EDITORIAL

Empirical MRSA Coverage for Nonpurulent Cellulitis
Swinging the Pendulum Away From Routine Use

Emily K. Shuman, MD; Preeti N. Malani, MD, MSJ

Cellulitis is an infection of the deep dermis and subcutaneous tissue, manifesting as expanding erythema, edema, and warmth of the skin.[1] In most instances of cellulitis, the causative microorganism cannot be definitively determined. However, based on studies using blood cultures, other laboratory markers (anti-streptolysin O and anti-DNase B antibodies), and clinical response to β-lactam antimicrobials, the vast majority of cellulitis is thought to be caused by β-hemolytic streptococci.[2] Staphylococci, including methicillin-resistant *Staphylococcus aureus* (MRSA), are a less common cause of cellulitis and are more likely to be encountered in cases of purulent cellulitis (drainage or exudate in the absence of a drainable abscess) or abscess formation.[3] Thus, current guidance from the Infectious Diseases Society of America advises that nonpurulent cellulitis without abscess should be treated with antimicrobials targeted primarily against streptococci.[3]

Related article page 2088

Annual US ambulatory visits for skin and soft tissue infection (including cellulitis and abscess) increased from 4.6 million in 1997 to 9.6 million in 2006 (the most recent available data), with the largest relative increase occurring in emergency departments.[4] During this time, community-associated MRSA emerged as a major cause of skin and soft tissue infection, primarily presenting with abscess formation. Accordingly, the prescription of antimicrobials directed against community-associated MRSA increased from 7% of visits during which an antimicrobial was prescribed in 1997 to 28% in 2005, with trimethoprim-sulfamethoxazole accounting for most of this increase.[4] Although prescribing antimicrobials with activity against MRSA may be reasonable in some cases of skin and soft tissue infection, it is likely that the pendulum has swung too far in the direction of covering empirically for MRSA "just in case." Trimethoprim-sulfamethoxazole has poor activity against streptococci, so interest has recently increased in use of combination therapy with a β-lactam for treatment of cellulitis to cover both streptococci and MRSA.

In this issue of *JAMA*, Moran and colleagues[5] report the results of a study attempting to answer the question of whether combination antimicrobial therapy with trimethoprim-sulfamethoxazole and a β-lactam (in this case, cephalexin) is superior to treatment with cephalexin alone for nonpurulent cellulitis without abscess. The investigators randomly assigned 500 patients with cellulitis who presented to 5 emergency departments to receive a 7-day course of cephalexin and trimethoprim-sulfamethoxazole or cephalexin and placebo. All patients underwent ultrasound to exclude abscess at study entry. Other exclusion criteria included underlying skin conditions at the site of infection, injection drug use with fever (fever alone was not an exclusion), concurrent infection at another site, and immunosuppression. Treatment failure was defined as fever or increased erythema (>25% from baseline), swelling or tenderness on day 3 or 4; fever or no decrease in erythema, swelling, or tenderness at the end of the treatment period (days 8-10); and fever or more than minimal erythema, swelling, or tenderness at the test-of-clinical-cure visit (days 14-21).

Among 500 randomized participants, 496 (99%) were included in the modified intention-to-treat analysis, defined as patients who took at least 1 dose of study medication and had an in-person or telephone assessment through the test-of-clinical-cure visit as well as those who withdrew from the trial, were lost to follow-up before final classification, or had missing or unassigned outcomes; and 411 (82.2%) were included in the per-protocol analysis, defined as participants who either took at least 75% of the total doses of study medication during the first 5 days and had an in-person test-of-clinical-cure visit or were determined to have had clinical failure before the test-of-cure visit and received at least 75% of the doses provided during the first 48 hours of the treatment period.

Among the per-protocol population, there was no significant difference in the clinical cure rate at 14 to 21 days between the cephalexin plus trimethoprim-sulfamethoxazole group (182/218 participants [83.5%]) and the cephalexin plus placebo group (165/193 participants [85.5%]) (difference, −2.0%; 95% CI, −9.7% to 5.7%; $P = .67$). However, in the modified intention-to-treat analysis, the cephalexin plus trimethoprim-sulfamethoxazole group had a higher clinical cure rate (189/248 participants [76.2%]) compared with the cephalexin plus placebo group (171/248 participants [69.0%]) (difference, 7.3%; 95% CI, −1.0% to 15.5%; $P = .09$).

Thirty-six participants had treatment failure with cephalexin plus trimethoprim-sulfamethoxazole, of whom 19 (52.8%) later had clinical evidence of abscess or purulent drainage. Among the 28 participants who did not respond to treatment with cephalexin plus placebo, 20 (71.4%) later had evidence of abscess or purulent drainage. Overall, 60 participants who had treatment failure had material available for culture at a follow-up visit; MRSA was isolated from 41 (68.3%), methicillin-susceptible *S aureus* from 8 (13.3%), and streptococcal species from 2 (3.3%). There was no

© 2017 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/936247/ by a Imperial College London User on 05/27/2017

difference in need for additional antimicrobials or surgical drainage between the 2 groups, and no patients developed an invasive infection. There was also no significant difference in adverse events between the 2 groups, with gastrointestinal upset being the most common symptom. One case of acute-on-chronic kidney injury occurred in the cephalexin plus trimethoprim-sulfamethoxazole group.

The results of this study indicate that most patients presenting with nonpurulent cellulitis without abscess can be safely treated without the addition of antimicrobials directed against MRSA. Although the modified intention-to-treat analysis does raise the possibility that the addition of trimethoprim-sulfamethoxazole may be somewhat superior to cephalexin alone, the results of this analysis were likely skewed by a relatively large number of patients who did not complete the recommended course of therapy and were thus excluded, although this likely reflects what occurs in everyday practice. Among the patients in both groups who experienced treatment failure, more than half developed clinical evidence of abscess, for which the primary therapy is drainage.[3] Even among patients with treatment failure, none developed invasive infection including bacteremia, underscoring the importance of close follow-up when managing skin and soft tissue infections.

The study by Moran et al has several strengths, most notably its design as a multicenter, double-blind, randomized trial. While the use of ultrasound in all patients to exclude abscess formation is a notable strength, this may limit applicability in settings where this technology is not readily available, although bedside ultrasound is available in most emergency departments. In addition, the absence of adverse outcomes in both study groups depended in large part on close follow-up after discharge from the emergency department, something that is not always achieved in clinical practice.

The notion of "double coverage" with antimicrobials for relatively straightforward diagnoses such as cellulitis is problematic and highlights the need for enhanced antimicrobial stewardship in ambulatory settings. A recent study by Fleming-Dutra et al[6] estimated that 154 million antimicrobial prescriptions were written in outpatient settings in 2010-2011, of which 30% were considered to be inappropriate. Along with a well-established risk of antimicrobial resistance, inappropriate and excessive use of antimicrobials also results in patient-specific harms.

In the study by Moran et al, there was no significant difference in adverse events between participants who received trimethoprim-sulfamethoxazole and those who did not,[5] perhaps related to the short duration of therapy (7 days) and the relatively younger study population (median age, 40 years). However, Brindle et al[7] found that the addition of clindamycin to flucloxacillin for treatment of cellulitis offered no benefit but was associated with a significant increase in diarrhea. Shehab et al[8] reported that antimicrobials are the most frequent cause of emergency department visits for drug-related adverse events, accounting for 19.6% of such visits, with sulfonamides and clindamycin the most commonly involved agents. In this study, sulfonamides were found to be associated with a higher rate of moderate to severe allergic reactions compared with other antimicrobials.

As these studies demonstrate, and as the study by Moran et al suggests, the addition of a second antimicrobial "just in case" may often do more harm than good and may not be necessary for treatment of nonpurulent cellulitis without abscess.

ARTICLE INFORMATION

Author Affiliations: Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, Ann Arbor (Shuman, Malani); Associate Editor, *JAMA* (Malani).

Corresponding Author: Preeti N. Malani, MD, MSJ, Division of Infectious Diseases, Department of Internal Medicine, University of Michigan Health System, 3119 Taubman Center, Ann Arbor, MI 48109-5378 (pmalani@umich.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

REFERENCES

1. Raff AB, Kroshinsky D. Cellulitis: a review. *JAMA*. 2016;316(3):325-337.

2. 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(4):217-226.

3. Stevens DL, Bisno AL, Chambers HF, et al; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America [corrected in *Clin Infect Dis*. 2015;60(9):1448]. *Clin Infect Dis*. 2014;59(2):e10-e52.

4. Hersh AL, Chambers HF, Maselli JH, Gonzales R. National trends in ambulatory visits and antibiotic prescribing for skin and soft-tissue infections. *Arch Intern Med*. 2008;168(14):1585-1591.

5. Moran GJ, Krishnadasan A, Mower WR, et al. Effect of cephalexin plus trimethoprim-sulfamethoxazole vs cephalexin alone on clinical cure of uncomplicated cellulitis: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.5653

6. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011. *JAMA*. 2016;315(17):1864-1873.

7. Brindle R, Williams OM, Davies P, et al. Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis. *BMJ Open*. 2017;7(3):e013260.

8. Shehab N, Patel PR, Srinivasan A, Budnitz DS. Emergency department visits for antibiotic-associated adverse events. *Clin Infect Dis*. 2008;47(6):735-743.

© 2017 American Medical Association. All rights reserved.

Downloaded From: http://jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/936247/ by a Imperial College London User on 05/27/2017