Trimethoprim-Sulfamethoxazole Resistance Among Urinary Coliform Isolates

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OBJECTIVE: **A large majority of urinary tract infections are caused by coliform organisms. Trimethoprim-sulfamethoxazole (TMP-SMX) resistance among uropathogens is increasing in many areas. The objective of this study was to determine risk factors for TMP-SMX-resistant coliforms in patients with urinary tract infections.**

DESIGN: **Retrospective case-control study.**

SETTING: **Emergency department of a tertiary care university hospital.**

PATIENTS: **We studied 448 emergency department patients aged 14 years or older with a urinary tract infection caused by a coliform organism. Cases consisted of all patients with a culture-documented urinary tract infection caused by a TMP-SMX-resistant coliform, while control patients were those with a TMP-SMX-sensitive organism.**

MEASUREMENTS AND MAIN RESULTS: **A univariate analysis of clinical variables associated with TMP-SMX resistance was performed. Multiple logistic regression was performed to determine independent predictors of TMP-SMX resistance. Resistance to TMP-SMX was seen in 15% of isolates. Numerous variables were associated with TMP-SMX resistance on the univariate screen. Independent predictors of resistance were diabetes (odds ratio [OR] 3.1; 95% confidence interval [CI] 1.2, 8.4), recent hospitalization (OR 2.5; 95% CI 1.1, 5.7), current use of antibiotics (OR 4.5; 95% CI 2.0, 10.2), and recent use of TMP-SMX (OR 5.1; 95% CI 2.2, 11.5). When those with recent hospitalization were excluded from analysis, independent predictors were current use of any antibiotic (OR 3.5; 95% CI 1.4, 8.4) and recent use of TMP-SMX (OR 5.9; 95% CI 2.4, 14.3).**

CONCLUSIONS: **Coliforms resistant to TMP-SMX are common in our emergency department. Diabetes, recent hospitalization, and the use of antibiotics, particularly the use of TMP-SMX, are independent risk factors for TMP-SMX resistance. Clinicians should consider these findings when deciding on antimicrobial therapy for patients with urinary tract infections.**

KEY WORDS: **trimethoprim-sulfamethoxazole resistance; urinary tract infection; coliform organisms; emergency department.**

J GEN INTERN MED 1999;14:606–609.

Highly resistant strains of pathogenic bacteria have evolved in recent years. This increase in resistance, usually seen among hospitalized patients, has been primarily due to evolutionary pressure from the use of antimicrobial agents.[1,2] However, increasing numbers of resistant bacteria are being found in outpatients.[3] The emergence of resistant strains of bacteria has been particularly challenging to physicians in outpatient settings as they usually rely upon empiric treatment of patients. In addition, physicians are frequently under pressure to limit the use of potent antimicrobial agents in order to decrease the cost of care and to avoid further resistance.

The *Enterobacteriaceae*, a group of aerobic gram-negative bacilli that includes *Escherichia coli*, cause a large majority of urinary tract infections in outpatient and emergency department settings.[4,5] Antimicrobial resistance among these gram-negative coliforms has been increasing in recent years. At many centers, the majority of *E. coli* isolates are now resistant to ampicillin, and this antibiotic is no longer recommended for the routine treatment of urinary tract infections.[4] The prevalence of strains resistant to trimethoprim-sulfamethoxazole (TMP-SMX) has also been increasing in many communities.[4] This is of particular concern as TMP-SMX is currently considered the first-line therapy for uncomplicated urinary tract infections.[6]

Few studies have examined risk factors for TMP-SMX-resistant strains of coliforms in patients with a urinary tract infection. In particular, there have been no studies focusing on an outpatient population. The purpose of this study was to analyze risk factors for TMP-SMX-resistant coliforms in patients with urinary tract infections.

METHODS

We conducted a retrospective case-control study of patients with culture-documented gram-negative coliform urinary tract infection. Case patients were those with urinary tract infections caused by coliforms that were resistant to TMP-SMX, while control patients were all those with TMP-SMX-susceptible strains. Patients were seen during a 3-year period from 1995 to 1997 and were treated in the emergency department of a large urban university hospital. Patients were identified via a computerized culture report log, and medical records were reviewed by a research assistant who was not aware of the specific purpose of the study. Patients with a urine culture of at least 10^3 colonies/mL and evidence of a urinary tract infection on review of the medical record were included in the study.[4] Susceptibility testing was done with the Kirby-Bauer disk diffusion test. The laboratory reports a result of 16 or higher as susceptible, 11 to 15 as intermediate, and 10 or less as resistant. We considered cultures with intermediate susceptibility to be sensitive in the analysis. Clinical

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Table 1. Prevalence of Resistance to Trimethoprim-Sulfamethoxazole (TMP-SMX) in Patients with Various Clinical Characteristics

Characteristic	Subjects, *n*	TMP-SMX Resistance,* % (95% CI)
Females		
All	375	14.7 (11, 19)
Healthy†	230	5.2 (3, 9)
Males		
All	73	16.4 (9, 27)
Healthy†	17	11.8 (1, 36)
Age ≥65 years		
All	54	24.1 (13, 38)
Healthy†	22	9.1 (1, 29)
Long-term care facility resident	14	28.6 (8, 58)
Use of urinary catheter	37	32.4 (18, 50)
Current antibiotic use	55	52.7 (39, 66)
Recent TMP-SMX use	52	55.8 (41, 69)

**Values are expressed as percentage resistant with 95% confidence intervals.*

†*Healthy patients are defined as those who do not reside in a long-term care facility, have not had recent hospitalization, do not use a urinary catheter, have no significant medical disorders, and are not taking antibiotics.*

evidence for urinary tract infection included the presence of fever, dysuria, frequency, urgency, suprapubic or flank pain, or other clinical presentation consistent with a urinary tract infection. Patients with more than a single isolate on culture were considered to have a contaminated specimen and were excluded. Patients aged 14 years or older were eligible for inclusion.

Data abstracted from each medical record included the causative organism, age, sex, residence in a long-term care facility, use of an indwelling urinary catheter or intermittent self-catheterization, hospitalization within the prior 3 months, history of at least two previous urinary tract infections at any time, cancer, self-reported history of diabetes, anatomic urologic disorder, or chronic neurologic disorder. If information regarding these variables was not recorded on the chart, they were considered to be absent. Patients were classified as having lower or upper tract infection on the basis of the presence or absence of fever, flank pain, or both. The current use of antibiotics was noted along with any use of TMP-SMX within the past 3 months. Bacterial isolates were classified as being either resistant or sensitive to TMP-SMX.

A univariate analysis was performed to compare clinical variables between the patients with and those without resistant strains. The χ^2 test was used to compare categorical variables; crude odds ratios and 95% confidence intervals were calculated for each variable. Continuous variables were analyzed with unpaired, two-tailed *t* test. Forward stepwise logistic regression analysis was performed to identify independent risk factors for TMP-SMX resistance. Variables with a *p* value of .20 or less by univariate analysis were entered into the logistic model, along with age and sex. In addition, the analysis excluded the individuals with recent hospitalization in order to look only at those with definite community-acquired infections. Statistical analysis was performed with SAS version 6.12 statistical software (SAS Institute Inc., Cary, NC). Confidence intervals of proportions were calculated with InStat software (GraphPad Software, Inc., San Diego, Calif). This study was considered exempt from review by the Institutional Review Board.

RESULTS

A total of 566 patients aged 14 years or older with a culture-documented urinary tract infection were seen in the emergency department during the 3-year study period. Of these infections, 448 (79%) were caused by coliform bacteria. Causative organisms included *Escherichia coli* (85%), *Proteus mirabilis* (6%), *Klebsiella pneumoniae* (4%), *Enterobacter* species (2%), *Citrobacter freundi* (2%), *Providencia* species (< 1%), and *Morganella morganii* (< 1%).

The mean age ± SD of the patients was 36 ± 19 years; 375 (84%) were female. Current antibiotic use was documented in 55 (12%) of the patients, and TMP-SMX use during the preceding 3 months was noted in 52 (12%).

Resistance to TMP-SMX was present in 67 (15%) of 448 isolates. Patients with TMP-SMX resistance (mean age 41.7 years) were older on average than those with sensitive (mean, 34.5 years) strains (difference between means, 7.2 years; 95% CI 2.3, 12.1 years; $p < .005$.) Patients with strains other than *E. Coli* (22.5%) were somewhat less likely to have TMP-SMX resistance compared with *E. coli* (13.5%) strains ($p < .08$; OR 1.9; 95% CI 0.99, 3.5). Table 1 shows the prevalence of TMP-SMX resistance stratified by various clinical criteria. Table 2 demonstrates the crude odds ratios for TMP-SMX resistance by univariate analysis. Variables that were significantly related to the presence of TMP-SMX resistance on the univariate analysis included the use of a urinary catheter, diabetes, history of recurrent

Table 2. Univariate Analysis of Risk Factors Associated with Trimethoprim-Sulfamethoxazole (TMP-SMX) Resistance on Urine Culture*

Variable	Resistant, % (*n* = 67)	Susceptible, % (*n* = 381)	Crude OR (95% CI)	*p* Value
Male sex	12 (17.9)	61 (16.0)	1.1 (0.6, 2.3)	.70
Age ≥65 years	13 (19.4)	41 (10.8)	2.0 (1.0, 4.0)	.04
Residence in long-term care facility	4 (6.0)	10 (2.6)	2.4 (0.7, 7.7)	.15
Use of urinary catheter	12 (17.9)	25 (6.6)	3.1 (1.5, 6.5)	.002
Upper tract infection	34 (50.7)	188 (49.3)	1.1 (0.6, 1.8)	.83
Diabetic	9 (13.4)	19 (5.0)	3.0 (1.3, 6.8)	.008
History of cancer	4 (6.0)	14 (3.7)	1.7 (0.5, 5.2)	.38
History of recurrent UTIs	28 (41.8)	99 (24.0)	2.0 (1.2, 3.5)	.008
Urologic abnormality	10 (14.9)	31 (8.1)	2.0 (0.9, 4.3)	.08
Neurologic abnormality	13 (19.4)	27 (7.1)	3.2 (1.5, 6.5)	<.001
Recently in hospital	12 (17.9)	32 (8.4)	2.4 (1.2, 4.9)	.016
Currently on antibiotic	29 (43.3)	26 (6.8)	10.4 (5.6, 19.5)	<.001
Currently or recently on TMP-SMX†	29 (43.3)	23 (6.0)	11.9 (6.3, 22.6)	<.001

**OR indicates odds ratio; CI, confidence interval; UTI, urinary tract infection; TMP-SMX, trimethoprim-sulfamethoxazole.*
†*Use at any time within the past 3 months, including current use.*

urinary tract infections, presence of a neurologic abnormality, recent hospitalization, current use of antibiotics, and recent use of TMP-SMX.

Variables with a *p* value of .20 or less on the univariate analysis (Table 2) were included in the final model along with the age and sex variables. Multivariate logistic regression analysis revealed four independent predictors of TMP-SMX resistance. A history of diabetes (OR 3.1; 95% CI 1.2, 8.4), recent hospitalization (OR 2.5; 95% CI 1.1, 5.7), current use of any antibiotic (OR 4.5; 95% CI 2.0, 10.2), and the current or recent use of TMP-SMX (OR 5.1; 95% CI 2.2, 11.5) were all independent predictors for TMP-SMX resistance. When those with recent hospitalization were excluded, the only independent predictors were current use of any antibiotic (OR 3.5; 95% CI 1.4, 8.4) and recent use of TMP-SMX (OR 5.9; 95% CI 2.4, 14.3).

DISCUSSION

Trimethoprim-sulfamethoxazole has been a useful combination of antimicrobials for treating a variety of urinary, gastrointestinal, and respiratory tract infections.[7] However, high-level plasmid-encoded resistance to both trimethoprim and sulfamethoxazole is easily transferred among gram-negative organisms.[8] The rate of TMP-SMX resistance has been steadily rising in recent years, particularly in developing countries.[7–9] Some industrialized countries, however, have also seen a marked increase in the number of resistant coliforms.[9–11]

Most authorities consider TMP-SMX the antimicrobial agent of choice for outpatients with uncomplicated urinary tract infections.[4,6] It is inexpensive, is usually well tolerated, and is taken on a twice-a-day basis. In addition, a short course of therapy with TMP-SMX has been shown to be effective treatment for uncomplicated cystitis in a population with a low prevalence of TMP-SMX resistance.[12]

Few studies have examined the prevalence of and risk factors for resistant coliforms in outpatient or emergency department patients.[5] In this study, many patients with urinary tract infections were infected with organisms that were resistant to a commonly used antimicrobial agent. A variety of clinical variables were associated with the presence of TMP-SMX resistance among coliforms in the univariate analysis. Multivariate analysis, however, revealed that most were not independent predictors of resistance to TMP-SMX.

A history of diabetes mellitus was found to be an independent predictor of TMP-SMX resistance. In a preliminary report, Eiband et al., looking at gram-negative urinary tract infections in a geriatric population, reported that diabetes mellitus was a risk factor for infection with a multiple-drug-resistant organism.[13] Other studies looking at risk factors for resistant organisms have not found diabetes to be a predictor.[14,15] Although the presence of diabetes is certainly a risk factor for urinary tract infection,[16] it is possible that our finding of increased resistance is the result of other factors not controlled for in the model. Diabetes, however, did not appear to be an independent risk factor in this study when those with potential hospital-acquired infections were excluded. Recent hospitalization was also a risk factor for the presence of a resistant organism. This finding is not surprising as hospitalization is known to be a risk factor for acquisition of resistant organisms, including the gram-negative pathogens analyzed in this study.[17]

The current use of any antibiotic and the current or recent use of TMP-SMX also were strong independent predictors of TMP-SMX resistance. We found that the use of antibiotics was predictive of resistance even when excluding the subgroup with recent hospitalization, thereby excluding those with potential hospital-acquired infections. The relation between antibiotic use and resistance is not surprising as the use of antibiotics is known to be the

major risk factor for the development of resistant organisms.[1,2] Multiple studies have shown that stool carriage of TMP-SMX-resistant *E. coli* is related to previous use of antibiotics.[9,10] Antibiotic resistance among the enteric flora, as demonstrated by mathematical modeling, emerges rapidly even when resistance genes and plasmids are present in very small numbers. In addition, modeling predicts that resistance will persist in the environment as long as a proportion of the population is treated with antibiotics.[18]

Resistance to TMP-SMX in urinary isolates is of uncertain clinical significance, given the high antibiotic concentration obtained in urine. There is, however, evidence that cure rates of outpatients with resistant uropathogens are lower than those with susceptible strains.[12,19–21] For instance, one study of TMP-SMX-treated patients showed an eradication rate of only 50% in TMP-SMX-resistant strains, compared to 80% for all strains.[20]

This study is limited by its retrospective methodology. Some useful variables that might be related to the presence of resistant organisms, such as the use of antibiotics by household members or method of birth control, could not be obtained. In addition, there is the possibility of misclassification bias as not all patients had accurate recording of all variables on the medical record. Most of the variables examined, however, were chosen because they were well documented on the majority of charts. For some of the variables studied, particularly residence in a long-term care facility, the number of subjects was small, which could have affected the results of the multivariate analysis. It is likely that some patients, particularly young women, did not have a specimen cultured and were not included in the study. If that were the case, these patients might be at lower risk of having a resistant strain and their exclusion would lead to a bias in our reported overall prevalence of TMP-SMX resistance. However, their exclusion would not alter the odds ratios obtained in the univariate or multivariate analysis. The number of patients who did not have a specimen cultured is unknown as records for this study were obtained from culture logs. The external validity of this study is also limited because it was performed at a tertiary care center located in the Southeastern United States. Centers in different geographic regions and centers with different demographic characteristics might have different resistance patterns.

In summary, we have found that TMP-SMX-resistant coliforms are common in outpatients with urinary tract infections. Several groups of individuals, including those who use urinary catheters, patients with neurologic or urologic disorders, recently hospitalized patients, diabetics, and those currently taking antibiotics, had an increased risk on univariate analysis. However, multivariate analysis revealed that the presence of diabetes, recent hospitalization, current use of antibiotics, and recent use of TMP-SMX were independent risk factors for TMP-SMX resistance. It would appear prudent to consider the use of a fluoroquinolone in some high risk-populations, such as those with urinary catheters and those recently or currently on antibiotics, given the high prevalence of TMP-SMX resistance in these patients. Managed care organizations should ensure that appropriate antimicrobial agents are available in their outpatient formularies for treatment of these high-risk patients.

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