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Risk Factors for Trimethoprim-Sulfamethoxazole Resistance in Patients with Acute Uncomplicated Cystitis▽

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Emerging antimicrobial resistance among uropathogens makes the management of acute uncomplicated cystitis increasingly challenging. Few prospective data are available on the risk factors for resistance to trimethoprim-sulfamethoxazole (TMP-SMX), the drug of choice in most settings. In order to evaluate this, we prospectively enrolled women 18 to 50 years of age presenting to an urban primary care practice with symptoms of cystitis. Potentially eligible women provided a urine sample for culture and completed a questionnaire regarding putative risk factors for TMP-SMX resistance. *Escherichia coli* isolates were tested for clonal group A (CGA) membership by a *fumC*-specific PCR. Of 165 women with cystitis symptoms, 103 had a positive urine culture and were eligible for participation. *E. coli* was the predominant uropathogen (86%). Fifteen (14.6%) women had a TMP-SMX-resistant (TMP-SMX^r) organism (all of which were *E. coli*). Compared with the women who had a TMP-SMX-susceptible organism, women in the TMP-SMX^r group were more likely to have traveled (odds ratio [OR], 15.4; 95% confidence interval [CI], 4.4 to 54.3; $P < 0.001$) and to be Asian (OR, 6.1; 95% CI, 1.0 to 36.4; $P = 0.048$). CGA was also independently associated with TMP-SMX resistance (OR, 105; 95% CI, 6.3 to 1,777.6; $P = 0.001$). No association with TMP-SMX resistance was demonstrated for the use of either TMP-SMX or another antibiotic in the past 3 months or with having a child in day care. Among these women with acute uncomplicated cystitis, Asian race and recent travel were independently associated with TMP-SMX resistance. TMP-SMX^r isolates were more likely to belong to CGA. Knowledge of these risk factors for TMP-SMX resistance could facilitate the accurate selection of empirical therapy.

Urinary tract infection (UTI) is one of the most common indications for antimicrobial therapy. Recent studies have demonstrated that fluoroquinolones are increasingly being used instead of trimethoprim-sulfamethoxazole (TMP-SMX) to treat UTIs in ambulatory women, the majority of whom likely have acute uncomplicated cystitis (9, 14, 25). Concurrently, and perhaps consequently, fluoroquinolone resistance among uropathogens is increasing in prevalence (5, 10). Clearly, strategies that can be used to decrease the rate of fluoroquinolone use, particularly for uncomplicated cystitis, are needed.

One such strategy is to facilitate the appropriate prescription of TMP-SMX as the preferred agent for the treatment of UTIs in women. The use of TMP-SMX for uncomplicated cystitis is declining (14). The reasons for this are not entirely clear, but a contributing factor may be concerns over the rising rates of TMP-SMX resistance among uropathogens (23). Guidelines for the treatment of acute uncomplicated cystitis recommend the use of alternative agents in settings where TMP-SMX is problematic due to anticipated resistance, intolerance, or other factors (8, 26). Unfortunately, local susceptibility data often come from hospital-based microbiology laboratories and may not accurately reflect the prevalence of TMP-SMX resistance among otherwise healthy outpatient women with UTIs, many of whom do not have urine cultures and susceptibilities performed (7). Thus, the actual prevalence of resistance in any given locale is usually unknown or may be overestimated on the basis of hospital-derived data, leading to the unnecessary avoidance of TMP-SMX as a first-line agent.

Knowledge of the individual host factors that predict TMP-SMX resistance would allow clinicians to make an informed prescribing decision on a case-by-case basis, eliminating the need to know population-specific resistance rates. Although several studies have attempted to elucidate such individual risk factors, most of those studies have been limited by being retrospective or including mixed gender and age groups that do not fulfill the traditional criteria for acute uncomplicated cystitis (1, 2, 16, 17, 24, 27). In this study, we evaluated specific risk factors as independent predictors of TMP-SMX resistance among prospectively enrolled women presenting with uncomplicated cystitis. We also assessed the relationship of the recently described *Escherichia coli* clonal group A (CGA) to TMP-SMX resistance in this study population (12).

MATERIALS AND METHODS

Study population. Women 18 to 50 years of age presenting to a primary care practice at an urban academic health center in Baltimore, MD, between 2002 and 2006 with symptoms of cystitis (frequency, urgency, or dysuria) and a positive urine culture ($\geq 10^4$ CFU/ml of a uropathogen) were eligible to participate in the study. Women who had a negative or contaminated urine culture, women who had an complicated UTI (pregnancy, known anatomical or functional abnormal-

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TABLE 1. Uropathogens susceptible to selected agents, stratified by species and TMP-SMX susceptibility

Agent	No. (%) of isolates susceptible to alternative agent		
	E. coli		Non-*E. coli*, TMP-SMX susceptible (n = 17)
	TMP-SMX susceptible (n = 71)	TMP-SMX resistant (n = 15)	
Fluoroquinolones	71 (100)[a]	13 (86)[a]	17 (100)
Gentamicin	71 (100)[b]	12 (80)[b]	17 (100)
Ampicillin-sulbactam	64 (90)[c]	11 (72)[c]	10/12 (83)
Cefazolin	70 (99)	14 (93)	11/12 (92)
Nitrofurantoin	71 (100)	15 (100)	12/16 (75)

[a] TMP-SMX resistance was significantly associated with resistance to the fluoroquinolones (P = 0.008) among the *E. coli* isolates.
[b] TMP-SMX resistance was significantly associated with resistance to gentamicin (P = 0.001) among the *E. coli* isolates.
[c] MP-SMX resistance exhibited a borderline statistically significant trend for resistance to ampicillin-sulbactam (P = 0.09) among the *E. coli* isolates.

TABLE 2. Variables exhibiting a univariate association with TMP-SMX resistance

Variable	No. of patients with a TMP-SMX-resistant uropathogen/total no. tested (%)		P value	Odds ratio	95% confidence interval
	Variable absent	Variable present			
Asian	10/93 (11)	5/10 (50)	0.006	8.30	2.04–33.74
Black	14/65 (22)	1/38 (3)	0.028	0.10	0.01–0.78
International travel[a]	7/91 (8)	8/12 (67)	<0.001	24.0	5.76–99.9
Travel[b]	5/82 (6)	10/20 (50)	<0.001	15.4	4.37–54.27
Travel distance[c]	NA[d]	NA	<0.001	5.53	2.62–11.66
Highest year of school	NA	NA	0.04	1.77	1.02–3.07
CGA	8/91 (9)	4/5 (80)	0.002	42.0	4.18–422.4

[a] International destinations included Japan, the Philippines, China, Bahamas, Caribbean, Peru, Brazil, Ecuador, the Dominican Republic, Puerto Rico, Mexico, Canada, and Europe.
[b] Out of state or country.
[c] 0, none; 1, out of state; 2, international.
[d] NA, not applicable.

ities, or immunosuppression), or women who were taking antibiotic prophylaxis were excluded. Approval was obtained from the institutional review board of each investigator's institution. All subjects provided written informed consent to participate.

The participants were interviewed regarding potential risk factors for TMP-SMX resistance and provided urine for standardized culture and susceptibility testing. Treatment selection was left to the provider's discretion.

Laboratory methods. Uropathogens were identified with the API 20E system (BioMérieux). Cultures with three or more bacterial species were considered contaminated. If the culture yielded $\geq 10^4$ CFU/ml of a uropathogen, disk diffusion antimicrobial susceptibility testing was performed, as specified by the Clinical and Laboratory Standards Institute. For *E. coli* isolates resistant to TMP-SMX, MICs were determined by broth microdilution (12).

Available *E. coli* isolates underwent phylotyping for groups A, B1, B2, and D by multiplex PCR, with boiled lysates used as the template DNA (18). Isolates from group D were screened for CGA status by PCR-based detection of a CGA-specific single-nucleotide polymorphism within *fumC* (3, 13). All testing was done in duplicate with appropriate positive and negative controls.

Statistical analysis. Comparisons between variables were assessed by using a Fisher exact test or the Pearson chi-square test. Odds ratios and 95% confidence intervals were determined by univariate logistic regression analysis. Multiple variables were assessed simultaneously as predictors of resistance by using stepwise multiple logistic regression analysis.

RESULTS

Study population and uropathogens. Of 165 women screened, 103 completed a questionnaire and had a positive urine culture and thus were eligible for analysis. The uropathogens recovered included *E. coli* (n = 86), *Klebsiella pneumoniae* (n = 11), *Staphylococcus saprophyticus* (n = 5), and *Enterobacter* species (n = 1). As shown in Table 1, 15 (14.6%) of the 103 women had a TMP-SMX-resistant organism, and all of these organisms were *E. coli*. Nitrofurantoin was active against all *E. coli* isolates, regardless of their TMP-SMX susceptibility, and against 12 (75%) of 16 non-*E. coli* isolates. All isolates were susceptible to imipenem and piperacillin-tazobactam.

Compared with the TMP-SMX-susceptible *E. coli* strains, the TMP-SMX-resistant *E. coli* strains were significantly more likely to be resistant to fluoroquinolones and gentamicin and trended toward having a greater prevalence of resistance to ampicillin-sulbactam (Table 1). The annual prevalence of TMP-SMX resistance in *E. coli* was stable over the 4-year study period (data not shown). The TMP-SMX MIC was >256 (TMP)/4,864 (SMX) μg/ml for each of the resistant *E. coli* isolates tested.

Univariate risk factors for TMP-SMX resistance. The host factors exhibiting a univariate association with having a TMP-SMX-resistant uropathogen are shown in Table 2. Women reporting that they were of Asian race had an eightfold greater odds of having a TMP-SMX-resistant organism than non-Asian women (50% and 11%, respectively; P = 0.006). On the other hand, women reporting that they were of black race had a 10-fold lower odds of having a TMP-SMX-resistant organism than non-black women (3% and 22%, respectively; P = 0.028). There was a linear trend for an increased TMP-SMX resistance prevalence with the level of education (P = 0.04, chi-square test for trend).

The host exposure most strongly associated with TMP-SMX resistance was travel. Of the women who reported travel outside of the state or country in the previous 3 months, 50% had a TMP-SMX-resistant uropathogen, whereas 6% of the women who did not report travel had a TMP-SMX-resistant uropathogen ($P < 0.001$). Similarly, 67% of the women who reported international travel had a TMP-SMX-resistant uropathogen, whereas 8% of the women who did not report international travel had a TMP-SMX-resistant uropathogen ($P < 0.001$). A "travel distance" variable (0 for no travel, 1 for travel out of state, and 2 for international travel) was also strongly associated with TMP-SMX resistance, yielding a 5.5-fold increased odds for each one-step increase in score, i.e., from 0 to 1 or from 1 to 2 ($P < 0.001$).

Factors not associated with TMP-SMX resistance. The variables found not to be associated with TMP-SMX resistance are shown in Table 3. Although 1 (50%) of the two women reporting Hispanic ethnicity had a TMP-SMX-resistant organism and only 14% of non-Hispanic women had a TMP-SMX-resistant organism, the small numbers of such women precluded the performance of a reliable statistical analysis. None of the variables measuring antimicrobial exposure, whether they were direct (i.e., the use of TMP-SMX or any antimicrobial in the

TABLE 3. Variables not significantly associated with TMP-SMX resistance

Variable	No. of patients with a TMP-SMX-resistant uropathogen/total no. tested (%)		Odds ratio	95% confidence interval
	Variable absent	Variable present		
Age	NA[a]	NA	0.87	0.76–1.01
Married	13/86	1/16	0.37	0.05–3.08
Hispanic	14/99	1/2	6.07	0.36–102.77
Ever diagnosed with bladder infection	2/26	13/77	2.44	0.51–11.61
Antibiotic use in last 3 mo	11/69	4/34	0.70	0.21–2.40
Antibiotic use for UTI in last 3 mo	14/90	1/13	0.45	0.05–3.76
TMP-SMX use in last 3 mo	15/95	0/5	0.82	0–6.41
Child ≤3 yr old in the household	14/89	1/12	0.49	0.06–4.08
RUTI[b] in lifetime	8/72	7/30	2.4	0.79–7.47
RUTI in past year	13/91	2/8	2.0	0.36–11.00
First UTI ≤15 yr of age	13/93	2/10	1.54	0.29–8.06
Age of first UTI	NA	NA	0.96	0.89–1.04

[a] NA, not applicable.
[b] RUTI, recurrent UTI (defined as three or more UTI episodes).

previous 3 months) or indirect (i.e., having young children in the household or children in day care), were associated with TMP-SMX resistance. Likewise, the use of antibiotics specifically for UTIs in the previous 3 months and the presence or number of UTI episodes in the prior year or lifetime were not associated with TMP-SMX resistance.

Multivariable analysis for independent risk factors for TMP-SMX resistance. All demographic and exposure variables that were univariately associated with TMP-SMX resistance at an alpha level of 0.10 or less were included as candidate variables in a forward stepwise multivariable logistic regression model, with travel distance used as the sole travel variable. In the resulting model, the two variables that were independently associated with TMP-SMX resistance were travel distance and Asian race (Table 4). The R^2 value for this model was 0.41.

CGA. Of the 80 *E. coli* isolates available for analysis, 5 (6%) proved to be CGA members. Four (80%) of the 5 CGA isolates were TMP-SMX resistant, whereas 7 (8%) of the 92 total non-CGA isolates were TMP-SMX resistant ($P < 0.001$). Thus, CGA accounted for 33% of the TMP-SMX-resistant isolates overall. There was a colinear relationship between Asian race and CGA status, and thus, when CGA was added as a candidate variable in the stepwise multivariable model, it replaced Asian race as an independent predictive factor and the model's R^2 value increased to 0.60 (Table 4).

TABLE 4. Independent predictors of having a TMP-SMX-resistant uropathogen causing acute uncomplicated cystitis

Model no.[a]	R^2	Variable in final model	*P* value	Odds ratio	95% confidence interval
1	0.41	Travel distance	<0.001	5.1	2.3–11.2
		Asian	0.048	6.1	1.0–36.4
2	0.60	Travel distance	<0.001	8.9	3.1–25.5
		CGA	0.001	105.5	6.3–1,777.6

[a] In model 1, all epidemiological variables with a univariate analysis *P* value of ≤0.10 (Table 2) were used as candidate variables in forward stepwise logistic regression. In model 2, CGA was added as a candidate variable.

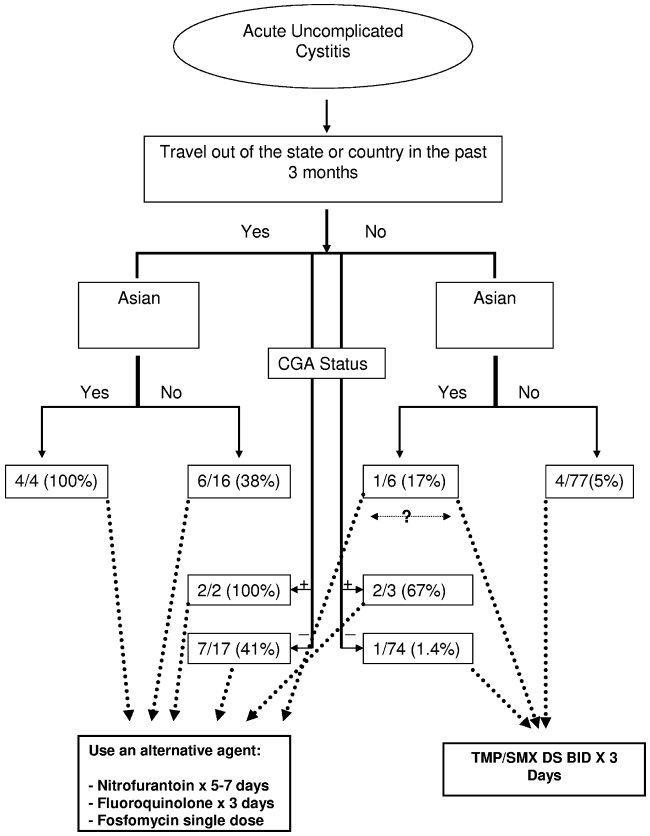

FIG. 1. Clinical algorithm for the treatment of women with acute uncomplicated cystitis, based on the expected prevalence of TMP-SMX resistance. BID, twice a day.

Clinical prediction pathway. On the basis of our findings, a decision pathway that could potentially be used to choose whether TMP-SMX should be used for a woman with uncomplicated cystitis was constructed (Fig. 1). Women who had traveled in the past 3 months or reported that they were of Asian race had the greatest odds of having a TMP-SMX-resistant organism and should thus be considered for treatment with an alternative agent. Only 5% of the women in the study who did not meet one of these criteria had a TMP-SMX-resistant organism, whereas 42% of those who met one or both of these criteria had a TMP-SMX-resistant organism ($P < 0.001$). Knowledge of CGA status and travel history could allow this 5% resistance prevalence among patients lacking key risk factors to be reduced even further, to 1.4%, while maintaining a high prevalence of TMP-SMX resistance among risk factor-positive patients (100%).

In the actual study population, the antimicrobials selected by the providers included a fluoroquinolone (48%), TMP-SMX (48%), and nitrofurantoin (3%). Since drug choice proved to

be random with respect to the actual susceptibility status of the urine organism, 40% of the subjects received fluoroquinolone therapy, even though they had a TMP-SMX-susceptible organism, whereas 8% received TMP-SMX, even though they had a resistant organism. Had the proposed clinical decision pathway been followed, these values could have been reduced substantially (Fig. 1).

DISCUSSION

An accurate understanding of the risk factors associated with TMP-SMX resistance is critically important for facilitating the appropriate antimicrobial prescription for acute cystitis. To our knowledge, this is the first study of the risk factors for TMP-SMX resistance among uropathogens specifically from prospectively enrolled women with acute uncomplicated cystitis. The potential inclusion of all eligible women presenting with a diagnosis of cystitis and the direct questioning of the women regarding their demographics and exposure histories closely mimic the realities of a general office practice setting and are clear strengths of our study compared to the methods used in previous retrospective studies.

Although previous studies have attempted to elucidate resistance-associated factors, ours is the first to allow the formulation of a clinical algorithm that yields a 5% chance or less of TMP-SMX resistance in women who lack the relevant risk factors, namely, being of Asian race or having traveled out of the state or the country in the last 3 months. These two variables were independently associated with TMP-SMX resistance, and on the basis of our study findings, their presence should lead clinicians to consider the use of alternative agents.

Interestingly, in a previous prospective study of 130 outpatients with *E. coli* UTIs in Denver, CO, the strongest independent factor associated with TMP-SMX resistance was travel outside the United States in the past 6 months (2). A history of UTI in the past 6 months was the only other independent variable identified. That study differed somewhat from ours methodologically, in that 68% of the participants were Hispanic and 5% or fewer were Asian. The inclusion in that study of pregnant women and a small number of men also differed from the population included in our study, which involved a more traditional acute uncomplicated cystitis population. Nonetheless, the previous study supports the concept that travel, and especially foreign travel, increases the risk of having a TMP-SMX-resistant uropathogen. A similar conclusion was reached in a recent study of the predictors of fecal colonization with antimicrobial agent-resistant *E. coli* among newly hospitalized adults and healthy vegetarians in Minnesota and Wisconsin, in which foreign travel (particular to the developing world) was the strongest independent risk factor associated with TMP-SMZ resistance (22).

The mechanisms for this association of travel with resistance are not clear; but the acquisition of resistant enteric flora during travel, the consumption of antibiotics (which may be more freely available in other countries or which may be brought along for the prevention or treatment of traveler's diarrhea) during travel, and cultural or ethnic dietary differences that lead to the ingestion of foods contaminated with resistant bacteria are all potential contributors. The risks posed by out-of-state travel may also be related to changes in diet or to an increased exposure to resistant organisms through close contact with other travelers or a less hygienic environment. These potential mechanisms deserve further study.

Similarly, the explanation for Asian race being an independent risk factor for TMP-SMX resistance is unclear. Others noted a high prevalence of TMP-SMX-resistant *E. coli* in an immigrant Asian population (19, 21). Although we did not assess immigration status in our study, it is possible that the Asian participants had either (i) dietary or cultural habits that directly increased their risk for TMP-SMX-resistant uropathogens or (ii) family members or intimate contacts with those risks. The strong colinearity between Asian race and having a *E. coli* CGA infection suggests that clonal spread rather than a specific ethnic or racial background may be the key factor related to TMP-SMX resistance. It is also important to note that other ethnic groups that were not well represented in our study may also be at high risk of having a TMP-SMX-resistant UTI. Specifically, Hispanic ethnicity has been postulated as increasing the risk of TMP-SMX resistance, and further evaluation of this potential association with a larger sample size would be of interest (19, 21).

We found that *E. coli* CGA was significantly and independently associated with TMP-SMX resistance. Indeed, inclusion of this variable increased the explanatory power of our multivariate model by 20%. This indicates that CGA, which was first identified as a prominent cause of TMP-SMX-resistant pyelonephritis across the United States in the mid-1990s and of TMP-SMX-resistant cystitis at student health centers in California, Minnesota, and Michigan in the late 1990s, remains a prominent contributor to TMP-SMX-resistant UTIs in some locales (11, 15). Accordingly, the discovery of the factors responsible for the emergence, dissemination, and persistence of this clinically significant clonal group, such as possible foodborne transmission (15), could conceivably lead to interventions to reduce the prevalence of TMP-SMX resistance among uropathogens. Likewise, a rapid office-based test for CGA could potentially assist practitioners in some locales in deciding when to use TMP-SMX as opposed to an alternative therapy.

Previous retrospective studies have identified the recent use of TMP-SMX as a strong predictor of TMP-SMX resistance. Our failure to find this association could have been due to a type II error. However, given the observed 15% prevalence of TMP-SMX resistance, our sample size was sufficient to provide an 80% power to detect a six- to eightfold between-group difference in TMP-SMX exposure proportions at an alpha level of 0.05. Although these risk estimates are in the range of the results from some previous retrospective studies, they are higher than the risk estimates of 2 to 5 that others have found (1, 16, 27). Thus, it is certainly possible that the association between TMP-SMX use and resistance lies in a range that is below the power of our study to detect or occurs in a time frame outside the 3-month period that we assessed. However, it is notable that another study that prospectively evaluated outpatients presenting with UTIs also did not find antibiotic use in the previous 6 months to be predictive of TMP-SMX resistance (2). This exposure, which has classically been linked to resistance, deserves further prospective investigation with a larger, geographically and ethnically diverse population.

The overall prevalence of TMP-SMX resistance among *E.*

coli isolates causing acute uncomplicated cystitis in this urban primary care practice during the study period was 17%. In contrast, the prevalence of resistance among *E. coli* isolates at the nearby University of Maryland Medical Center increased from 27% to 32% during the study period (Harold Standiford, personal communication). The lower prevalence of resistance in our outpatient setting is not surprising, since patients in a tertiary-care center are likely to be sicker, more heavily exposed to antimicrobial agents, and more likely to have complicated UTIs. Thus, the appropriateness of primary care practitioners relying on nearby hospitals' antimicrobial susceptibility data for guidance when treating otherwise healthy ambulatory women for cystitis is questionable (7).

The main limitation of our study was the relatively small number of patients studied from one geographic location. We would expect that with a greater number and a broader geographic and demographic range of study participants, additional information might be obtained regarding the contributions of exposures, such as Hispanic ethnicity and recurrent UTIs, to the risk of having a TMP-SMX-resistant UTI. We also do not have information about other potentially important factors, such as diet, the types of travel activities, household member travel and antimicrobial use, and immigration history. Additionally, since this was not a longitudinal study, we also do not have outcomes data with which to assess whether TMP-SMX resistance makes a difference clinically, although other studies have demonstrated this (1, 4, 6, 20).

Our findings could conceivably be utilized to improve empirical antimicrobial selection for uncomplicated cystitis by allowing more accurately targeted empirical therapy on the basis of patient-specific characteristics. This could both increase the proportion of women who receive an antimicrobial agent active against their uropathogen and reduce the unnecessary prescribing of fluoroquinolones for cystitis caused by TMP-SMX-susceptible organisms.

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