ONLINE EXCLUSIVE

Low-dose penicillin for recurrent cellulitis?

Giving patients with leg cellulitis low-dose penicillin helps prevent recurrence, this study shows—but optimal dose and duration are still unknown.

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PRACTICE CHANGER

Prescribe low-dose penicillin to patients with recurrent leg cellulitis to decrease the frequency of recurrent episodes.[1]

STRENGTH OF RECOMMENDATION

B: Based on a single randomized controlled trial (RCT).

Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. *N Engl J Med.* 2013; 368:1695-1703.

ILLUSTRATIVE CASE

An obese 50-year-old man presents with cellulitis of his right lower leg. He has a history of chronic venous insufficiency and has had 2 previous episodes of leg cellulitis in the past year. Should you initiate prophylactic antibiotics?

The incidence of cellulitis is 24.6 in 1000 person-years, according to a US population-based study of insurance claims for the years 1997 to 2002—the most recent data available.[2] The lower extremities are most commonly affected, accounting for 70% to 80% of cases.[3] Risk factors associated with recurrence include venous insufficiency, lymphedema, overweight, skin breakdown, and leg edema, which are often difficult to modify.[4,5]

Keeping well hydrated to avoid skin breakdown, elevating affected extremities to decrease edema, wearing compression stockings, and treating tinea pedis can help reduce the incidence of recurrent cellulitis.[6,7] Prophylactic antibiotics can help, as well.

Which drug? What dose and duration?

These questions aren't easily answered, as recommendations vary among specialty groups. The Infectious Diseases Society of America recommends benzathine penicillin (1.2 million units/month IM), erythromycin 250 mg PO BID, penicillin V 1 g PO BID, or nasal mupirocin BID for 5 days per month for "frequent" cellulitis, but "frequent" is not clearly defined.[6,8-11] The British Lymphology Society (BLS)'s first-line recommendation for patients with ≥2 episodes of cellulitis per year is penicillin V 250 mg BID (or penicillin V 500 mg BID for patients with a BMI ≥33) for one year, then penicillin V 250 mg daily for an additional year. The BLS suggests lifelong antibiotic prophylaxis if cellulitis recurs after 2 years of prophylaxis.[6]

Consensus is lacking as to the optimal duration of prophylactic antibiotics. Kremer et al[11] found that prophylactic erythromycin for 18 months reduced recurrent cellulitis; Thomas et al[12] showed an insignificant reduction in cellulitis recurrence with 6 months of low-dose penicillin in patients who'd had one prior episode. The study detailed in this PURL provides additional evidence about the use of prophylactic antibiotics for recurrent lower extremity cellulitis and tests the efficacy of a particular dose and duration.

STUDY SUMMARY

Low-dose penicillin reduces recurrence rate

This double-blind RCT compared penicillin

with placebo for the prevention of recurrent leg cellulitis. To be included in the study, patients had to have had at least 2 episodes of cellulitis within the previous 3 years, one of which occurred in the preceding 6 months. Participants (N=274) were recruited at hospitals in the United Kingdom and Ireland. Baseline characteristics included obesity (mean BMI, 35), mean age late 50s, and 3 to 4 prior episodes of cellulitis. About 25% of the participants had a history of venous insufficiency, as well.

The study had 2 phases—one for prophylaxis, the other for follow-up. During the prophylaxis phase, which lasted 12 months, patients received either penicillin 250 mg PO BID or placebo. Participants were followed for up to 3 years. They received phone calls every 3 months during the prophylaxis phase and every 6 months during the follow-up phase to assess adverse events, use of health care services, and recurrence of cellulitis.

Protection diminishes after prophylaxis ends

The primary outcome was the time from randomization to recurrence of cellulitis: Median times to recurrent cellulitis were 626 days for the penicillin group and 532 days for patients on placebo. Recurrence rates were 45% lower in those who received penicillin (hazard ratio=0.55; 95% confidence interval, 0.35-0.86; number needed to treat=5; *P*=.01) during the prophylaxis phase, but there was no difference in incidence in the follow-up phase.

Secondary outcomes measured were the proportions of patients with recurrent cellulitis in both the prophylaxis and follow-up phases, new leg edema or ulceration, duration of hospital admission for cellulitis, cost-effectiveness, and adverse drug effects/events of interest. The penicillin group had fewer episodes of recurrent cellulitis (119 vs 164; *P*=.02). The percentage of patients with new edema or ulceration between the 2 groups (40% penicillin vs 48% placebo; *P*=.46) and difference in cost-effectiveness between the 2 groups were not significant. Mean duration of hospitalization was 10 days (penicillin) and 9.2 days (placebo). There was no significant difference in the number of participants who experienced one or more adverse events (37 for those taking penicillin vs 48 for the placebo group; *P*=.50), including nausea, diarrhea, vulvovaginitis/thrush, rash, and death. There were 8 deaths in the penicillin group and 3 in the placebo group, although none was considered study related.

WHAT'S NEW

Evidence that low-dose penicillin is effective

This trial provides strong evidence that a lower dose of penicillin than is currently recommended by the IDSA (250 mg vs 1 g BID) is effective in reducing leg cellulitis recurrence. It also shows that 12 months of prophylaxis significantly reduces the risk of recurrent leg cellulitis, but that the effect may diminish when the penicillin is stopped.

CAVEATS

Questions about dose and duration remain

Participant characteristics predictive of prophylaxis failure in this study included BMI≥33 and ≥3 previous episodes of cellulitis. It could be that patients with higher BMIs need a higher dose of penicillin. And we still don't know whether prophylactic treatment for longer than 12 months would provide continued benefit, what the optimal time period for prophylactic antibiotics should be, and whether the higher recommended dose of penicillin would be more effective than the low dose that was used in this study. Antibiotic resistance associated with long-term penicillin use is a concern, as well.

CHALLENGES TO IMPLEMENTATION

Even when we know that patients are likely to benefit, we are often hesitant to prescribe long-term antibiotics because of reasonable fears of resistance and adverse effects. JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

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