EDITORIALS

Choosing an Antibiotic for Skin Infections

Michael R. Wessels, M.D.

Since the mid-1990s, methicillin-resistant *Staphylococcus aureus* (MRSA) has become the predominant pathogen responsible for suppurative skin infections (i.e., furuncles, carbuncles, and skin abscesses) in the United States and in many other countries. Emergency department visits for skin abscesses have increased during this period, as MRSA has become endemic in the community, but a similar increase in visits for cellulitis (i.e., infectious inflammation of the skin without a drainable collection of pus) has not occurred.[1,2] The microbiologic characteristics of cellulitis are less well defined because material for culture is not readily available. Although *S. aureus* is the organism most frequently isolated from needle aspirates or punch biopsy samples in cellulitis, cultures are negative in more than 70% of such samples, and serologic evidence suggests that *Streptococcus pyogenes* and other beta-hemolytic streptococci cause most cases.[3,4]

Given the immense importance of MRSA during the past two decades, prospective clinical trial data to inform the choice of an outpatient treatment regimen for skin infections in the MRSA era are surprisingly sparse. Furthermore, despite the lack of evidence that MRSA is a major cause of cellulitis (as opposed to skin abscesses), there has been a shift toward prescribing agents active against MRSA for the treatment of cellulitis. In this issue of the *Journal,* Miller et al. address these knowledge gaps with a prospective, randomized, double-blind trial comparing clindamycin with trimethoprim–sulfamethoxazole (TMP-SMX) in the treatment of outpatients with skin infections.[5] More than 500 adults and children were enrolled from four centers in areas in which community-acquired MRSA is endemic. Patients with multiple abscesses or a single abscess larger than 5 cm in diameter (or proportionally smaller for young children) underwent incision and drainage. Patients with smaller abscesses were not included in the analysis. Cultures were obtained from all patients with purulent lesions and from patients with cellulitis only if fluid that could be cultured was present. Not surprisingly, *S. aureus* was isolated from 72.7% of patients with abscesses with or without cellulitis; of these isolates, 83.0% were MRSA. Cultures were obtained from 20% of patients with cellulitis only (32 patients with cellulitis only [11.4%] had MRSA, 1 had *S. pyogenes* [0.4%], and 1 had group B streptococcus [0.4%]). Clinical cure rates were high and not significantly different for clindamycin and TMP-SMX — 89.5% and 88.2%, respectively — in the population that could be evaluated. No significant difference in cure rate was seen in any of the subgroup analyses.

Although the trial did not have a formal noninferiority design, the results support the authors' conclusion that there is unlikely to be a large difference in efficacy between the two treatment regimens for skin infections in outpatients. However, the design of the study obscures possible differences between the outcomes in the two major subgroups, differences that favor TMP-SMX for abscesses and clindamycin for cellulitis. There was a nonsignificant difference favoring TMP-SMX in patients who could be evaluated who had abscess only or abscess plus cellulitis, and there was a nonsignificant difference favoring clindamycin in those who had cel-

lulitis without abscess. These opposing trends in the subgroups do not reach significance, but they tend to neutralize one another in the overall analysis. Such differences, although small, are not unexpected: clindamycin resistance was detected in 12.4% of *S. aureus* isolates, and the lower cure rate for clindamycin treatment of these patients approached significance (P=0.06). Although it was not proved in this study, infection with beta-hemolytic streptococci probably accounted for many if not most cellulitis cases, and clindamycin is likely to be more active than TMP-SMX in the treatment of those infections. The authors' suggestion that TMP-SMX may be active against *S. pyogenes* has yet to be verified in human infections, with the possible exception of impetigo.[6] In addition, a higher failure rate for TMP-SMX might be observed in patients with cellulitis who were not included in this trial: those with a temperature higher than 38.5°C or lymphangitis, as well as patients with coexisting conditions such as diabetes, cancer, or severe obesity.

In light of these new data, which antibiotic, if any, should we choose for outpatient treatment of skin infections? As documented in this trial, MRSA is the predominant cause of skin abscesses. Previous studies have shown little or no benefit of adding an antibiotic after incision and drainage in uncomplicated cases.[7,8] Antibiotic treatment may have a small effect in reducing the time to recurrence and is recommended for patients with symptoms or signs of systemic illness or coexisting conditions.[9] In an area with a high rate of clindamycin resistance, TMP-SMX might be preferred for empirical treatment of skin abscess if an antibiotic is prescribed.

For cellulitis, therapy should be directed primarily at beta-hemolytic streptococci. An earlier well-designed trial showed no benefit of adding TMP-SMX to cephalexin for the treatment of cellulitis, so targeting MRSA in such patients appears to be unnecessary.[10] Penicillin or another beta-lactam is the agent of choice for streptococcal infections. Dicloxacillin or a first-generation cephalosporin, such as cephalexin or cefadroxil, is also highly active and extends the spectrum to methicillin-sensitive *S. aureus.* Clindamycin is also active against streptococci, and resistance rates for *S. pyogenes* are acceptably low in the United States, but it is not preferable to a beta-lactam for this indication.

The study by Miller et al. is reassuring in showing that outcomes are good for the vast majority of patients with uncomplicated skin infections treated with either of two popular agents. There remains a need for additional carefully designed clinical trials to define the most effective therapies for skin abscesses and cellulitis in more severely ill patients and patients with underlying chronic illness.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Division of Infectious Diseases, Boston Children's Hospital, and the Department of Pediatrics, Harvard Medical School — both in Boston.

1. Karamatsu ML, Thorp AW, Brown L. Changes in community-associated methicillin-resistant Staphylococcus aureus skin and soft tissue infections presenting to the pediatric emergency department: comparing 2003 to 2008. Pediatr Emerg Care 2012; 28:131-5.
2. Qualls ML, Mooney MM, Camargo CA Jr, Zucconi T, Hooper DC, Pallin DJ. Emergency department visit rates for abscess versus other skin infections during the emergence of community-associated methicillin-resistant Staphylococcus aureus, 1997-2007. Clin Infect Dis 2012;55:103-5.
3. Chira S, Miller LG. Staphylococcus aureus is the most common identified cause of cellulitis: a systematic review. Epidemiol Infect 2010;138:313-7.
4. Jeng A, Beheshti M, Li J, Nathan R. The role of beta-hemolytic streptococci in causing diffuse, nonculturable cellulitis: a prospective investigation. Medicine (Baltimore) 2010;89:217-26.
5. Miller LG, Daum RS, Creech CB, et al. Clindamycin versus trimethoprim–sulfamethoxazole for uncomplicated skin infections. N Engl J Med 2015;372:1093-103.
6. Bowen AC, Tong SY, Andrews RM, et al. Short-course oral cotrimoxazole versus intramuscular benzathine benzylpenicillin for impetigo in a highly endemic region: an open-label, randomised, controlled, non-inferiority trial. Lancet 2014;384:2132-40.
7. Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of cephalexin versus clindamycin for uncomplicated pediatric skin infections. Pediatrics 2011;127(3):e573-e580.
8. Rajendran PM, Young D, Maurer T, et al. Randomized, double-blind, placebo-controlled trial of cephalexin for treatment of uncomplicated skin abscesses in a population at risk for community-acquired methicillin-resistant Staphylococcus aureus infection. Antimicrob Agents Chemother 2007;51:4044-8.
9. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis 2014;59:147-59.
10. Pallin DJ, Binder WD, Allen MB, et al. Clinical trial: comparative effectiveness of cephalexin plus trimethoprim-sulfamethoxazole versus cephalexin alone for treatment of uncomplicated cellulitis: a randomized controlled trial. Clin Infect Dis 2013;56:1754-62.

DOI: 10.1056/NEJMe1500331