

The Gift That Keeps on Giving

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Case 1: A 39-year-old man with chronic lower extremity lymphedema was admitted to the hospital with acute fever, chills, and left lower extremity pain, swelling, and erythema for the third time in as many months. Examination revealed a temperature of 39°C (102.2°F), and erythematous induration on the left leg (Figure). The patient was treated with IV clindamycin and cefazolin, with clinical improvement. He was discharged with azithromycin, 500 mg daily for 3 days, done twice monthly. Case 2: A 52-year-old morbidly obese man with stasis dermatitis presented with acute lower extremity pain, swelling, and associated fever. He had been taking prophylactic antibiotics for his recurrent cellulitis for more than a decade and had significantly decreased his number of recurrences while on this therapy. He was admitted to the hospital, treated with IV cefazolin, and had a rapid improvement over 48 hours. He was subsequently discharged with continued suppressive antibiotic therapy.

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Cellulitis is frequently encountered by physicians. The pathogens involved in “routine” cellulitis are typically gram-positive cocci, and treatment can be with either oral or IV medications, depending on the severity of the infection.

A subset of patients experience recurrent episodes of cellulitis. In a study of 143 patients over a 3-year period, 29% of those initially identified with primary erysipelas later developed recurrences. Nineteen of the 143 patients (13%) with primary erysipelas had two or more episodes. Identifying the predisposing factors for recurrence, placing the patient on appropriate antibiotics, and consideration of prophylactic therapy are important factors in the management of patients with recurrent cellulitis.¹

Causes

Physiologic impairment (i.e., lymphedema or venous stasis) or breaches in the skin barrier are predisposing factors implicated in recurrent cellulitis. In a case-control study,² investigators found that disruption of the cutaneous barrier (from ulcer, tinea pedis, or dermatosis) increased the likelihood of developing erysipelas by 23.8% (95% confidence interval [CI], 10.7%–52.5%) while lymphedema increases

the likelihood by 71.2% (95% CI, 5.6%–908%). Venous insufficiency and obesity increase the likelihood by 2.9% (95% CI, 1.0%–8.7%) and 2.0% (95% CI, 1.1%–3.7%), respectively. The investigators found no association with diabetes, smoking, or alcohol use in this study.²

In another study,³ lymphography of the infected leg was performed on 19 patients who had a first episode of cellulitis, as well as on the contralateral, apparently healthy leg of 11 of the patients. Fourteen of the 19 (74%) patients had clinical signs of lymphedema, while lymphography documented lymphedema in 16 of the 19 affected legs (84%). Six of the 11 (55%) contralateral apparently healthy legs had radiographic evidence of lymphedema. The investigators concluded that these data suggested that lymphedema was a predisposing factor in the cellulitis and was not caused by the infection.³ In another study,⁴ the lymphatic drainage of 30 patients with recurrent cellulitis was studied via lymphoscintigraphy. Seventy-seven percent (23 out of 30) were found to have significant lymphatic abnormalities correlating well with the aforementioned data that show the major role of lymphedema in recurrent disease.⁴

Venous insufficiency has been the most commonly associated finding in recurrent

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Table I. Antibiotic Options for Recurrent Cellulitis

IV	ORAL	ORAL AGENTS FOR PATIENTS ALLERGIC TO PENICILLIN
Cefazolin	Amoxicillin	Gram-positive fluoroquinolone
Clindamycin	Amoxicillin/clavulanic acid	Macrolide (if <i>Staphylococcus</i> is not a concern)
Daptomycin	Clindamycin	
Nafcillin	Linezolid	
Linezolid		
Vancomycin		

Figure. Cellulitis in a patient with chronic lymphedema



cellulitis. It may be related to either surgical procedures (i.e., coronary artery bypass graft requiring saphenous venectomy) or peripheral vascular disease. A 6.2% incidence of cellulitis after saphenous venectomy has been reported.⁵ In a study of 31 patients who developed cellulitis following saphenous venectomy, none of whom had experienced an episode of cellulitis before the surgical procedure, the focus of the cellulitis was the scar from the saphenous venectomy, and the clinical presentation consisted of mild erythema and edema. Of note, 25 of the 31 patients had associated tinea pedis. While the proximal cause of the cellulitis was unclear, the investigators believed the background was multifactorial, resulting from both the surgical disruption of the lymphatic drainage and the impaired venous return from the physical loss of a prominent vein.⁶ Breaches in the skin barrier may also predispose patients to cellulitis, frequently as a cofactor in patients with lymphedema.⁶

In another study,⁷ 25 of 31 patients with cellulitis after saphenous venectomy had associated tinea pedis, which likely played a pivotal role in the source of the infection, due to interdigital skin breakdown. Other predisposing factors for recurrent cellulitis include recurrent trauma (e.g., in laborers), pelvic manipulation during surgery with or without radiation therapy,⁸ and chronic open wounds, as in patients with arterial insufficiency or diabetes.

Microbiology

Pathogens identified in recurrent cellulitis are typically β hemolytic streptococci (e.g., *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus equisimilis*, or group G streptococci) or *Staphylococcus aureus*. In the majority of patients, no specific pathogen will be identified. One investigator⁹ reported a case series of four patients with recurrent cellulitis caused by group G streptococci that appeared to be associated with streptococcal anal colonization; however, three of the four patients had associated venous stasis, lymphedema, or tinea pedis, thereby putting into question the significance of anal colonization.

It would be useful to be able to predict the causative agents involved with recurrent cellulitis. In a study examining the utility of culturing the interdigital spaces in patients with cellulitis and tinea pedis (as compared with patients with tinea pedis and no cellulitis), only the recovery of β -hemolytic streptococci was associated with the occurrence of cellulitis ($p < 0.01$). Isolation of *S. aureus* and gram-negative species did not correlate with active cellulitis.¹⁰ Superficial cultures combined with antistreptolysin O titers is a simple, noninvasive means of determining the etiologic agent for cellulitis, as compared with tissue aspiration or biopsy of the infected area.

Treatment

Treatment of the acute infection frequently requires IV antibiotics, as patients may present with the acute onset of fever, chills, and lower extremity pain and, at times, may have an associated bacteremia. Preferred IV antibiotics are listed in Table I. If the patient appears toxic and group A streptococcal infection is a significant possibility, clindamycin should be administered due to its more rapid inhibition of toxin production, as opposed to β -lactam antibiotics such as penicillin. The keys to determining the

appropriate antibiotic include previous bacteriologic diagnosis (if available), the severity of disease and pain, and the overall toxicity of the patient. If the diagnosis is made early, or if the infection is not severe, oral therapy may be appropriate. Oral antibiotics are listed in Table I. The duration of therapy, regardless of route, is 7–10 days.

Depending on the severity of the infection, or the failure to respond to standard therapy, imaging of the infected area may be indicated. Plain radiographs can demonstrate the presence of gas in the tissue and therefore indicate the need for surgical intervention. When considering a deep abscess or fasciitis, a CT scan or MRI is recommended, followed by a surgical evaluation if a deep process is found to be present.

Prophylaxis

It may be assumed that prophylactic antibiotics may prevent recurrence; however, there are limited data supporting this hypothesis. Investigators¹¹ have studied the efficacy of daily phenoxymethylpenicillin as compared with a nonmedicated control group (20 patients per study arm). While the data suggested a trend toward statistical significance in regard to reducing the number of recurrences ($p=0.06$), the protective benefit was not dramatic.

Traditionally, a regimen of monthly benzyl penicillin injections has been one of the preferred prophylactic regimens of choice; however, the IM injection can be quite painful as well as inconvenient due to required doctor's office visits. Erythromycin therapy at 250 mg b.i.d. was compared with an untreated control group (36 patients, 18 per study arm). None of the treated patients developed recurrent cellulitis, while 50% (nine of 18) of the control group had at least one episode of cellulitis. No significant side effects or com-

Table II. Prophylaxis for Recurrent Cellulitis

Benzyl penicillin (monthly)
Azithromycin (twice monthly)
Erythromycin
Oral penicillin

plications were noted in the erythromycin-treated group, suggesting that it is a safe and effective prophylactic therapy.¹²

The current recommendations regarding prophylaxis are to use either a penicillin or a macrolide for long-term suppressive therapy (Table II). No data are available regarding potential resistance issues in patients undertaking such extended therapy.^{11,13,14} We have had success using twice-monthly courses of azithromycin (a 3-day "tripak" or 5-day "Z-pak" on the first and the fifteenth of the month). This regimen has the potential to improve compliance and limit associated side effects, while maintaining the efficacy desired with prophylactic treatments.

While antibiotics are crucial in primary treatment and prophylaxis, supportive care is also important. Decongestive physiotherapy (i.e., support stockings), treatment of mycotic infections, and topical skin and wound care are all key components in the management of recurrent cellulitis.¹¹

Conclusions

Recurrent cellulitis can be a challenge for physicians to manage and a cause of morbidity for patients. Evaluation of underlying causes and instituting preventive strategies are reasonable methods for limiting recurrences. Prompt initiation of oral antibiotics at the first sign or symptom of infection may prevent hospitalization, but often patients will require IV antibiotics. If patients have nontreatable underlying disease or are refractory to preventive measures, prophylactic antibiotics may be indicated.

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