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Dose of Trimethoprim-Sulfamethoxazole To Treat Skin and Skin Structure Infections Caused by Methicillin-Resistant *Staphylococcus aureus*▽

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We undertook this study to investigate whether treatment with a higher dose of trimethoprim-sulfamethoxazole (TMP/SMX) led to greater clinical resolution in patients with skin and soft tissue infections (SSTIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA). A prospective, observational cohort with nested case-control study was performed at a public tertiary health system. Among patients with MRSA SSTIs during the period from May 2008 to September 2008 who received oral monotherapy with TMP/SMX and whose clinical outcome was known, the clinical characteristics and outcomes were compared between patients treated with a high dose of TMP/SMX (320 mg/1,600 mg twice daily) for 7 to 15 days and patients treated with the standard dose of TMP/SMX (160 mg/800 mg twice daily) for 7 to 15 days. In patients with MRSA SSTIs, those treated with the high dose of TMP/SMX ($n = 121$) had clinical characteristics similar to those of patients treated with the standard dose of TMP/SMX ($n = 170$). The only exception was a higher proportion of patients with a history of trauma upon admission among the patients treated with the higher dose. The proportion of patients with clinical resolution of infection was not different in the two groups (88/121 [73%] versus 127/170 [75%]; $P = 0.79$). The lack of significance remained in patients with abscess upon stratified analysis by whether surgical drainage was performed. The study found that patients with MRSA SSTIs treated with the higher dose of TMP/SMX (320/1,600 mg twice daily) for 7 to 15 days had a similar rate of clinical resolution as patients treated with the standard dose of TMP/SMX (160/800 mg twice daily) for 7 to 15 days.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant cause of skin and soft tissue infections (SSTIs) and a significant cause of morbidity and mortality (7). Patients with these infections are typically treated with oral antimicrobial agents such as trimethoprim-sulfamethoxazole (TMP/SMX), clindamycin, linezolid, and doxycycline (12). One of the several gaps in our knowledge of therapy with these antimicrobial agents is whether the standard adult TMP/SMX dose of 160 mg/800 mg, or one double-strength (DS) tablet twice daily, is adequate. TMP/SMX acts against MRSA through inhibition of dihydropteroate synthase (sulfamethoxazole) and tetrahydrofolate reductase (trimethoprim), leading to impaired thymidine biosynthesis (8). Clinicians advocating for treating MRSA SSTIs with a higher dose of TMP/SMX (320 mg/1,600 mg or 2 DS tablets twice daily) for adults contend that the high content of thymidine in infected tissue may potentially lead to decreased activity of TMP/SMX and that a higher dose is necessary. We undertook this study to investigate whether treatment with a higher dose of TMP/SMX led to increased clinical resolution in patients with SSTIs caused by MRSA.

MATERIALS AND METHODS

We conducted a prospective observational cohort with nested case-control study at the University Health System (UHS), San Antonio, TX, a tertiary, public academic health system affiliated with the University of Texas Health Science Center at San Antonio. The health system has a 498-bed tertiary care hospital and several satellite clinics throughout the city. Patients were included in the cohort if MRSA was isolated upon exudate culture performed in the UHS microbiology laboratory during the period from 1 May 2008 to 31 September 2008 and the following additional inclusion and exclusion criteria were met upon review of the electronic medical record. The inclusion criteria were presence of signs and symptoms of skin and soft tissue infection, such as tenderness, induration, erythema, purulent secretions, and edema; age of ≥18 years; and occurrence of the episode of SSTI for the first time during the study period. The exclusion criteria were recurrent episodes of MRSA SSTIs during the study period, occurrence of folliculitis only, or presence of complicated infection involving deep tissues, such as bone, bursae, or tendons. At the UHS microbiology laboratory, identification of MRSA was done by using MRSA CHROMagar medium (BD Diagnostics, Sparks, MD), and susceptibility to oxacillin, clindamycin, erythromycin, trimethoprim-sulfamethoxazole, doxycycline, moxifloxacin, and vancomycin was routinely tested by the disk diffusion method. Inducible clindamycin resistance testing was routinely performed on all isolates, as previously described (2). There was no active MRSA screening surveillance program in the hospital at the time of this study.

Review of medical records was performed for patients who received oral therapy with TMP/SMX, to obtain demographic, clinical, and laboratory data. Treatment outcome was ascertained upon review of medical records or by contacting the patient over the phone if there was no clear documentation of clinical resolution in the medical record. Criteria from a previous study (10) were used to define treatment failure. To be considered a treatment failure, the patient must have had a documented worsening of the infection beyond 2 days of initiation of therapy plus at least one of the following: need for additional surgical drainage, hospital admission, occurrence of a new MRSA SSTI at a different location while on antimicrobial therapy, or persistent infection. Patients

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TABLE 1. Comparison of clinical characteristics and outcomes of patients treated with two different doses of TMP/SMX

Clinical parameter	Result for TMP/SMX twice-daily dose of:		Odds ratio	95% confidence interval	*P* value
	160/800 mg (n = 170)	320/1,600 mg (n = 121)			
Median (range) age (yr)	38 (24–52)	40 (28–52)			0.433
No. (%) female gender	87 (51.2)	52 (43.0)	0.72	0.45–1.15	0.19
Median (range) body wt (kg)	77 (44.5–156)	86 (42–141)			0.553
Median (range) body mass index	28 (16.8–54)	30 (18–58.8)			0.454
No. (%) of patients with:					
Diabetes mellitus	32 (18.8)	23 (19.0)	1.01	0.56–1.84	0.968
Malignancy	3 (1.8)	0 (0.0)			0.269
End-stage renal disease	0 (0.0)	0 (0.0)			
End-stage liver disease	4 (2.4)	1 (0.8)	0.35	0.04–3.13	0.406
Human immunodeficiency virus infection	2 (1.2)	5 (4.1)	3.62	0.69–18.98	0.13
Injection drug use	12 (7.1)	13 (10.7)	1.59	0.70–3.61	0.269
Residence in a correctional facility	13 (7.6)	8 (6.6)	0.86	0.34–2.13	0.737
Active tobacco smoking	64 (37.6)	45 (37.2)	0.98	0.61–1.59	0.937
History of trauma on admission	4 (2.4)	9 (7.4)	3.34	1.00–11.09	0.046[a]
History of MRSA colonization or infection within previous 1 yr	17 (10.0)	12 (9.9)	0.99	0.46–2.16	0.981
Abscess	135 (79.4)	102 (84.3)	1.39	0.75–2.57	0.291
Receipt of incision and drainage	82 (48.2)	77 (63.6)	1.88	1.17–3.03	0.009[a]
Requirement for hospitalization for SSSI management	9 (5.3)	4 (3.3)	0.61	0.18–2.03	0.568
Median (range) treatment duration (days)	10 (7–13)	9 (6–12)			0.5
No. (%) of patients with clinical resolution	127 (74.7)	88 (72.7)	0.90	0.53–1.53	0.705

[a] $P \leq 0.05$.

with unknown treatment outcomes were excluded. The clinical characteristics and treatment outcomes were compared between patients treated with oral TMP/SMX at 320 mg/1,600 mg twice daily (cases) and those treated with a dose of 160 mg/800 mg twice daily (controls). Statistical analyses were performed using SPSS for Windows (version 17.0; SPSS Inc., Chicago, IL). All tests were two-tailed, and the critical value of α was 0.05. The Institutional Review Board at the University of Texas Health Science Center, San Antonio, TX, approved the study.

RESULTS

During the 5-month study period, 618 unique adult patients with skin and soft tissue infections caused by MRSA were identified. The majority of these patients (425, 68.8%) received oral antimicrobial therapies with or without additional surgical drainage. Trimethoprim-sulfamethoxazole was used in the majority (328, 77.2%), followed by clindamycin (56, 13.2%), while the remaining patients received other oral antimicrobial agents, such as linezolid, doxycycline, or minocycline. Of the 328 patients who received oral therapy with TMP/SMX, 188 (57.3%) received the standard dose of 160/800 mg twice daily for 7 to 15 days, and the remaining patients (140, 42.7%) were treated with a higher dose of 320/1,600 mg twice daily. We were able to ascertain the treatment outcome in 170 of the 188 (90.4%) patients who received the standard dose and 121 of the 140 (86.4%) patients who received the high dose of TMP/SMX and included these patients in the analysis. The MRSA isolates in all these patients were susceptible to TMP/SMX.

When patients who received TMP/SMX at 160/800 mg twice daily (standard-dose group; n = 170) were compared with patients who received TMP/SMX at 320/1,600 mg twice daily (high-dose group; n = 121), all demographic, epidemiological, and clinical characteristics were similar between the two groups except a history of trauma at admission (Table 1). Patients with a history of trauma were more likely to receive 320/1,600 mg of TMP/SMX (7% versus 2%; odds ratio [OR], 3.3; 95% confidence interval [CI], 1.002 to 11.093; P = 0.046). Among the patients treated with the standard dose of TMP/SMX, 135 (79.4%) had an abscess, and of these, 82/135 (60.7%) underwent incision and drainage. Of the 121 patients who received the high dose of TMP/SMX, 102 (84.3%) had an abscess, and of these, 77/102 (75.5%) underwent incision and drainage. Although there was no significant difference in the proportion of patients with abscess (84.3% versus 79.4%; P = 0.36), patients who received oral TMP/SMX at 320/1,600 mg twice daily were more likely to receive surgical drainage (76/102 [74.5%] versus 82/135 [60.7%]; OR, 1.889; 95% CI, 1.078 to 3.309; P = 0.027). None of the patients in either group had documented adverse events due to therapy with TMP/SMX.

The treatment outcomes were similar between the two groups. Of the 170 patients who received the standard dose of 160 mg/800 mg twice daily, 127 (75%) had clinical resolution of the infection. Seventy-three percent (88/121) of the patients who received treatment with the high dose of TMP/SMX achieved clinical resolution of the infection (OR, 0.96; 95% CI, 0.76 to 1.2; P = 0.79). The lack of significance remained even upon stratified analysis by whether surgical drainage was performed or not. The causes for treatment failure were not different between the two groups. The causes (not mutually exclusive) were need for additional surgical drainage after 48 h of antimicrobial therapy (27/43 [63%] versus 24/33 [73%]; P = 0.5), change of antimicrobial agent due to lack of response (19/43 [44%] versus 8/33 [24%]; P = 0.06), admission to the hospital at least 48 h after beginning antimicrobial therapy

(7/43 [16%] versus 1/33 [3%]; $P = 0.1$), and occurrence of a new infection or persistent infection on therapy (42/43 [98%] versus 30/33 [91%]; $P = 0.4$).

DISCUSSION

In this prospective observational cohort with nested case-control study, we investigated whether patients with MRSA SSTIs treated with a higher dose of TMP/SMX had better outcomes than patients treated with the standard dose. TMP/SMX was the most commonly used oral antimicrobial agent for treating MRSA SSTIs in the study population. The available data to support the use of TMP/SMX for the treatment of skin and skin structure infections caused by MRSA are not the result of large randomized, blinded clinical trials. Currently available evidence is mostly from small, observational, retrospective studies on patients with any MRSA infection. According to the recent clinical practice guidelines published by the Infectious Diseases Society of America (5), TMP/SMX is recommended for treating MRSA SSTIs (level A-II recommendation), and the recommended dose was 1 to 2 double-strength tablets twice daily. The guidelines did not comment on the relative effectiveness of the two dosing regimens. It is interesting that 43% of the patients treated with TMP/SMX in this study but only 3% of the patients in an earlier previous retrospective observational cohort study (3) conducted within the same population base during the year 2006 received the higher dose (320/1,600 mg twice daily), potentially indicating increased popularity of the higher dose. Recent studies that evaluated TMP/SMX for the treatment of MRSA SSTIs have used either the 160/800-mg twice-daily dose (3, 4) or the 320/1,600-mg twice-daily dose (6, 11). None of these previous studies evaluated whether a higher dose of TMP/SMX led to greater clinical resolution.

The key finding of this study is that receiving a higher dose of TMP/SMX did not lead to greater clinical resolution among patients with SSSIs caused by MRSA. As we did not identify any differences in the clinical characteristics of patients who received the 320/1,600-mg dose versus the 160/800-mg dose twice daily, except for a history of trauma, it is likely that the choice of dose is clinician dependent. The patients who received the higher dose did not have a higher body weight than the patients who received the standard dose. That patients who received a higher dose of TMP/SMX were also more likely to have received surgical drainage may be a reflection of the larger size of the abscess, although such documentation was missing in the medical records. The comparability of outcomes in the standard-dose and the high-dose groups remained even after the outcomes were analyzed after stratification by whether surgical drainage was performed or not among patients with abscess. Pharmacokinetic and pharmacodynamic parameters were not evaluated in this study. In the absence of these data, we are unable to comment on whether the higher dose of TMP/SMX was truly unnecessary among these patients with MRSA SSTIs. The overall rate of clinical resolution (73.9%) among patients treated with oral TMP/SMX in this study is comparable to that in the study by Cenizal et al. (1) and higher than the 61% reported in the study by Frei et al. (3) Trimethoprim-sulfamethoxazole does appear to be an effective drug in the treatment of SSTIs caused by MRSA, and earlier studies have shown that the drug is at least as effective as other available oral antimicrobial choices such as doxycycline (1) or clindamycin (3, 4). The study by Rajendran et al. (9) reported a high placebo response rate of up to 90.5% in patients with uncomplicated skin abscesses that were surgically drained. Some patients in either treatment group in this study may not have needed any antimicrobial therapy. Therefore, placebo effect may be a significant confounder in this study, although the magnitude of effect was not measurable. No adverse outcome as a result of TMP/SMX therapy was documented in the medical records of any patient in either study group, although one might anticipate a higher rate of adverse events in those who received the higher dose. Additional limitations of this study are those inherent to single institutional observational studies based on medical record review.

In conclusion, we found that patients with MRSA SSTIs treated with two different doses of TMP/SMX (160/800 mg twice daily versus 320/1,600 mg twice daily for 7 to 15 days) had similar clinical resolutions. A higher dose of TMP/SMX may not be necessary to treat patients with skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus*.

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