effective at 5 days than intravenous flucloxacillin at reducing temperature or participant-assessed improvement in people with lower-limb cellulitis (low-quality evidence).

Note
We found no direct information about whether antibiotics are better than no active treatment.

For GRADE evaluation of interventions for cellulitis and erysipelas, **see table, p 8 .**

Benefits: We found no systematic review.

Antibiotics versus placebo:
We found no RCTs of sufficient quality (see Methods).

Different antibiotics versus each other:
We found 11 RCTs comparing different antibiotic regimens in people with various skin infections (see table 1, p 7). [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] Four of the RCTs were conducted solely in people with moderate to severe cellulitis; [7] [8] [9] two RCTs were conducted solely in people with erysipelas; [10] [17] and the other six RCTs were conducted in people with a range of skin infections and provided subgroup analysis of people with cellulitis or erysipelas. [11] [12] [13] [14] [15] [16] Nine of the RCTs and subgroup analyses found no significant difference between different antibiotics in clinical cure after 4–30 days. [8] [10] [11] [12] [13] [14] [15] [16] [17] However, most of the RCTs included only small numbers of people with cellulitis or erysipelas, and were designed to test equivalence rather than detect a clinically important difference in cure rates between antibiotics. One of the RCTs conducted solely in people with cellulitis (58 people with moderate to severe cellulitis) found that intravenous ceftriaxone significantly increased clinical cure after 4–6 days compared with intravenous flucloxacillin. [7] The results of this study should be treated with caution because only 45 people (78%) completed the study, and it would not seem that an intention to treat analysis was performed. [7] A second RCT in people with lower-limb cellulitis, compared intravenous flucloxacillin plus intravenous benzylpenicillin versus intravenous flucloxacillin alone. [9] It did not report on clinical cure, but found no significant difference between flucloxacillin plus benzylpenicillin and flucloxacillin alone in temperature reduction, or in participant assessed improvement. Analysis was not by intention to treat. A third RCT (112 adults hospitalised with erysipelas of the leg) found no significant difference in treatment success (defined as absence of erythema, oedema, pain, and a normal temperature) at 10 days or time to recovery between intravenous benzylpenicillin and intramuscular bipenicillin (a mixture of benzylpenicillin and procaine penicillin). [17]

Harms: We found no systematic review.

Antibiotics versus placebo:
We found no RCTs of sufficient quality (see methods).

Different antibiotics versus each other:
The RCTs found no evidence of a difference in rates of adverse events with different antibiotic regimens. The RCT comparing flucloxacillin versus ceftriaxone (58 people with moderate to severe

cellulitis) found no significant difference in the proportion of people experiencing adverse effects, including diarrhoea, nausea and vomiting, abdominal pain, and vaginal candidiasis (6/22 [27%] with flucloxacillin *v* 3/22 [14%] with ceftriaxone; RR 2.00, 95% CI 0.57 to 7.00). [7] The RCT comparing cefazolin plus probenecid versus ceftriaxone plus placebo (134 people with moderate to severe cellulitis) found no significant difference in the proportion of people who experienced adverse effects, including nausea and vomiting, diarrhoea, headache, and dizziness (14/67 [21%] with cefazolin plus probenecid *v* 7/67 [10%] with ceftriaxone plus placebo; RR 2.00, 95% CI 0.86 to 4.64). [8] The RCT comparing penicillin versus roxithromycin (69 people with erysipelas) found no significant difference in the proportion of people experiencing drug-related rashes (2/38 [5%] with penicillin *v* 0/31 [0%] with roxithromycin). [10] The RCT comparing flucloxacillin plus benzylpenicillin versus flucloxacillin alone (81 people with lower-limb cellulitis) found no treatment-related adverse events. [9] The RCTs comparing different antibiotics in a variety of skin infections gave no discrete information about adverse effects in people with cellulitis. [11] [12] [13] [14] [15] [16] The RCT comparing intravenous benzyl penicillin versus intramuscular bipenicillin reported that complications were more common with intravenous benzylpenicillin than with intramuscular bipenicillin (local complications including leg abscesses: 9% with intravenous benzylpenicillin *v* 7% with intramuscular bipenicillin; absolute numbers not reported; inflammation of veins related to route in injection: 26% with intravenous benzylpenicillin *v* 0% with intramuscular bipenicillin; absolute numbers not reported; P = 0.00005). [17]

Comment: None.

OPTION DIFFERENT ROUTES OF ADMINISTRATION OF ANTIBIOTICS

Cure rates

Oral compared with intravenous antibiotics Oral pencillin may have similar rates of clinical efficacy to intravenous penicillin in people with erysipelas (very low-quality evidence).

Note

We found no clinically important results comparing oral, intravenous, or intramuscular routes of administration of antibiotics in the treatment of people with cellulitis or erysipelas.

For GRADE evaluation of interventions for cellulitis and erysipelas, see table, p 8 .

Benefits:

Oral versus intravenous antibiotics:
We found no RCTs of sufficient quality. We found one small quasi-randomised trial (73 people with erysipelas in hospital with a body temperature of more than 38.5 °C, but excluding people with clinical signs of septicaemia; alternate allocation design) comparing oral versus intravenous penicillin. It reported no difference in clinical efficacy between oral and intravenous penicillin, which was assessed by indirect measures such as temperature fall, length of hospital stay, and absence from work. [18] It was difficult to reach a conclusion about relapse rates from the data provided.

Oral versus intramuscular antibiotics:
We found no systematic reviews or RCTs.

Intravenous versus intramuscular antibiotics:
We found no systematic reviews or RCTs.

Harms:

Oral versus intravenous antibiotics:
The small quasi-randomised trial (73 people with erysipelas; see benefits above) comparing oral versus intravenous penicillin reported adverse events in 15 people taking oral penicillin (4 with rash, 7 with diarrhoea, 4 with abscess) and in 10 people taking intravenous penicillin (2 with rash, 4 with diarrhoea, 4 with cannula phlebitis). [18]

Oral versus intramuscular antibiotics:
We found no RCTs.

Intravenous versus intramuscular antibiotics:
We found no RCTs.

Comment: None.

OPTION DURATION OF ANTIBIOTICS

Cure rates

10 days' treatment compared with 5 days' treatment Ten days of levofloxacin treatment is no more effective at increasing clinical cure rates at 14 days (without recurrence at 28 days) than 5 days of treatment with levofloxacin in people with uncomplicated cellulitis (moderate-quality evidence).

For GRADE evaluation of interventions for cellulitis and erysipelas, **see table, p 8 .**

Benefits: **Different duration of antibiotics:**
We found one RCT (87 people with uncomplicated cellulitis, showing improvement after 5 days of levofloxacin treatment) comparing 10 days of levofloxacin treatment versus 5 days of levofloxacin treatment plus 5 days of placebo. [19] It found no significant difference between treatments in clinical cure rates at 14 days without recurrence at 28 days (42/43 [98%] with 10 days of levofloxacin *v* 43/44 [98%] with 5 days of levofloxacin; P less than 0.05). [19] Most people took levofloxacin orally.

Harms: **Different duration of antibiotics:**
The RCT comparing 10 days of levofloxacin treatment versus 5 days of levofloxacin treatment plus 5 days of placebo reported no serious adverse events. However, 3/121 [3%] people enrolled into the study before randomisation stopped taking levofloxacin because of adverse effects (2/121 [2%] with gastrointestinal intolerance, 1/121 [1%] with rash; significance not reported). [19]

Comment: None.

QUESTION What are the effects of treatments to prevent recurrence of cellulitis and erysipelas?

OPTION ANTIBIOTICS (PROPHYLACTIC)

Recurrence rates
Compared with no treatment Antibiotic prophylaxis may be more effective at 15–18 months than no treatment at preventing recurrence of cellulitis or erysipelas infections (low-quality evidence).

For GRADE evaluation of interventions for cellulitis and erysipelas, **see table, p 8 .**

Benefits: We found two RCTs, which compared long-term prophylactic treatment with antibiotics versus no treatment for the prevention of recurrent cellulitis. [20] [21] The first RCT compared erythromycin (250 mg twice daily for 18 months) versus no treatment in people who had two or more episodes of cellulitis or erysipelas in the previous year. [20] It found that prophylactic antibiotic treatment significantly reduced recurrence compared with no treatment at 18 months (32 people; AR: 0/16 [0%] with antibiotic *v* 8/16 [50%] with no treatment; P less than 0.001). The second RCT compared prophylaxis with penicillin V (1–4 g twice daily based on weight) or erythromycin if allergic (0.25–1.25 g twice daily based on weight) versus no treatment in people with recurrent erysipelas who also had major predisposing factors including venous insufficiency, lymphoedema, or both. [21] It found fewer recurrences with prophylactic antibiotic treatment compared with no treatment after a median follow-up of 15 months, but this difference did not reach significance (40 people; AR: 2/20 [10%] with antibiotics *v* 8/20 [40%] with no treatment; P = 0.06). This RCT may have been underpowered to detect a clinically important difference between groups.

Harms: The first RCT found that three people (19%) taking erythromycin experienced nausea and abdominal pain, and were switched to penicillin V. [20] The second RCT found that two people (10%) taking penicillin prophylaxis discontinued treatment because of diarrhoea or nausea. [21]

Comment: **Clinical guide:**
We found limited evidence that prophylactic antibiotics may reduce future attacks of cellulitis or erysipelas in people with previous episodes. There is insufficient evidence about which people are more likely to benefit, or which antibiotics, doses, and durations of treatment are most likely to be effective.

OPTION TREATMENT OF PREDISPOSING FACTORS

We found no direct information about the effects of treating predisposing factors to prevent recurrence of cellulitis or erysipelas.

For GRADE evaluation of interventions for cellulitis and erysipelas, **see table, p 8 .**

Benefits: We found no systematic review or RCTs of sufficient quality about the effects of treating predisposing factors to prevent recurrence of cellulitis or erysipelas.

Harms: We found no RCTs.

Comment: Although there is a consensus that successful treatment of predisposing factors, such as lymphoedema, leg ulcers, toe web intertrigo, and traumatic wounds, reduces the risk of developing cellulitis or erysipelas (see aetiology), we found no RCTs or observational studies to support or refute this.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antibiotic versus placebo or versus each other One RCT added, which found no significant difference between rates of cure or time to recovery between intravenous benzylpenicillin and intramuscular bipenicillin, but found higher rates of local complications in the intravenous benzyl penicillin group; [17] categorisation unchanged (Unknown effectiveness).

REFERENCES

1. Hospital Episode Statistics. Available online at http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=203 (last accessed 4 December 2006).
2. Bernard P, Bedane C, Mounier M, et al. Streptococcal cause of erysipelas and cellulitis in adults. *Arch Dermatol* 1989;125:779–782.[PubMed]
3. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. *BMJ* 1999;318:1591–1594.[PubMed]
4. Aly AA, Roberts NM, Seipol K, et al. Case survey of management of cellulitis in a tertiary teaching hospital. *Med J Aust* 1996;165:553–556.[PubMed]
5. Burns ST, Breathnach SM, Cox, N, et al., eds. Rooks textbook of dermatology, 7th ed. *Oxford: Blackwell Scientific Publications*, 2004.
6. Jorup-Ronstrom C, Britton S. Recurrent erysipelas: predisposing factors and costs, of prophylaxis. *Infection* 1987;15:105–106.[PubMed]
7. Vinen J, Hudson B, Chan B, et al. A randomized comparative study of once-daily ceftriaxone and 6-hourly flucloxacillin in the treatment of moderate to severe cellulitis. Clinical efficacy, safety and pharmacoeconomic implications. *Clin Drug Invest* 1996;12:221–225.
8. Grayson ML, McDonald M, Gibson K, et al. Once-daily intravenous cefazolin plus oral probenecid is equivalent to once-daily ceftriaxone plus oral placebo for the treatment of moderate-to-severe cellulitis in adults. *Clin Infect Dis* 2002;34:1440–1448.[PubMed]
9. Leman P, Mukherjee D. Flucloxacillin alone or combined with benzylpenicillin to treat lower limb cellulites: a randomised controlled trial. *Emerg Med J* 2005;22:342–346.[PubMed]
10. Bernard P, Plantin P, Roger H, et al. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. *Br J Dermatol* 1992;127:155–159.[PubMed]
11. Daniel R, Austad J, Debersaques J, et al. Azithromycin, erythromycin and cloxacillin in the treatment of infections of skin and associated soft tissues. *J Int Med Res* 1991;19:433–445.[PubMed]
12. Kiani R. Double-blind, double-dummy comparison of azithromycin and cephalexin in the treatment of skin and skin structure infections. *Eur J Clin Microbiol Infect Dis* 1991;10:880–884.[PubMed]
13. Tack KJ, Littlejohn TW, Mailloux G, et al. Cefdinir versus cephalexin for the treatment of skin and skin-structure infections. *Clin Ther* 1998;20:244–255.[PubMed]
14. Tassler H. Comparative efficacy and safety of oral fleroxacin and amoxicillin/clavulanate potassium in skin and soft tissue infections. *Am J Med* 1993;94:159S–165S.
15. Parish LC, Jungkind DL. Systemic anti-microbial therapy for skin and skin structure infections: comparison of fleroxacin and ceftazidime. *Am J Med* 1993;94:166S–173S.
16. Chan JC. Ampicillin-sulbactam versus cefazolin or cefoxitin in the treatment of skin and skin-structure infections of bacterial etiology. *Adv Ther* 1995;12:139–146.[PubMed]
17. Zeglaoui F, Dziri C, Mokhtar I, et al. Intramuscular bipenicillin vs. intravenous penicillin in the treatment of erysipelas in adults: randomized controlled study. *J Eur Acad Dermatol Venereol* 2004;18:426–428
18. Jorup-Ronstrom C, Britton A, Gavlevik K, et al. The course, costs and complications of oral versus intravenous penicillin therapy of erysipelas. *Infection* 1984;12:390–394.[PubMed]
19. Hepburn MJ, Skidmore PJ, Starnes WF. Comparison of short-course (5 days) and standard (10 days) treatment for uncomplicated cellulitis. *Arch Intern Med* 2004;164:1669–1674.[PubMed]
20. Kremer M, Zuckerman R, Avraham K, et al. Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections. *J Infect* 1991;22:37–40.[PubMed]
21. Sjöblom AC, Eriksson B, Jorup-Ronstrom C, et al. Antibiotic prophylaxis in recurrent erysipelas. *Infection* 1993;21:390–393.[PubMed]

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Competing interests: AM declares that he has no competing interests.

TABLE 1 **Different antibiotic regimens: results of comparative RCTs.**

Ref	Regimen	Participants	Clinical cure (significance)
[7]	iv ceftriaxone 1 g od for 7 days *v* iv flucloxacillin 1 g qds for a mean of 9 days	58 people with cellulitis	21/23 [92%] with ceftriaxone *v* 14/22 [64%] with flucloxacillin after 4–6 days; RR 1.43, 95% CI 1.02 to 2.02; NNT 4, 95% CI 2 to 17
[8]	iv cefazolin 2 g od plus oral probenecid 1 g od *v* ceftriaxone 1 g od plus placebo for median 6–7 days	132 people with cellulitis	51/67 [76%] with cefazolin plus probenecid *v* 55/67 [82%] with ceftriaxone plus placebo after 6–7 days; RR 0.93, 95% CI 0.78 to 1.10
[9]	iv flucloxacillin 1 g qds plus iv benzylpenicillin 1.2 g *v* iv flucloxacillin 1 g qds alone for 5 days (outcomes analysed after 24 hours)	81 people with cellulitis	Clinical cure rates not reported. Mean temperature reduction: 0.36 °C with flucloxacillin plus benzylpenicillin *v* 0.42 °C with flucloxacillin alone; mean difference: –0.07 °C, 95% CI –0.76 °C to +0.62 °C; P = 0.84 Participant assessed improvement (scale of "improved", "unchanged", or "worse"): 25/34 [74%] improved, 9/34 [26%] unchanged, 0/34 [0%] worse with flucloxacillin plus benzylpenicillin *v* 21/31 [68%] improved, 9/34 [26%] unchanged, 0/34 [0%] worse with flucloxacillin alone; P = 0.32
[10]	iv penicillin 2.5 MU 8 times daily followed by 6 MU orally od for mean 13 days *v* oral roxithromycin 150 mg bd for mean 13 days	69 people with erysipelas	29/38 [76%] with penicillin *v* 26/31 [84%] with roxithromycin after 30 days; RR 0.91, 95% CI 0.72 to 1.15
[11]	Oral azithromycin total dose 1.5 g over 5 days *v* oral erythromycin 500 mg qds for 7 days	Subgroup analysis in 128 people with cellulitis	52/72 [72%] with azithromycin *v* 37/50 [74%] with erythromycin after 4–11 days; RR 0.97, 95% CI 0.78 to 1.21
[11]	Oral azithromycin total dose 1.5 g over 5 days *v* oral cloxacillin 500 mg qds for 7 days	Subgroup analysis in 62 people with cellulitis	27/41 [66%] with azithromycin *v* 11/21 [52%] with cloxacillin after 4–9 days; RR 1.26, 95% CI 0.79 to 2.00
[12]	Oral azithromycin total dose 750 mg over 5 days *v* cefalexin 500 mg bd for 10 days	Subgroup analysis in 95 people with suspected cellulitis, 47 of whom had microbiologically proved cellulitis	12/24 [50%] with azithromycin *v* 14/23 [61%] with cefalexin after 11 days; RR 0.82, 95% CI 0.49 to 1.38
[13]	Cefdinir 300 mg bd for 10 days *v* cefalexin 500 mg qds for 10 days	Subgroup analysis in 78 people with suspected cellulitis, 34 of whom had microbiologically proved cellulitis	In the 34 people with microbiologically proved cellulitis: 13/17 [76%] with cefdinir *v* 14/17 [82%] with cefalexin after 7–16 days; RR 0.93, 95% CI 0.66 to 1.31
[14]	Oral amoxicillin–clavulanate potassium 125–500 mg tds *v* oral fleroxacin 400 mg od	Subgroup analysis in 11 people with cellulitis or erysipelas	7/7 [100%] with co-amoxiclav *v* 4/4 [100%] with fleroxacin after 3–9 days
[15]	iv fleroxacin 400 mg od *v* iv ceftazidime 0.52 g bd/tds	Subgroup analysis in 39 people with cellulitis	26/27 [96%] with fleroxacin *v* 9/12 [75%] with ceftazidime after 21 days; RR 1.28, 95% CI 0.92 to 1.78
[16]	iv ampicillin/sulbactam 0.5–1 g qds *v* iv cefazolin 500 mg qds for 6–7 days	Subgroup analysis in 20 people with cellulitis	8/8 [100%] with ampicillin/sulbactam *v* 9/12 [75%] with cefazolin after 10 days
[17]	iv benzylpenicillin 4 MU six times daily *v* intramuscular bipenicillin (benzylpenicillin plus procaine penicillin) 2 MU twice daily for 10 days	112 adults hospitalised with erysepalas of the leg	Treatment success: 80% with intravenous benzylpenicillin *v* 86% with intramuscular bipenicillin at 10 days; absolute numbers not reported; P = 0.40 Mean time to treatment success: 6.3 days with intravenous benzylpenicillin *v* 6.5 days with intramuscular bipenicillin; P = 0.75

bd, twice daily; iv, intravenous; od, once daily; qds, four times daily; ref, reference; tds, three times daily.

TABLE **GRADE evaluation of interventions for cellulitis and erysipelas**

Important outcomes	**Cure rates, relapse rates, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consis-tency**	**Direct-ness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for cellulitis and erysipelas?									
1 (58) [18]	Cure rates	Ceftriaxone *v* flucloxacillin	4	–3	0	0	0	Very low	Quality points deducted for sparse data, no intention-to-treat analysis, and poor follow-up
1 (81) [8]	Symptom severity	Intravenous flucloxacillin plus intravenous benzylpenicillin *v* intravenous flucloxacillin	4	–2	0	0	0	Low	Quality points deducted for sparse data and no intention-to-treat analysis.
1 (112) [16]	Clinical cure	Intravenous benzylpenicillin *v* intramuscular bipenicillin	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (132) [7]	Clinical cure	Cefazolin plus oral probenecid *v* ceftriazone	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (69) [9]	Clinical cure	Penicillin *v* roxithromycin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 subgroup analysis (237) [10] [11]	Clinical cure	Oral azithromycin *v* oral erythromycin/oral cloxacillin/cefalexin	4	–1	0	0	0	Moderate	Quality point deducted for subgroup analysis of RCT
1 subgroup analysis (34) [12]	Clinical cure	Cefdinir *v* cefalexin	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis of RCT
1 subgroup analysis (11) [13]	Clinical cure	Oral amoxicillin–clavulanate potassium *v* oral fleroxacin	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis of RCT
1 subgroup analysis (39) [14]	Clinical cure	Fleroxacin *v* ceftazidime	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis of RCT
1 subgroup analysis (20) [15]	Clinical cure	Ampicillin/sulbactam *v* cefazolin	4	–2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis of RCT
1 (73) [19]	Clinical efficacy	Oral *v* intravenous penicillin	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, quasi-randomisation, and uncertainty about methods of measuring outcomes
1 (87) [20]	Clinical cure rates	Different durations of antibiotics *v* each other	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatments to prevent recurrence of cellulitis and erysipelas?									
2 (72) [21]	Recurrence rates	Antibiotics *v* no treatment	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of predisposing conditions

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion.
Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio