ORIGINAL RESEARCH

Trimethoprim-Sulfamethoxazole or Clindamycin for Community-Associated MRSA (CA-MRSA) Skin Infections

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Background: **In the United States, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as the predominant cause of skin infections. Trimethoprim-sulfamethoxazole (TMP-SMX) and clindamycin are often used as first-line treatment options, but clinical data are lacking.**

Methods: **We conducted a retrospective cohort study of outpatients with skin and soft tissue infections managed from July 1 to December 31, 2006. Patients younger than 18 years of age were excluded, as were those who had no clinical admission or progress notes; were hospitalized within the 90 days before admission; were hospitalized with polymicrobial, surgical site, catheter-related, or diabetic foot infections; or were discharged to places other than home. Patient demographics, comorbidities, diagnoses, cultures, prescribed antibiotics, susceptibilities, surgical procedures, and health outcomes were extracted from electronic medical records. Patients were divided in 2 cohorts for further analysis: TMP-SMX and clindamycin. The primary study outcome was composite failure defined as an additional positive MRSA culture from any site 5 to 90 days after treatment initiation or an additional intervention during a subsequent outpatient or inpatient visit. Baseline characteristics and failure rates were compared using χ^2, Fisher's exact, and Wilcoxon rank sum tests.**

Results: **A total of 149 patients were included in this study. These patients had a median age of 36 years, 55% were men, 71% were Hispanic, 42% were uninsured, and 60% received an incision and drainage procedure. Patients who did not receive incision and drainage were twice as likely to experience the composite failure endpoint (57% vs 29%; $P < .001$). Failure rates were 25% for patients who received incision and drainage plus antibiotics compared with 60% for patients who received incision and drainage minus antibiotics ($P = .03$). When patients who did not receive incision and drainage were excluded, there were no significant differences between the TMP-SMX (n = 54) and clindamycin (n = 20) cohorts with respect to composite failures (26% vs 25%), microbiologic failures (13% vs 15%), additional inpatient interventions (6% vs 5%), or additional outpatient interventions (20% vs 20%).**

Conclusions: **Our findings reinforce the belief that incision and drainage and antibiotics are critical for the management of CA-MRSA skin infections. Patients who receive TMP-SMX or clindamycin for their CA-MRSA skin infections experience similar rates of treatment failure. (J Am Board Fam Med 2010;23:714–719.)**

Keywords: **Trimethoprim-Sulfamethoxazole, Clindamycin, Methicillin-Resistant *Staphylococcus aureus*, CA-MRSA, Skin Infections**

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) has emerged as a common pathogen for skin and soft-tissue infections for which patients increasingly seek treatment in the ambulatory care setting. As of 2005, almost half

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(47.9%) of all *S. aureus* infections documented in the outpatient setting nationwide were methicillin resistant,[1] and this percentage is likely to have grown since. Vancomycin has long been the drug of choice for treating CA-MRSA in the hospital setting; however, a major limitation to its use in the outpatient setting is its lack of oral bioavailability. Thus, there is a critical need for establishing effective treatment options for outpatient management of these infections.

Clinicians have begun to use alternative antibiotics, including trimethoprim-sulfamethoxazole (TMP-SMX) and clindamycin, as treatment options in outpatient settings because of their favorable in vitro activity, high oral bioavailability, and excellent tissue penetration. TMP-SMX and clindamycin are recommended by current guidelines as options for the management of skin and soft-tissue infections.[2] Nevertheless, there is limited clinical data to support these recommendations. Moreover, even fewer studies exist to support their use in the outpatient setting.[3] Clinical outcomes data are critically needed to establish TMP-SMX and clindamycin as first-line treatment options for outpatient CA-MRSA skin and soft-tissue infections.[4]

This study reports and compares health outcomes for ambulatory patients who received one of these 2 antibiotics for the treatment of a CA-MRSA skin infection. The primary objective was to compare composite failure rates of oral TMP-SMX and oral clindamycin used for the treatment of CA-MRSA.

Methods

Institutional review board approval was obtained from the University of Texas Health Science Center at San Antonio before beginning this study. This was a retrospective review of patients who were managed in medical clinics in the University Health System (UHS), San Antonio, TX. Patients were included in this study if they had an International Classification of Diseases 9 (ICD-9) code for a skin infection (680 to 684) and an MRSA-positive wound, tissue, or genital culture between July 1, 2006, and December 31, 2006. Patients younger than 18 years of age, those discharged to places other than home, and those who had polymicrobial, surgical site, catheter-related, or diabetic foot infections were excluded. Patients for whom no clinical admission or progress notes could be found were excluded, as were those who were hospitalized during the 90 days before infection.

Clinical data were collected from the patients' electronic medical records by a clinical pharmacist. The UHS has a "paperless" electronic charting system that houses inpatient and outpatient admission, progress, and discharge notes. The system also contains all laboratory test results and surgical notes. Data collected included patient demographics, comorbidities, diagnoses, cultures, antibiotics received, antibiotic susceptibilities, surgical procedures related to the primary infection, and health outcomes. UHS routinely performs the D-test for inducible clindamycin resistance and all positive isolates are reported as resistant to clindamycin.

Patients were divided in 2 cohorts for further analysis: TMP-SMX (n = 87) and clindamycin (n = 34). The primary study outcome was composite failure defined as an additional positive MRSA culture from any site 5 to 90 days after treatment initiation or an additional intervention during a subsequent outpatient or inpatient visit. Positive MRSA surveillance cultures, including nasal cultures, were not considered to be clinical failures. For the purpose of this study, an intervention was defined as either a new course of antibiotics or an additional incision and drainage procedure. These were considered "new" if they occurred during a subsequent clinic visit or hospital admission for the same skin infection. Time to treatment failure was defined as the first date a "new" intervention was required minus the original visit date.

JMP 7.0 statistical software (SAS Institute, Cary, NC) was used for all statistical comparisons. $P < 0.05$ was considered to be statistically significant and 2-tailed tests were used throughout. Descriptive statistics were used to characterize the entire sample and the subgroups. χ^2, Fisher's exact, and Wilcoxon rank sum statistics were used to assess differences between patients who received TMP-SMX or clindamycin. Finally, we conducted a subgroup analysis in which we excluded patients who did not receive incision and drainage.

Results

A total of 149 patients met inclusion criteria for this study. These patients had a median age of 36 years (interquartile range, 27–48 years), 55% were men,

71% were Hispanic, 42% were uninsured, and 60% received an incision and drainage procedure. Patients who did not receive incision and drainage during their initial clinic visit were twice as likely to experience the composite failure endpoint (57% vs 29%; $P < .001$). The 149 patients had a median baseline pain score of 8 out of 10 (interquartile range, 6–9), with 10 representing the greatest pain. The majority of patients who were treated in the outpatient clinics were prescribed an antibiotic at clinic discharge (90%). TMP-SMX was the most commonly prescribed medication (58%), followed by clindamycin (23%) and cephalexin (6%). The remaining discharge prescriptions accounted for only 3% of the total antibiotics prescribed.

Two cohorts were created based on the most common medications prescribed by clinicians in outpatient clinics: TMP-SMX (n = 87) and clindamycin (n = 34). Most TMP-SMX patients (97%) received one double-strength tablet twice daily; only 3 patients received 2 double-strength tablets twice daily. Most clindamycin patients (85%) received 300 mg every 6 hours. No more than 2 patients received any other clindamycin regimen. No significant differences were noted between the 2 cohorts with respect to age, sex, or comorbidities (Table 1). CA-MRSA isolates had susceptibility rates in excess of 90% to vancomycin, TMP-SMX, doxycycline, and clindamycin (Table 2).

There were no significant differences between the 2 cohorts with respect to composite failures, microbiologic failures, additional inpatient and outpatient interventions, number of interventions, or time to composite failure (Table 3). Also, the largest percentage of patients who failed therapy

Table 1. Baseline Characteristics for Patients with Community-associated Methicillin-resistant *Staphylococcus aureus* Skin Infections Who Were Treated in Ambulatory Settings

Characteristic	Antibiotic Regimen		
	TMP-SMX (n = 87)	CLIN (n = 34)	*P**
Age, median years (interquartile range)	38 (27–48)	35 (24–46)	.3
Male (%)	55	53	.8
Hispanic (%)	72	71	.8
No insurance (%)	45	47	.8
Incision and drainage (%)	62	59	.7
Comorbidities (%)			
Diabetes	15	15	1.0
Hypertension	23	18	.5
Hyperlipidemia	9	12	.7
Hepatitis C	5	0	.6
Depression	6	12	.3
HIV	2	0	1.0
Drug abuse	9	9	1.0
Alcohol abuse	3	6	.6
Smoker	25	24	.8
Previous skin infection	5	6	.7
None	25	32	.4
Baseline pain (interquartile range)	8 (7–9)	8 (6–10)	.4

All data provided as % unless otherwise indicated.
*Statistical comparisons between groups were made using the χ^2, Fisher's Exact, and Wilcoxon Rank Sum tests.
TMP-SMX, trimethoprim-sulfamethoxazole; CLIN, clindamycin; HIV, human immunodeficiency virus.

Table 2. Antimicrobial Susceptibilities for Community-associated Methicillin-resistant *Staphylococcus aureus* Isolates Obtained from Patients Who Were Treated for Skin Infections in Ambulatory Settings

Drug	TMP-SMX Cohort (%)	CLIN Cohort (%)
Vancomycin	100	100
TMP-SMX	100	100
Doxycycline	99	97
CLIN	94	94

TMP-SMX, trimethoprim-sulfamethoxazole; CLIN, clindamycin.

Table 3. Health Outcomes for Patients with Community-associated Methicillin-resistant *Staphylococcus aureus* Skin Infections Treated in Ambulatory Settings

Outcome	Antibiotic Regimen		
	TMP-SMX (n = 87)	CLIN (n = 34)	*P**
Composite failure (%)	39	32	.5
Microbiologic failure	10	9	1.0
IP intervention	13	6	.3
Additional OP intervention	26	26	1.0
Interventions (median [interquartile range])	1 (1–2)	1 (1–2)	.7
Days to composite failure (median [interquartile range])	8 (4–36)	4 (3–22)	.08

*Statistical comparisons between groups were made using χ^2, Fisher's Exact, and Wilcoxon Rank Sum tests.
IP, inpatient visit; OP, outpatient visit; TMP-SMX, trimethoprim-sulfamethoxazole; CLIN, clindamycin.

did so within the first 5 days after they were initially treated (Figure 1). For most patients, the additional interventions were an incision and drainage procedure with or without additional antibiotics.

Overall, failure rates were 25% for patients who received incision and drainage plus antibiotics compared with 60% for patients who received incision and drainage without antibiotics ($P = .03$). Two patients with clindamycin-resistant MRSA received clindamycin as their initial therapy, and neither of these received baseline incision and drainage. One of these 2 patients failed therapy. Three of the 9 cephalexin-treated patients received initial incision and drainage. One of the 3 who received initial incision and drainage failed therapy (33%), whereas 4 of 6 who did not receive initial incision and drainage failed therapy (67%). Of the 14 patients who were not initially prescribed antibiotics, 10 received initial incision and drainage and 4 did not. When patients who did not receive incision and drainage were excluded from the analysis; there were no significant differences between the TMP-SMX (n = 54) and clindamycin (n = 20) cohorts with respect to composite failures (26% vs 25%), microbiologic failures (13% vs 15%), additional inpatient interventions (6% vs 5%), or additional outpatient interventions (20% vs 20%).

Discussion

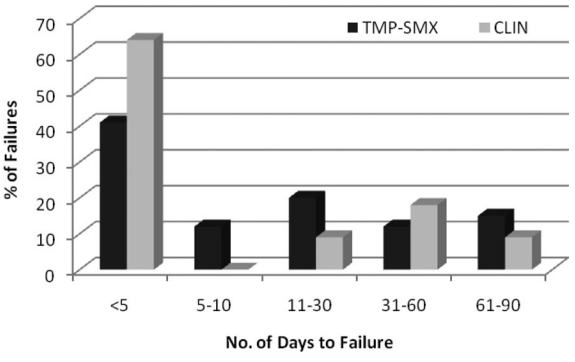
The most commonly prescribed medications for UHS outpatients during the study period were TMP-SMX and clindamycin. Another study conducted in the same geographical region also documented TMP-SMX and clindamycin as commonly prescribed anti-MRSA antimicrobials in the outpatient setting.[5] A separate study of clinics in the northeastern United States observed a shift in prescribing patterns for skin infections throughout the duration of their study.[6] Initially, the majority of clinicians prescribed beta-lactams, but by the end of their 7-year investigation most clinicians prescribed TMP-SMX as first-line empiric treatment.[6] It is likely that UHS experienced a similar shift in prescribing patterns; however, this study only included data from a 6-month period in 2006.

The most common TMP-SMX dose prescribed in this study was one double-strength tablet twice daily, rather than the dose supported by the pharmacokinetic-pharmacodynamic literature of 2 double-strength tablets twice daily.[2,7,8] The importance of TMP-SMX dosing in CA-MRSA skin infections has not yet been validated in the clinical setting, and this study suggests these prescribers might not have been familiar with the pharmacokinetic-pharmacodynamic literature for TMP-SMX. It is possible that TMP-SMX, dosed at 2 double-strength tablets twice daily, might be superior to clindamycin, but that cannot be determined from this study. Ultimately, this study reports that TMP-SMX, even at a suboptimal dose, was similar to clindamycin in this instance.

It is interesting to note the favorable susceptibilities observed for TMP-SMX and clindamycin, which were each >90% susceptible. In an outpatient study by Szumowski et al,[6] the researchers observed a low level of resistance for TMP-SMX (<1%); however, clindamycin resistance was present in 48% of MRSA isolates. The Szumowski et al[6] study differs considerably from the current study in many ways, making it difficult to compare these rates of resistance. For instance, Szumowski et al[6] included patients in their study who had recently been hospitalized with a skin or soft-tissue infection and their study contained a high proportion of HIV-positive patients.

The present study is unique in that it is one of only a few to have evaluated composite failure rates in patients presenting with a CA-MRSA infection in the outpatient setting. Composite failure rates were 39% for TMP-SMX and 32% for clindamycin. Cenizal et al[9] observed a failure rate of 9% for TMP-SMX within a time frame of 10 to 14 days after initiation of treatment, which is lower than the failure rates observed in the present study.

Figure 1. Days to composite failure for patients with community-associated methicillin-resistant *Staphylococcus aureus* skin infections treated in ambulatory settings. TMP-SMX, trimethoprim-sulfamethoxazole; CLIN, clindamycin.



In a study of military outpatient clinics by Barnes et al,[10] no treatment failures were observed when patients were prescribed TMP-SMX or clindamycin for skin and soft-tissue infections. Although they defined failure at 14 days without disease resolution, the authors noted they were able to monitor patients' prognosis up to 90 days after treatment initiation. Although that study was limited to a system of clinics at a single military institution and included a small sample of patients (n = 30), their results demonstrate promising efficacy with these antibiotics.[10]

Rajendran et al[11] conducted a placebo-controlled trial within their outpatient clinic comparing failure rates of incision and drainage coupled with cephalexin, a commonly used oral antibiotic for skin tissue infections that does not possess activity against MRSA, with incision and drainage alone. The investigators reported very low failure rates for patients who only underwent the incision and drainage procedure, which suggests that antibiotics may not even be necessary for the resolution of CA-MRSA infections.[11] In light of this information, we conducted a subgroup analysis by limiting our sample to only those patients who received initial incision and drainage. In our study, failure rates were 25% for patients who received incision and drainage plus antibiotics compared with 60% for patients who received incision and drainage without antibiotics (P = .03). Individual failure rates for the different antibiotics were cephalexin (n = 3; 33%), TMP-SMX (n = 54; 26%), and clindamycin (n = 20; 25%). This finding contradicts those by Rajendran et al[11] and suggests that antibiotics are indeed necessary for CA-MRSA skin infections. Furthermore, it is noteworthy that the antibiotics with anti-MRSA activity (ie, TMP-SMX and clindamycin) had numerically lower failure rates than cephalexin, although the cephalexin cohort was small.

It is important to recognize that our CA-MRSA definition differs from the CA-MRSA definition provided by the United States Centers for Disease Control and Prevention (CDC).[12] Both definitions consider CA-MRSA to be MRSA infections acquired by persons outside of hospitals and health care facilities; however, our definition excludes patients who were admitted to the hospital during the last 90 days whereas the CDC definition excludes patients who were admitted to the hospital or having a medical procedure (eg, dialysis, surgery, catheters) during the last year. The difference in these definitions makes it difficult to compare our study to prior studies that have used the CDC definition.

The observational approach used in this study has some limitations. First, this approach is subject to bias with respect to which patients received which therapies. Baseline characteristics like age, sex, Hispanic ethnicity, lack of insurance, incision and drainage, comorbidities, substance abuse, history of skin infection, and baseline pain scores were similar between patients who received TMP-SMX and clindamycin; however, the clinic and surgical notes did not possess enough clinical details about the actual skin lesions to determine whether patients who were treated with different therapies had similar disease severity. Patient allergies to TMP-SMX or clindamycin might have influenced the treatment decision or patient outcomes, but data about patient allergies were not collected. Adverse effects might have influenced patient adherence or outcomes, but we did not collect data about adverse effects or measure patient adherence in this study. Other unassessed variables might also be at work and could only be dealt with by proper randomization.

Failure rates are difficult to compare across studies in part because there is currently no uniform definition of failure. Our composite failure endpoint had 3 components. Two of these are fairly straightforward: (1) subsequent inpatient intervention and (2) additional outpatient intervention. The other one, "microbiologic failure," is potentially problematic because the subsequent MRSA cultures could represent colonization or infection. We were unable to differentiate these in this study. Importantly, we have reported the results of the composite endpoint and the 3 individual components so the reader can focus on the information most meaningful to them. The rates of failure observed in this study seem to be considerably higher than other studies, which may be explained by our broad definition of composite failure, failure to optimize pharmacokinetics-pharmacodynamics, or lack of patient adherence to prescribed therapies.

This study was conducted at a single health system in one geographic region. Because not all regions of the country have the same susceptibility patterns as those reported in this study, future studies should include more geographically diverse sites. Furthermore, this was an "open" system, so patients may have visited clinics or hospitals outside

the UHS system for additional interventions. Our inability to account for these visits could have caused us to underestimate the true rate of failure in these patients because patients without follow-up notes were considered to have experienced treatment success.

Finally, data collection was performed by a clinical pharmacist rather than the managing physician. We acknowledge that it is difficult for anyone not involved in the patient's care to interpret the decision making and clinical outcomes from retrospective review of the clinic notes. This may be even more difficult across disciplines. Even with its limitations, this study provides some of the earliest clinical evidence to support current prescribing practices for CA-MRSA.

Conclusions

Our findings reinforce the belief that incision and drainage and antibiotics are critical for the management of CA-MRSA skin infections. Also, ambulatory patients who receive oral TMP-SMX or clindamycin for their CA-MRSA skin infections experience similar rates of treatment failure.

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