JCM Journals.ASM.org

Susceptibility of *Streptococcus pyogenes* to Trimethoprim-Sulfamethoxazole

Michael S. Gelfand, Kerry O. Cleveland, Daniel C. Ketterer

Department of Medicine, Division of Infectious Diseases, University of Tennessee Health Science Center, Memphis, Tennessee, USA

With interest we read the recent paper by Bowen et al. in which they propose that detection of *in vitro* susceptibility of *Streptococcus pyogenes* to trimethoprim-sulfamethoxazole (TMP-SMX) is enhanced by testing on media containing low concentrations of thymidine (1). Whether their data on *in vitro* susceptibility can be extrapolated to the clinical use of TMP-SMX in clinical infections due to this organism is unclear.

Traditional teaching in infectious diseases and microbiology has suggested that *S. pyogenes* is largely resistant to TMP-SMX, and, in fact, the drug has been incorporated into selective media for isolation of *S. pyogenes* from throat cultures (2–4).

Recently we observed two patients with skin and soft tissue infections due to *S. pyogenes* who were treated with oral TMP-SMX and suffered adverse outcomes.

The first patient, a 40-year-old previously healthy man, presented with a hand wound related to an occupational cut. After the wound was cleaned, he was discharged on TMP-SMX (160 mg of TMP component twice daily). He returned 48 h later with a hand infection that had progressed to necrotizing fasciitis. Wound and blood cultures grew *S. pyogenes*. Susceptibility testing with TMP-SMX was not done.

The second patient, a 38-year-old woman with multiple skin abscesses, was treated with surgical debridement and tigecycline (50 mg intravenous [i.v.] administration twice daily) for 3 days followed by oral TMP-SMX (160 mg of TMP component twice daily) for 6 days. A wound culture grew *S. pyogenes* (no susceptibility testing for TMP-SMX was performed) and methicillin-sensitive *Staphylococcus aureus* (MRSA) susceptible to TMP-SMX. She expired after presenting in septic shock 24 h after discharge.

In vitro susceptibility of *S. pyogenes* to TMP-SMX is less relevant than the clinical efficacy of this agent in treating infections due to that organism. Thymidine may become available to infecting microorganisms from damaged host tissues and bacteria, allowing microorganisms to overcome the metabolic block (5). Clinical failures in the treatment of MRSA infections have been attributed to this mechanism, and animal model data in MRSA infections support this explanation (5).

Human sera and urine contain detectable concentrations of thymidine and folates (6, 7). Even when an organism is demonstrated to have *in vitro* susceptibility to the drug, use of TMP-SMX has been discouraged for enterococcal urinary tract infections because of concern about exogenous thymidine and folates being available to the infecting organism (7). As pointed out, TMP-SMX has not proven to be an effective agent for treatment of streptococcal pharyngitis (1).

We urge caution in the use of TMP-SMX for *S. pyogenes* skin and soft tissue infections before the availability of human clinical studies. The study of impetigo being conducted by the authors may not resolve the question of clinical utility of TMP-SMX for these infections, as spontaneous resolution of impetigo is not uncommon (8). Data from animal models of infection would be desirable in helping to resolve this question.

ACKNOWLEDGMENTS

We declare that we have no conflicts of interest.

No financial support was received for this work.

REFERENCES

1. **Bowen AC, Lilliebridge RA, Tong SY, Baird RW, Ward P, McDonald MI, Currie BJ, Carapetis JR.** 2012. Is *Streptococcus pyogenes* resistant or susceptible to trimethoprim-sulfamethoxazole? J. Clin. Microbiol. **50**:4067–4072.
2. **Bisno AL, Stevens DL.** 2009. *Streptococcus pyogenes*, p 2593–2610. *In* Mandell GL, Bennett JE, Dolin R (ed), Mandell, Douglas, and Bennett's principles and practice of infectious diseases, 7th ed, vol 2. Churchill Livingstone Elsevier, Philadelphia, PA.
3. **Milatović D.** 1981. Comparison of five selective media for beta-haemolytic streptococci. J. Clin. Pathol. **34**:556–558.
4. **Mirrett S, Monahan JS, Reller LB.** 1987. Comparative evaluation of medium and atmosphere of incubation for isolation of *Streptococcus pyogenes*. Diagn. Microbiol. Infect. Dis. **6**:217–221.
5. **Proctor RA.** 2008. Role of folate antagonists in the treatment of methicillin-resistant *Staphylcoccus aureus* infection. Clin. Infect. Dis. **46**:584–593.
6. **Holden L, Hoffbrand AV, Tattersall MH.** 1980. Thymidine concentrations in human sera: variations in patients with leukaemia and megaloblastic anaemia. Eur. J. Cancer **16**:115–121.
7. **Wisell KT, Kahlmeter G, Giske CG.** 2008. Trimethoprim and enterococci in urinary tract infections: new perspectives on an old issue. J. Antimicrob. Chemother. **62**:35–40.
8. **Koning S, van der Sande R, Verhagen AP, van Suijlekom-Smit LW, Morris AD, Butler CC, Berger M, van der Wouden JC.** 2012. Interventions for impetigo. Cochrane Database Syst. Rev. **1**:CD003261. doi:10.1002/14651858.CD003261.pub3.

Address correspondence to Kerry O. Cleveland, kcleveland@uthsc.edu.

For the author reply, see doi:10.1128/JCM.03373-12.

doi:10.1128/JCM.03329-12