Antibiotic prophylaxis for preventing recurrent cellulitis: A systematic review and meta-analysis

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Summary Importance: A significant proportion of patients who have had a first episode of erysipelas or uncomplicated cellulitis will subsequently develop a recurrence. There is disagreement about how effective antibiotic prophylaxis is for preventing recurrent cellulitis. Objective: To determine if antibiotic prophylaxis is effective in preventing recurrent cellulitis compared to no prophylaxis using a systematic review and meta-analysis. Data sources: Studies in any language identified by searching Medline, EMBASE, Cochrane Library, CINAHL, TRIP database, clinical practice guidelines websites, and ongoing trials databases up to 31st August 2012. Search terms included cellulitis, erysipelas, controlled clinical trial, randomized, placebo, clinical trials, randomly, and trial. Study selection: Only controlled trials comparing antibiotic prophylaxis to no antibiotic prophylaxis in patients age 16 years and above, and after 1 or more episodes of cellulitis, were included. Data extraction and synthesis: Independent extraction of articles was done by 2 investigators using predefined data extraction templates, including study quality indicators. PROSPERO registration number: CRD42012002528. Meta-analyses were done using random-effects models.

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Main outcomes and measures: The primary outcome was the number of patients with a recurrence of cellulitis. Secondary outcomes were (1) the time to next episode of recurrence, (2) quality of life measures, and (3) adverse events (e.g. allergic reactions, nausea).

Results: Five randomized controlled trials (n = 535), with 260 patients in the intervention arm and 275 in the comparator group met our inclusion criteria. 44 patients (8%) in the antibiotic prophylaxis group and 97 patients (18%) in the comparator group had an episode of cellulitis. Antibiotic prophylaxis significantly reduced the number of patients having recurrent cellulitis, with a risk ratio (RR) of 0.46 (95% CI 0.26–0.79). None of the studies reported severe adverse effects to antibiotics. There was methodological heterogeneity amongst the studies in terms of types of antibiotic used, delivery modes, number of recurrences of cellulitis at study entry, and study quality.

Conclusion and relevance: Antibiotic prophylaxis can prevent recurrent cellulitis. Future research should aim to identify the ideal type, dosage, and duration of antibiotics for prophylaxis, as well as to identify the group of patients who will benefit most from antibiotic prophylaxis.

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Introduction

Cellulitis of the lower extremities is an acute, painful and potentially serious infection of the skin and subcutaneous tissue associated with significant morbidity and healthcare costs. Erysipelas or uncomplicated cellulitis refers to non-suppurative, acute and spreading skin infection. Specifically, erysipelas tends to be more superficial and has prominent lymphatic involvement; while cellulitis extends deeper and involves subcutaneous tissues. We will use the terms erysipelas and cellulitis interchangeably in this paper. Risk factors for developing cellulitis of the leg include prior history of cellulitis, lymphoedema, toe web maceration, obesity and diabetes.

Cellulitis is typically caused by b-haemolytic streptococci of group A, less often by group B, C, or G streptococci or Staphylococcus aureus. Prior history of cellulitis is strongly associated with acute cellulitis.

An attack of acute cellulitis may lead to a vicious circle of impaired lymphatic function leading to increased susceptibility to further recurrences of cellulitis.

However, the causal association is not clear.

In 2003, 428,274 patients were hospitalized in the US with a principle diagnosis of cellulitis, with cellulitis being responsible for 1.1% of all hospital discharges. Sixteen to 30% of patients who have had a first episode of erysipelas or uncomplicated cellulitis will subsequently develop a recurrence.

There is disagreement about how effective antibiotic prophylaxis is for preventing recurrent cellulitis. We undertook a systematic review and meta-analysis to evaluate the level and quality of available evidence regarding the efficacy and reported adverse effects of antibiotic prophylaxis against recurrent cellulitis.

Methods

This systematic review protocol was registered with PROSPERO on 11th September 2012 with registration number CRD42012002528.

Inclusion criteria

The defined cellulitis population included patients aged 16 years and above, and after one or more episodes of cellulitis. Participants with cellulitis secondary to filarial lymphoedema were excluded. We use cellulitis and erysipelas interchangeably in this paper.

The intervention was any antibiotic prophylaxis used for recurrent cellulitis. Any form of delivery, dose and duration of antibiotics was considered. The control group was patients without prophylactic antibiotics. Other forms of standard care (e.g. local skin care) were allowed in the control group.

The primary outcome was the number of patients with a recurrence of cellulitis. This outcome was recorded as (1) the number of patients with cellulitis, and (2) the number of episodes per patient. Also noted where possible was the total number of recurrences within a time period. Recurrence must have been diagnosed by a physician.

Secondary outcomes were (1) the time to next episode of recurrence, (2) quality of life measures, and (3) adverse events (e.g. allergic reactions, nausea). For these outcomes, there was no limit to the follow-up period after completion of antibiotics, but any events occurring during the taking of the antibiotic treatment was particularly noted.

Search strategy

Two authors (OCC, HCK) searched and scanned the electronic databases and other sources of studies. They developed and checked the search strategies used for each database with each other. The search strategies were ‘translated’ for each database where needed.

A search was done in the following databases: Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), CDSR, HTA, DARE, NHS EED), MEDLINE via OVID SP, EMBASE, CINAHL via EBSCOhost, guidelines websites (UK NICE, US National Guidelines Clearinghouse, Scotland SIGN), TRIP database, and ongoing trials databases (Clinicaltrials.gov; World Health Organization...
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We did not impose a language restriction to our searches. The date of last search was 31st August 2012. The authors also contacted experts in this field to enquire if there were upcoming related trials, and they contacted the Cochran Skin Group editorial centre, as well as the authors of the PATCH I and II trials. The search string used in Medline via OVID SP is included in the Appendices as an example.

This systematic review specifically sought out randomized controlled trials (RCTs), systematic reviews (SRs) and evidence based clinical practice guidelines (EBPGs). Two authors independently reviewed the articles and decided on the inclusion of studies, having read the methods section of each study and applied the stated P (Participant), I (Intervention), C (Control), and O (Outcome) criteria. Differences were resolved by consensus, and in cases where disagreements persisted, other co-authors (MPC, LHY) were consulted to decide whether to include or exclude articles.

For any studies that were possibly relevant but had missing or unclear information or data, we contacted the authors by email for further information. Articles in languages other than English were translated into English.

A short narrative (descriptive) synthesis is presented summarizing the PICO, risk of bias, and study quality for each study, as well as across studies. Data was extracted using a PICO template to ensure that all relevant study details and results were captured.

Two authors (OC, HCHK) independently assessed and rated the methodological quality of each trial using the Cochran Collaboration tool for assessing risk of bias. The quality of studies were judged by evaluating the following six domains: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other sources of bias. Each domain was judged as either being (1) low risk of bias, (2) high risk of bias, or (3) unclear risk (lack of information or uncertainty over the potential for bias). Reasons were recorded to by why judgements were given.

Because only one type of intervention (i.e. antibiotics) for a defined primary outcome (e.g. number of patients who get recurrent cellulitis during treatment) was chosen, a meta-analysis was done to calculate a weighted treatment effect across trials. The results were expressed as a risk ratio with 95% confidence intervals (CI) for dichotomous outcomes.

The appropriateness of meta-analysis in the presence of significant clinical or methodological/statistical heterogeneity for the other outcomes of interest was considered. Meta-analyses was performed using the Cochrane Collaboration Review Manager software (RevMan). Random effects meta-analysis was used for outcome effect estimates from groups of studies with high heterogeneity, to produce a more conservative effect estimate. Statistical indications of heterogeneity between the studies in effect measures were assessed using both the Chi-squared test and the I-squared statistic. We considered an I-squared value >50% indicative of moderate heterogeneity and >75% indicative of substantial heterogeneity. Methodological heterogeneity amongst the collection of studies was also an indicator for using a random effects meta-analysis, and was used where the studies had a high degree of methodological variability between them.

We assessed the reporting of withdrawals, drop-outs, protocol deviations, and whether participants were analysed in the group to which they were originally randomized (ITT). We examined the methods, and a priori published protocols (if present), of the selected studies to determine if all relevant results reported matched the proposed outcomes to be reported.

Subgroup analyses was used to explore heterogeneity in effect estimates according to: study quality; study populations (1st occurrence of cellulitis vs 2nd or more recurrence of cellulitis); intervention content (i.e. type of antibiotic used, administration method), and the effect of small and large studies on the effect estimate. Assessment of publication bias was not done as there were only five studies, and it has been recommended that useful analysis of publication bias requires at least 10 studies.

We conducted sensitivity analyses based on study quality (i.e. higher quality vs lower quality studies).

Results

Our literature search yielded 1472 articles from all sources. Fig. 1 shows the numbers of studies screened, resulting in five studies that matched our criteria. Of these, two studies were done by the UK’s ‘Prophylactic Antibiotics for the Treatment of Cellulitis at Home’ (PATCH) group.

There were 535 participants from all five studies, with 260 participants taking antibiotics and 275 participants on placebo or not taking any antibiotics. There were 209 males and 262 females in the studies, with the lowest average age from any group of participants being 45 years, and the oldest average age being 67.5 years. Table 1 outlines the key population, intervention, control and outcome characteristics of the studies.

Antibiotics were given for six, 12, or 18 months in three studies, and for an unclear duration in two studies. All studies’ comparators were no antibiotic treatments. Only the two PATCH studies used placebo tablets in their comparison arms. The other studies did not mention any placebo treatment, or reported that no antibiotic was given to the comparison group.

The quality of the individual studies, or risk of bias of the studies’ methodology, is summarized in Fig. 2. It highlights that the PATCH studies were of consistently good methodological quality, whilst the other studies had unclear or low quality.

The primary outcome of the total number of recurrences within a time period reported in Chakroun 1994 was that 0/24 (0%) intervention group patients and 9/34 (26.5%) comparison group patients had recurrences after an average of 11.6 months follow-up. Kremer 1991 reported that 0/16 (0%) intervention group patients and 8/16 (50%) comparison group patients had recurrences after an 18 month follow-up. PATCH I reported that 30/136 (22%) patients in the intervention group and 51/138 (37%) patients in the comparison group had recurrences after a 36 month follow-up. PATCH II reported that 12/60 (20%) intervention group patients and 21/63 (33%) comparison group patients...
Figure 1  PRISMA flowchart of the study selection process.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome</th>
<th>Follow-up time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kremer 1991.22</td>
<td>≥2 previous episodes of soft tissue infection (cellulitis or erysipelas).</td>
<td>Erythromycin. 250 mg, tablets, b.i.d., 18 months. Patients allergic to erythromycin given penicillin V-K, 250 mg b.i.d. N = 20.</td>
<td>No medication. N = 20.</td>
<td>Number of patients with recurrences; number of recurrences; adverse events.</td>
<td>18 months.</td>
</tr>
<tr>
<td>Chakrour 1994.21</td>
<td>Infectious cellulitis. Most had prior antibiotics.</td>
<td>Penicillin G. 1.2 million units i.m. 720 mg, intramuscular injection, every 15 days, unclear duration. N = 24. Note: 77.8% had prior antibiotics.</td>
<td>Unclear. N = 34. Note: 29.4% had prior antibiotics.</td>
<td>Patients with recurrences.</td>
<td>11.6 months average follow-up.</td>
</tr>
<tr>
<td>Sjoblom 1993.23</td>
<td>≥2 episodes of erysipelas during the last 3 years.</td>
<td>Phenoxymethylpenicillin. 1 g for BW &lt;90 kg. 1 g + 2 g for BW 90–120 kg. 2 g for BW &gt;120 kg. Tablets, b.i.d., unclear duration. Patients allergic to penicillin were given erythromycin: 0.25 g b.i.d. for BW &lt;90 kg. 0.25 + 0.5 g b.i.d. for BW 90–120 kg. 0.5 g b.i.d. for BW &gt;120 kg. N = 20.</td>
<td>No treatment. N = 20.</td>
<td>Number of patients with recurrences; adverse events.</td>
<td>Follow-up time possibly varied.</td>
</tr>
<tr>
<td>PATCH I 2012.26</td>
<td>≥2 episodes of cellulitis. Within 3 years of index occurrence.</td>
<td>Penicillin VK. 250 mg, tablets, b.i.d., 12 months. N = 136.</td>
<td>Placebo tablets, b.i.d., 12 months. N = 138.</td>
<td>Number of patients with recurrences; number of recurrences; adverse events; time to next episode.</td>
<td>36 months.</td>
</tr>
<tr>
<td>PATCH II 2012.27</td>
<td>≥1 episode of cellulitis. Index episode diagnosed within last 12 weeks.</td>
<td>Penicillin VK. 250 mg, tablets, b.i.d., 6 months. N = 60.</td>
<td>Placebo tablets, b.i.d., 6 months. N = 63.</td>
<td>Number of patients with recurrences; number of recurrences; adverse events; time to next episode.</td>
<td>36 months.</td>
</tr>
</tbody>
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had recurrences after a 36 month follow-up. Chakroun 1994 reported that 2/20 (10%) intervention group patients and 8/20 (40%) comparison group patients had recurrences after up to a maximum of approximately 3 years of follow-up.

The primary outcome of the number of episodes per patient reported in Kremer 1991 was that 7/16 (44%) patients had 1 recurrence of cellulitis, and that 1/16 (6%) patients had 2 relapses of cellulitis in the comparison group (there were no recurrences of cellulitis in the intervention group). Patch I reported that there were 3 patients with 2 recurrences, 2 patients with 3 recurrences, 2 patients with 4 recurrences, and 1 patient with 7 recurrences. It was unclear which treatment groups had which numbers.

The secondary outcome of time to next episode of occurrence, reported as the median time to next episode in PATCH I, was longer, at 626 days, for the intervention group than for the 532 days for the comparison group.

As for adverse events, the most commonly reported problems were nausea and diarrhoea, but these figures were similar between treatment and comparison groups within each study. A small number of deaths were also reported in PATCH I, PATCH II, and Sjöblom 1993, however these were not related to the study treatments. Kremer 1991 reported that 3/16 (19%) intervention group patients experienced nausea and abdominal pain.

For the primary outcome of the total number of recurrences of cellulitis, a random effects meta-analysis of all five studies showed that prophylactic antibiotics were beneficial for preventing recurrence of cellulitis with an RR of 0.46, 95% CI 0.26–0.79 (Fig. 3).

Fig. 4 shows the risk of bias across studies for the various bias components, showing a mix of low, high and unclear risk of bias in methodology of the body of evidence.

Subgroup analyses for previous episodes of cellulitis showed there was no statistically significant advantage to using prophylactic antibiotics for patients with two or more prior episodes of cellulitis (RR 0.35, 0.12–1.02) compared to delivering no antibiotics. For antibiotic administration routes, there was a statistically significant benefit for oral administration of antibiotics for preventing recurrence of cellulitis (RR 0.52, 95% CI 0.33–0.82) vs no antibiotics. Only one study examined intramuscular administration, but the difference in recurrence was not statistically significant between treatment groups (RR 0.07, 95% CI 0.00–1.21), however we should caution that this analysis only used one small study so interpretation of this result should be done conservatively. For the type of antibiotics used, penicillin shows a statistically significant benefit for preventing recurrent cellulitis (RR 0.54, 95% CI 0.36–0.80). Erythromycin also showed statistically significant benefit for prophylaxis (RR 0.06, 95% CI 0.00–0.94), however this analysis only used one small study so this result should be interpreted with caution.

Sensitivity analyses from analysis of only high quality studies (two studies)24,25 and lower or unclear quality studies (three studies)26–28 both agreed that antibiotic prophylaxis was effective for reducing recurrent cellulitis (RR 0.60, 95% CI 0.43–0.83, and RR 0.16, 95% CI 0.05–0.50, respectively).

Discussion

Antibiotic prophylaxis reduced the risk of recurrent cellulitis compared to no antibiotic prophylaxis, with an RR of 0.46 (95% CI 0.26–0.79) in patients with a history of cellulitis. This review also suggests that in patients with
two or more baseline episodes of cellulitis, antibiotic prophylaxis seemed to half the recurrence of cellulitis as compared to no antibiotic prophylaxis; while not statistically significant (RR 0.35, 95% CI 0.12–1.02) this finding hints to a possibly clinically important effect pending more trials conducted with larger sample size and power to detect a difference. Studies that used oral administration of antibiotics showed RR 0.52 (95% CI 0.33–0.82), but it is unclear if intramuscular injection is effective (RR 0.97, 95% CI 0.66–1.43). The difference in RR was not significant (95% CI 0.66–0.94). Penicillin was effective at reducing the recurrence of cellulitis (RR 0.54, 95% CI 0.36–0.80), as was erythromycin (RR 0.66, 95% CI 0.30–1.4). 

Strengths of this systematic review were that it included studies in languages other than English, searched for unpublished data, and solicited views from experts in this field. Clinical practice guidelines and health technology assessments on the topic were also searched to determine if there was already published high level evidence and recommendations on the topic. Sensitivity analysis results from analysis of only high quality studies (two studies) and lower or unclear quality studies (three studies) both agreed that antibiotic prophylaxis was effective for reducing recurrent cellulitis (RR 0.60, 95% CI 0.43–0.83, and RR 0.16, 95% CI 0.05–0.50, respectively). The UK NICE (National Institute for Health and Care Excellence) clinical knowledge summary on cellulitis (last revised in September 2012) also stated that if the cellulitis is recurrent (more than two episodes at the same site within 1 year), one should consider routine referral to a dermatologist for advice about starting prophylactic antibiotics. 

A limitation of the methods is the small number of relatively heterogeneous studies (only five studies) and small aggregate population able to be used in this analysis (n = 535). Caution should be used when interpreting the subgroup analyses regarding the patient types to be treated (two or more prior episodes of cellulitis at baseline), the type of antibiotic used (penicillin or erythromycin), and administration routes (oral or intramuscular injection), as the number of studies and patients for each analyses may be small.

As a further note on administration routes, it should be noted that it is difficult to compare oral vs intramuscular administration of antibiotics, as absorption (and therefore bioavailability) is different for the different routes. The variability and quality of data between studies did not allow us to make a recommendation on the optimal antibiotic or duration of treatment.

The studies were conducted in mainly Caucasian patients in France, UK/Ireland, Sweden, and Ireland, so generalizability to other ethnicities and geographic settings may be limited. 

A previous systematic review on antibiotics prophylaxis for recurrent cellulitis in BMJ Clinical Evidence published in 2008 only found two studies, which have also been included in our systematic review. This review found that antibiotic prophylaxis was likely to be beneficial. Our systematic review is has identified more studies, used a transparent and rigorous systematic review methodology, and has summarized the current state of research on antibiotic prophylaxis for recurrent cellulitis up to August 2012.

In a study by Forcade et al. the impact of CA-MRSA in the United States was discussed. The patients described in this study had symptoms suggestive of Staphylococcus Aureus infection, and would not be expected to benefit from penicillin prophylaxis. This highlights the importance of selecting the appropriate group of patients who may benefit from penicillin prophylaxis. While current guidelines state that it is reasonable to give antibiotic prophylaxis for prevention of recurrent cellulitis, our data suggests that the benefit of giving prophylactic antibiotics is considerable in a patient population with recurrent cellulitis and should be strongly considered.

Some papers in the literature indicate that despite antibiotic prophylaxis, cellulitis still recurs. Postulated reasons for failure of preventive therapy may be that the recurrence of erysipelas include noncompliance; incorrect antibiotic; other causative micro-organisms; or insufficient antibiotic concentrations. In half of the cases, no valid explanation could be obtained. The exact diagnosis of cellulitis (caused by streptococcus) may not always be possible and one must also consider other differential diagnoses for red and swollen limbs. 

One study using monthly intramuscular injections of benzathine penicillin G to prevent recurrences of cellulitis found that monthly benzathine penicillin G prophylaxis benefited only patients without predisposing factors for cellulitis. We recognize some limitations of applying long-term prophylaxis in clinical practice. Long-term compliance will be an obstacle. If oral prophylaxis is being prescribed,
patient information is a crucial issue, and the importance of prophylactic treatment to prevent further damage of the vessels and serious infections should be stressed to try to increase compliance by the patients.

Other aspects of cellulitis prevention should not be neglected. These include the treatment of toe web intertrigo, reducing lower limbs oedema and managing underlying venous insufficiency.7 Resistance of group A Streptococcus pyogenes to macrolides has dramatically increased and in many areas of the world, this class of antibiotics cannot be relied upon to provide effective protection. Although clindamycin remains more effective against group A streptococci, it has a very broad spectrum of activity and potential for causing an antibiotic-associated diarrhea or colitis, which may severely limit its use for long term prophylaxis.8 In light of the reasons above, patients with allergy to penicillin have very limited choices.

According to the PATCH II study, this intervention represents an improvement which costs £18 per 6-month course. Assuming an NNT of 8, this equates to a treatment cost of £144 per episode of cellulitis prevented.23 In another study, the cost of treating a single erysipelas episode was 8.3 times higher than the cost of one year of prophylaxis.

In conclusion, our analyses support the use of antibiotics for prophylaxis against recurrent cellulitis or erysipelas. Antibiotics used for this indication were generally well tolerated, without increased risk of major adverse effects. However, more RCTs need to be done to better answer the following questions: (1) when oral antibiotic prophylaxis should be started (after 1st or 2nd episode of cellulitis), (2) which patient population may benefit the most from antibiotic prophylaxis (e.g. which age groups, excluding which comorbidities), (3) what is the optimal duration and dosage of antibiotics, (4) what is the best choice of antibiotics for those allergic to penicillin.

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