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Extrapolating evidence about preventing recurrent cellulitis for an individual patient concern

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Extrapolating evidence about preventing recurrent cellulitis for an individual patient concern

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ABSTRACT A critical appraisal and clinical application of Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis, *N Engl J Med.* 2013, May 2;368(18):1695-1703. doi: [10.1056/NEJMoa1206300](https://doi.org/10.1056/NEJMoa1206300)

Keywords: antibiotic, recurrent cellulitis, prophylaxis, shared decision-making

Clinical Context

Our patient was a 29 year old male with morbid obesity, who presented with a two day history of left lower leg erythema, warmth, and swelling from his ankle to just below the knee. Borders of the erythema were marked with permanent ink. An initial WBC count was 26.7K. Blood cultures from the time of admission were negative throughout the hospital stay. He was started on IV Vancomycin 2000 mg for Methicillin Resistant Staphylococcus Aureus (MRSA) coverage based on prior cultures from a previous hospitalization. His leg improved over the next few days with receding erythema. His WBC count resolved from 26.7K to 8.3K and his erythema continued to improve. He was in the last stages of evaluation for bariatric surgery. He and his mother were concerned that a recurrence might delay this procedure. We also assessed him as high-risk for recurrence of lower extremity cellulitis due to his body habitus, venous insufficiency, and lymphatic insufficiency.

Clinical Question

Is therapy available for preventing recurrence of lower extremity cellulitis in high-risk patients?

Research Article

Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis, *N Engl J Med.* 2013, May 2;368(18):1695-1703. doi: [10.1056/NEJMoa1206300](https://doi.org/10.1056/NEJMoa1206300)

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Literature Review

Our initial search for research articles related to antibiotic prophylaxis was done via PubMed, using search terms “antibiotic”, “prophylaxis”, and “cellulitis.” We reviewed references in the relevant papers we found, to find other primary research relevant to our clinical questions. In all, we found a total of six clinical trials and one meta-analysis for review. The six studies included PATCH I¹ and PATCH II², as well as studies from Chakroun et al.³, Kremer et al.⁴, and Sjoblom et al.⁵. Based on the study methodology, the PATCH I and II were the most clinically useful. Both of these studies were double blind clinical trials with placebo control. All of the subjects in each study were followed for 3 years. The other studies by Kremer, Chakroun and Sjoblom did not have a clear placebo, and follow-up time varied. All of the studies showed evidence to support the use of antibiotic prophylaxis in cases of recurrent cellulitis. This was discussed in the meta-analysis by Oh, et al.⁶, which concluded that antibiotic prophylaxis for cellulitis is well tolerated and shows a benefit in reducing recurrences.

We chose the PATCH I trial for this review because it had the best available methodology and power to determine efficacy. This study included random sequence generation; allocation concealment; and blinding of participants, personnel, and outcome assessment. It also had low attrition. PATCH I included a larger number of study participants ($n=274$) compared to PATCH II ($n=123$). The number of participants in the other studies was significantly lower; for Kremer ($n=40$), Chakroun ($n=58$) and Sjoblom ($n=40$).

We reviewed current guidelines on UpToDate.com regarding cellulitis. There is a recommendation for prophylactic antibiotic treatment in cases of recurrent cellulitis. UpToDate® also referenced the meta-analysis by Oh et al. in coming to this recommendation.

Critical Appraisal

Participants were recruited from 28 hospitals over Ireland and the United Kingdom; subjects were considered for the study if they had a history of two episodes of cellulitis in the past 3 years, with the most recent episode within the last 24 weeks. Important exclusion criteria included use of antibiotics for cellulitis prevention over the last 6 months, allergy to penicillin, previous leg ulceration or surgery. The patients treated with penicillin had a hospital stay two days longer than those in the placebo group; however, this was not statistically significant. We thought the inclusion and exclusion criteria described a population of patients similar to our patient. A total of 274 patients were recruited, stratified according to the presence or absence of edema or ulceration, and then randomized via computer to either the treatment or the placebo group. The primary outcome was increased median length of time to first episode of recurrent cellulitis and the secondary outcome was decreased rate of recurrent cellulitis in the treatment group. Participants were prescribed penicillin 250mg taken by oral route twice per day for duration of 12 months, or were provided placebo tablets. An intention-to-treat analysis was used, accounting for all patients who underwent randomization.

As discussed in the literature review, the article had low risk of selection bias (random assignment to treatment versus placebo group), performance bias (blinding of participants and personnel), and detection bias (blinding of the outcome assessment). However, the placebo tablets were not identical to the penicillin tablets. The investigators felt this to be a minor consideration given the wide geographic range of the participants. The data collection method represents another limitation, in that adherence to treatment regimen was assessed by self-reporting of the percentage of pills taken, and adverse events were recorded in a diary.

The median time to recurrence of the patients treated with penicillin, compared to placebo, was 626 versus 532 days. Using Table 2, the Number Needed to Treat to prevent one recurrence of cellulitis with penicillin compared to placebo over twelve months is 6.7. Inexplicably, the authors report a Number Needed to Treat of 5. Additionally, subgroup analysis showed higher risk of failure in patients with BMI > 33 or pre-existing edema.

Using the Oxford Centre for Evidence-based Medicine criteria, the strength of the evidence is Ib.

Clinical Application

Although the patient did not meet inclusion criteria for this study, he and his mother were extremely concerned about any possible delay for his upcoming bariatric surgery. Given his concern, we shared the evidence from this article for penicillin prophylaxis with the patient. We told him the information could be reasonably extrapolated to

his clinical situation, which included venous insufficiency, lymphatic insufficiency, and increased interstitial pressure that blistered his skin causing a break in the epidermis.

These factors put him at risk for cellulitis from any skin organisms despite adequate treatment for MRSA during this episode. Though ulceration was an exclusion criterion in this trial, this patient's unroofed blister was a simple skin erosion and not an ulceration. Though he had two risk factors for decreased efficacy, there was no indication in the paper that therapy would not be beneficial.

When evidence is limited, doctors need to use clinical judgment to make appropriate decisions. After a thorough discussion, he and his mother desired to proceed with treatment.

Take Home Points

Using the evidence from this study and applying it to the care of this patient, we believe the following points are important for clinicians:

- 1.) Risk stratification can help clinicians decide which patients may benefit most from penicillin prophylaxis.
- 2.) Prophylactic penicillin treatment to prevent recurrent cellulitis was underutilized in our practice, and we intend to include this therapy for a very frequent problem at our inpatient service.
- 3.) This case demonstrates a patient extrapolating evidence to his own personal situation.

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