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#### [Intervention Review]

## Interventions for the prevention of recurrent erysipelas and cellulitis

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#### ABSTRACT

#### Background

Erysipelas and cellulitis (hereafter referred to as 'cellulitis') are common bacterial skin infections usually affecting the lower extremities. Despite their burden of morbidity, the evidence for different prevention strategies is unclear.

#### Objectives

To assess the beneficial and adverse effects of antibiotic prophylaxis or other prophylactic interventions for the prevention of recurrent episodes of cellulitis in adults aged over 16.

#### Search methods

We searched the following databases up to June 2016: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and LILACS. We also searched five trials registry databases, and checked reference lists of included studies and reviews for further references to relevant randomised controlled trials (RCTs). We searched two sets of dermatology conference proceedings, and BIOSIS Previews.

#### **Selection criteria**

Randomised controlled trials evaluating any therapy for the prevention of recurrent cellulitis.

#### Data collection and analysis

Two authors independently carried out study selection, data extraction, assessment of risks of bias, and analyses. Our primary prespecified outcome was recurrence of cellulitis when on treatment and after treatment. Our secondary outcomes included incidence rate, time to next episode, hospitalisation, quality of life, development of resistance to antibiotics, adverse reactions and mortality.

#### **Main results**

We included six trials, with a total of 573 evaluable participants, who were aged on average between 50 and 70. There were few previous episodes of cellulitis in those recruited to the trials, ranging between one and four episodes per study.

Five of the six included trials assessed prevention with antibiotics in participants with cellulitis of the legs, and one assessed selenium in participants with cellulitis of the arms. Among the studies assessing antibiotics, one study evaluated oral erythromycin (n = 32) and four

Interventions for the prevention of recurrent erysipelas and cellulitis (Review) Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. studies assessed penicillin (n = 481). Treatment duration varied from six to 18 months, and two studies continued to follow up participants after discontinuation of prophylaxis, with a follow-up period of up to one and a half to two years. Four studies were single-centre, and two were multicentre; they were conducted in five countries: the UK, Sweden, Tunisia, Israel, and Austria.

Based on five trials, antibiotic prophylaxis (at the end of the treatment phase ('on prophylaxis')) decreased the risk of cellulitis recurrence by 69%, compared to no treatment or placebo (risk ratio (RR) 0.31, 95% confidence interval (CI) 0.13 to 0.72; n = 513; P = 0.007), number needed to treat for an additional beneficial outcome (NNTB) six, (95% CI 5 to 15), and we rated the certainty of evidence for this outcome as moderate.

Under prophylactic treatment and compared to no treatment or placebo, antibiotic prophylaxis reduced the incidence rate of cellulitis by 56% (RR 0.44, 95% CI 0.22 to 0.89; four studies; n = 473; P value = 0.02; moderate-certainty evidence) and significantly decreased the rate until the next episode of cellulitis (hazard ratio (HR) 0.51, 95% CI 0.34 to 0.78; three studies; n = 437; P = 0.002; moderate-certainty evidence).

The protective effects of antibiotic did not last after prophylaxis had been stopped ('post-prophylaxis') for risk of cellulitis recurrence (RR 0.88, 95% CI 0.59 to 1.31; two studies; n = 287; P = 0.52), incidence rate of cellulitis (RR 0.94, 95% CI 0.65 to 1.36; two studies; n = 287; P = 0.74), and rate until next episode of cellulitis (HR 0.78, 95% CI 0.39 to 1.56; two studies; n = 287). Evidence was of low certainty.

Effects are relevant mainly for people after at least two episodes of leg cellulitis occurring within a period up to three years.

We found no significant differences in adverse effects or hospitalisation between antibiotic and no treatment or placebo; for adverse effects: RR 0.87, 95% CI 0.58 to 1.30; four studies; n = 469; P = 0.48; for hospitalisation: RR 0.77, 95% CI 0.37 to 1.57; three studies; n = 429; P = 0.47, with certainty of evidence rated low for these outcomes. The existing data did not allow us to fully explore its impact on length of hospital stay.

The common adverse reactions were gastrointestinal symptoms, mainly nausea and diarrhoea; rash (severe cutaneous adverse reactions were not reported); and thrush. Three studies reported adverse effects that led to discontinuation of the assigned therapy. In one study (erythromycin), three participants reported abdominal pain and nausea, so their treatment was changed to penicillin. In another study, two participants treated with penicillin withdrew from treatment due to diarrhoea or nausea. In one study, around 10% of participants stopped treatment due to pain at the injection site (the active treatment group was given intramuscular injections of benzathine penicillin).

None of the included studies assessed the development of antimicrobial resistance or quality-of-life measures.

With regard to the risks of bias, two included studies were at low risk of bias and we judged three others as being at high risk of bias, mainly due to lack of blinding.

#### Authors' conclusions

In terms of recurrence, incidence, and time to next episode, antibiotic is probably an effective preventive treatment for recurrent cellulitis of the lower limbs in those under prophylactic treatment, compared with placebo or no treatment (moderate-certainty evidence). However, these preventive effects of antibiotics appear to diminish after they are discontinued (low-certainty evidence). Treatment with antibiotic does not trigger any serious adverse events, and those associated are minor, such as nausea and rash (low-certainty evidence). The evidence is limited to people with at least two past episodes of leg cellulitis within a time frame of up to three years, and none of the studies investigated other common interventions such as lymphoedema reduction methods or proper skin care. Larger, high-quality studies are warranted, including long-term follow-up and other prophylactic measures.

### PLAIN LANGUAGE SUMMARY

#### Preventive treatments for repeated episodes of cellulitis and erysipelas

#### Background

Cellulitis and erysipelas are both bacterial infections of the skin that most commonly affect the leg. Erysipelas affects the upper layers of the skin, and cellulitis affects its deeper parts, but in practice it is often hard to tell the difference between them, so we consider them together for this review (and refer to them as 'cellulitis'). Up to 50% of people with cellulitis experience repeated episodes. Despite the burden of this condition, there is a lack of high-certainty, evidence-based information about the desirable treatment for the prevention of recurrent cellulitis.

#### **Review question**

What are the best available treatments to prevent repeated episodes of cellulitis in adults aged over 16 years compared to no treatment, placebo, another intervention, or the same intervention with a different plan of treatment, and what are their side effects?

#### Study characteristics

We searched relevant databases and registers up to June 2016. We identified six trials, with 573 participants, who had an average age between 50 and 70. Both genders were included, but there were nearly twice as many women. Five trials used antibiotic treatment (four

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penicillin and one erythromycin), which was compared to either no treatment or placebo, and one trial used selenium compared to physiological salt solution. Treatments lasted from six to 18 months.

The most common setting was the hospital, and two studies were multicentre. The studies were conducted in the UK, Sweden, Tunisia, Israel, and Austria. There was a small number of previous episodes of cellulitis in those recruited to the trials, ranging between one and four episodes in each study. The antibiotic trials assessed prevention with antibiotics in people with cellulitis of the legs, and the selenium trial assessed people with cellulitis of the arms.

#### **Key results**

Our main outcome was prevention of repeated episodes of cellulitis. Our other outcomes included the number of repeated attacks of cellulitis, time to next attack, hospitalisation, quality of life, development of antibiotic resistance, adverse reactions and death.

Combining the results of all five trials that used antibiotics, we found moderate-certainty evidence that for those people under preventative treatment, antibiotic treatment in general, and penicillin in particular, is probably both effective and safe for the prevention of repeated episodes of leg cellulitis when compared with no treatment or placebo.

The analyses showed that, compared with no treatment or placebo, taking antibiotics decreased the risk of future episodes by 69%, reduced their number by more than 50%, and significantly reduced the rate until the next attack (moderate-certainty evidence). However, we found low-certainty evidence that the protective effect of antibiotics for these three outcomes tailed off over time after treatment had been stopped. In addition, the beneficial effect of antibiotics was relevant for people with at least two past episodes of cellulitis within a time frame of up to three years.

We found low-certainty evidence that there is no difference between antibiotics and no treatment/placebo for side effects and hospitalisation. The evidence did not allow for full exploration of the treatment's effect on length of hospital stay.

No serious adverse effects were reported, and common side effects included diarrhoea, nausea, rash (severe skin adverse reactions were not reported) and thrush. In three studies, adverse effects caused those taking part to stop taking the antibiotic. Three people taking erythromycin had abdominal pain and nausea, causing them to stop taking the treatment and to take penicillin instead. In one study, two people withdrew from treatment with penicillin because of diarrhoea or nausea. In another study, because of pain at the site of injection, around 10% of those taking part stopped taking intramuscular injections of benzathine penicillin.

None of the included studies measured quality of life or the development of antibiotic resistance.

#### **Certainty of evidence**

Evidence for the effects of antibiotics compared with no treatment or placebo on the recurrence, incidence rate and time to next episode of cellulitis under preventive treatment was of moderate certainty, and was limited by the small number of participants and events. Evidence for the remaining reported outcomes was of low certainty for the same reasons, as well as imprecise results.