Prevalence and Predictors of Trimethoprim-Sulfamethoxazole Resistance among Uropathogenic *Escherichia coli* Isolates in Michigan

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Resistance among uropathogenic *Escherichia coli* to trimethoprim-sulfamethoxazole (TMP-SMX) has increased. Risk factors for resistance and the impact on clinical failure have been poorly described. We performed a retrospective cohort study of women with acute uncomplicated cystitis seen at a university health center and at primary care clinics in southeastern Michigan from 1992 to 1999. The prevalence of TMP-SMX resistance increased from 8.1% to 15.8% (*P* = .01). Women who had taken TMP-SMX recently were >16 times as likely as women who had not taken antibiotics recently to be infected with an isolate resistant to this agent; those who had taken any other antibiotic were more than twice as likely to be infected with a resistant isolate. Women infected with a TMP-SMX–resistant isolate who were treated with TMP-SMX were >17 times as likely to have treatment failure. Recent antibiotic use is a risk factor for infection with a TMP-SMX–resistant isolate; patients who are infected with a TMP-SMX–resistant isolate and who are treated with this agent are at a higher risk for clinical failure.

Urinary tract infection (UTI) is a common clinical entity that affects 11 million women annually, accounting for >7 million visits to the physician each year in the United States [1–3]. Because the microbiologic characteristics of acute, uncomplicated UTI are highly predictable in otherwise healthy women, antimicrobial therapy is usually empiric; obtaining a urine sample for culture for microbiologic confirmation and antimicrobial susceptibility testing is generally not recommended [4, 5]. Short-course (i.e., 3-day) therapy is commonly used; thus, the results of cultures and antimicrobial susceptibility testing are usually not clinically useful, because the course of therapy will be almost complete by the time susceptibility data are available to the clinician.

Recently, there has been concern about an increase in the prevalence of resistance among *Escherichia coli* to trimethoprim-sulfamethoxazole (TMP-SMX), a first-line agent for the management of UTI [6–15]. In light of these reports, many experts, including the Practice Guidelines Committee of the Infectious Diseases Society of America, have proposed that the use of TMP-SMX as a first-line empiric therapy for acute uncomplicated cystitis be abandoned in communities where the prevalence of TMP-SMX resistance is ≥20% [16]. Other experts have suggested that an even lower threshold prevalence of resistance of 10% should prompt a
change in the recommended empiric therapy for UTI [17].

Unfortunately, data regarding the prevalence of TMP-SMX resistance is generally not available for most communities, and resistance rates may vary by geographic region. In a recently published multicenter treatment study, the prevalence of resistance to TMP-SMX among E. coli isolates recovered from women with acute uncomplicated pyelonephritis was 7% in medical centers in the eastern United States, 14% in the Midwest, and 32% in the western United States [18]. Although that study demonstrated a significant association between resistance and clinical and bacteriologic failure in women with pyelonephritis, there are few data regarding the impact of in vitro resistance on clinical failure in women with acute cystitis, and untreated acute cystitis rarely progresses to symptomatic upper UTI [19].

Few studies have addressed the risk factors for resistance to first-line agents among women with acute uncomplicated UTI. This information could aid clinicians in determining which patients should be treated with alternative agents, even if data regarding the true prevalence of resistance in the local community are lacking. To further explore these issues, we determined the susceptibilities to 6 commonly used antimicrobials for 601 E. coli isolates recovered from women with acute, uncomplicated cystitis who had been seen at a university health center or at primary care clinics in southeastern Michigan from 1992 to 1999. Risk factors for antimicrobial resistance and the risk of clinical failure for patients infected with TMP-SMX–resistant isolates were assessed.

PATIENTS AND METHODS

Urinary tract isolates. Urinary tract isolates of E. coli were obtained from women aged 18–65 years who had acute uncomplicated cystitis during the period of September 1992 through April 1999 as part of 3 prospective studies of the epidemiology of UTI ([20, 21]; B. Foxman, S.D. Manning, P. Tallman, R. Bauer, L. Zhang, J.S. Kopman, B. Gillespie, J.D. Sobel, C.F. Mars, unpublished data). Study collection 1 comprises 325 isolates recovered from women aged 18–39 years who had varying UTI histories (208 isolates were recovered during the patients’ first episodes of infection) and who presented to University Health Services (UHS) at the University of Michigan, Ann Arbor. Collection 2 comprises 60 isolates recovered from women aged 40–65 years, 55 of whom had a history of ≥1 previous episode of UTI; these women presented to outpatient primary care clinics throughout southeastern Michigan. Collection 3 comprises 165 isolates recovered from women aged 18–39 years who presented to UHS with their first episode of UTI. Collection 4 comprises 24 isolates recovered from women represented in collection 3 who presented with a second episode of UTI. Collection 5 comprises 27 isolates recovered from women aged 18–39 years who presented to UHS and who had self-reported ≥3 episodes of UTI during the 12 months before presentation.

Only 1 isolate was included from each episode of infection. A UTI was defined by ≥1 urinary symptom (e.g., dysuria, urgency, frequency, and hematuria) in the presence of ≥1000 cfu of E. coli per mL of urine isolated from a clean-catch sample using a standard calibrated loop technique. Isolates were stored in Luria broth–glycerol at −70°C. Isolate identification was confirmed and antimicrobial susceptibility testing was performed by use of an automated microtiter broth dilution technique (Dade MicroScan). Isolates with intermediate resistance were grouped with resistant isolates in the analysis; however, only 1 isolate demonstrated intermediate resistance to TMP-SMX.

Patient characteristics. Women included in the study had no history of diabetes, recent instrumentation of the urinary tract, or recent hospitalization. Each woman completed a detailed questionnaire regarding her UTI history. Patient age and history of antibiotic use (including the name of any antibiotics used) in the 2 weeks preceding the diagnosis of UTI were recorded, as was the history of oral contraceptive (OC) use and use of hormone replacement therapy. Women who had taken an antibiotic within 24 h of presentation were excluded. Of the 601 isolates, 232 were recovered from women during their first episode of UTI.

Impact of TMP-SMX resistance on clinical failure. The medical records of patients who had isolates included in study collection 1 and who were infected with a TMP-SMX–resistant isolate were reviewed to determine which antimicrobial was prescribed and the duration of treatment prescribed and to look for evidence of clinical failure, which was defined as a phone call or an additional visit within 2 weeks of the initial visit because of ≥1 persistent symptom of UTI. In addition, the medical records of 93 randomly selected patients infected with TMP-SMX–susceptible isolates were reviewed.

Statistical methods. Differences between groups were tested by use of the χ² and Student’s t test. The Mantel-Haenzel χ² was used to test changes in resistance rates over time. The effects of covariates were estimated by use of the risk ratio (RR) and 95% CI, calculated by use of Epi Info, version 6.04b (Centers for Disease Control and Prevention). Logistic-regression analysis was used to assess individual effect of year of diagnosis, recent antibiotic use, and UTI type on TMP-SMX resistance and clinical treatment failure.

Research was approved by the Institutional Review Board of the University of Michigan.
RESULTS

The susceptibility data for 601 E. coli isolates obtained from women who had acute uncomplicated cystitis during the period of 1992 to 1999 are summarized in table 1. The prevalence of resistance to ampicillin and cephalothin was high throughout the study period, and the prevalence of resistance to ciprofloxacin and gentamicin remained very low. A significant increase in the prevalence of resistance to TMP-SMX (from 8.1% to 15.8%) was observed during the study period (P = .01, by Mantel-Haenzel χ²). In addition, although the overall prevalence of resistance to nitrofurantoin was low, a significant increase in resistance during the study period was observed (0%–2.4%; P = .03, by Mantel-Haenzel χ²). The increase in the prevalence of TMP-SMX resistance remained significant even after controlling for UTI history. When data were controlled for year collected, no significant differences were seen between the prevalence of resistance among women in the 18–39-year age group (11%) and among those in the 40–65-year age group (10%).

Data regarding OC use were available for 481 (89%) of 541 patients in the 18–39-year age group; 28.7% of women had used an OC in the 2 weeks before the diagnosis of UTI. However, there was no significant association between OC use and the risk of infection with a TMP-SMX–resistant isolate (P = .37). A total of 338 women (70.3%) had used an OC at some time; however, they were no more likely to have infection with a resistant isolate than those who had never used an OC (P = .86). Data regarding the use of hormone replacement therapy were available for 53 (88%) of 60 women in the 40–65-year age group. No significant association between infection with a resistant isolate and the use of hormone replacement therapy ever (for 21 patients [39.5%]) or within the 2 weeks preceding the diagnosis of UTI (for 13 [24.4%]) was seen.

Information regarding recent antibiotic use by patients was available for 574 of the isolates. An antibiotic had been taken in the 2 weeks preceding the diagnosis of UTI by 57 participants (9.9%), 7 (1.2%) of whom took TMP-SMX. Women who had taken TMP-SMX in the 2 weeks preceding the diagnosis of UTI were more likely than those who had not taken an antibiotic to be infected with an isolate that was resistant to TMP-SMX, ciprofloxacin, and nitrofurantoin (P < .001). By use of logistic-regression analysis, which controlled for year of sample collection, UTI history, and recent antibiotic use, we found that women who had taken any antibiotic (except TMP-SMX) in the 2 weeks preceding the diagnosis of UTI were more than twice as likely to be infected with a TMP-SMX–resistant isolate (OR, 2.37; 95% CI, 1.14–4.95; P = .02); women who had taken TMP-SMX in the 2 weeks preceding the diagnosis of UTI were 16 times as likely as those who had not received antibiotic therapy to be infected with a TMP-SMX–resistant isolate (OR, 16.74; 95% CI, 2.90–96.95; P = .002; table 2). After adjustment for recent antibiotic use in the logistic-regression model, a history of frequent, recurrent UTI (defined as ≥3 infections in the preceding 12 months) was not an independent predictor of infection with a TMP-SMX–resistant isolate (OR, 1.65; 95% CI, 0.55–4.92; P = .37).

A total of 44 women with isolates included in study collection 1 were infected with a TMP-SMX–resistant isolate, and 33 of these women were treated with TMP-SMX. Among 93 randomly selected women infected with a TMP-SMX–susceptible isolate, 71 were treated with TMP-SMX. For women infected with a resistant isolate who were treated with TMP-SMX, the clinical failure rate was 45.5%, whereas, among those infected with a susceptible isolate who were treated with TMP-SMX, the rate of clinical failure was 4.2%. Women infected with a TMP-SMX–resistant isolate were more than twice as likely to have treatment failure with TMP-SMX than were those infected with a TMP-SMX–susceptible isolate (RR, 10.76; 95% CI, 3.34–34.62; P < .0001). Data regarding the duration of prescribed antibiotic therapy were available for 32 (97%) of 33 women infected with a TMP-SMX–resistant isolate. The mean duration of prescribed TMP-SMX treatment was 3.4 days for the patients who experienced clinical failure and 4.9 days for the patients who did not (P = .0037). In a

<table>
<thead>
<tr>
<th>Date of isolate recovery</th>
<th>No. of isolates</th>
<th>Percentage of isolates resistant, by agent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ampicillin</td>
<td>Cephalothin</td>
</tr>
<tr>
<td>1992–1993</td>
<td>123</td>
<td>34.1</td>
</tr>
<tr>
<td>1994–1995</td>
<td>107</td>
<td>29.0</td>
</tr>
<tr>
<td>1996–1997</td>
<td>206</td>
<td>25.7</td>
</tr>
<tr>
<td>1998–1999</td>
<td>165</td>
<td>30.9</td>
</tr>
</tbody>
</table>

**NOTE.** TMP-SMX, trimethoprim-sulfamethoxazole.

* Test for trend (Mantel-Haenzel χ²) revealed significance (P < .01).

* Test for trend (Mantel-Haenzel χ²) revealed significance (P < .03).
Table 2. Logistic-regression model predicting trimethoprim-sulfamethoxazole (TMP-SMX) resistance in 574 women with acute uncomplicated cystitis for whom data regarding recent antibiotic use were known, Michigan, 1992 to 1999.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%) of women with characteristic</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent* antibiotic use, except TMP-SMX</td>
<td>57 (9.9)</td>
<td>2.37 (1.14–4.95)</td>
<td>.02</td>
</tr>
<tr>
<td>Recent* TMP-SMX use</td>
<td>7 (1.2)</td>
<td>16.74 (2.90–96.95)</td>
<td>.002</td>
</tr>
<tr>
<td>3 UTIs during the 12 months before diagnosis</td>
<td>24 (4.2)</td>
<td>1.65 (0.55–4.92)</td>
<td>.37</td>
</tr>
</tbody>
</table>

NOTE. UTI, urinary tract infection.
* Within 2 weeks before diagnosis.

logistic-regression model, after controlling for susceptibility of the isolate and duration of prescribed TMP-SMX therapy, we found that women infected with a TMP-SMX–resistant isolate were 17 times as likely to have TMP-SMX failure than were women infected with a susceptible isolate (OR, 17.45; 95% CI, 4.44–68.57; P < .0001). Differences in the duration of prescribed treatment did not achieve statistical significance in the logistic-regression model.

DISCUSSION

The prevalence of TMP-SMX resistance among isolates of uropathogenic E. coli recovered from women with acute uncomplicated cystitis in Michigan doubled between 1992 and 1999, from 8.1% to 15.8%. Despite a significant increase in resistance rates, the overall prevalence of TMP-SMX resistance in our patient population is lower than that reported in other recent studies [6, 11–15]. Among E. coli isolates recovered from women in Seattle, Washington, who had acute uncomplicated cystitis, who were seen in a setting in which women with UTI routinely provide samples for culture, Gupta et al. [6] reported that the prevalence of TMP-SMX resistance increased from 9% in 1992 to 18% in 1996. In a prospective multinational, multicenter study from 17 countries in Europe and Canada conducted from January 1999 through January 2000 (the ECOSENS project), the overall prevalence of TMP-SMX resistance among E. coli isolates recovered from women with uncomplicated UTI was 15% [7]. However, resistance rates have varied from 8.7% (The Netherlands) to 34.8% (Portugal and Spain).

Geographic differences in the prevalence of resistance may reflect differences in patterns of antimicrobial use. By use of genomic DNA restriction pattern analysis, Perrin et al. [22] demonstrated that tremendous genomic diversity is noted among antibiotic-resistant E. coli isolates recovered from persons with community-acquired as well as nosocomially acquired UTIs, which suggests that resistance occurs as a result of selection from the endogenous flora of patients, rather than from clonal spread of resistant isolates. The prevalence of ciprofloxacin resistance remained very low throughout the study period, which is consistent with the prevalences reported in other studies in the United States. In the ECO-SENS study, the overall prevalence of ciprofloxacin resistance was 3%; however, the prevalence of resistance was 20% in Spain and 37% in Portugal [7].

Study methodology may also be an important factor in explaining the differences seen in resistance rates among different studies. Studies that use laboratory-based, passive surveillance are likely to overestimate the true prevalence of resistance, because women with complicated infections or who have experienced therapeutic failure may be overrepresented. Baerheim et al. [23] found that resistance rates for UTI isolates reported from the local hospital microbiology laboratory were significantly higher than were the rates observed among patients with acute cystitis seen in outpatient clinics in the same geographic region.

Two previous, retrospective, case-control studies identified diabetes, recent hospitalization, recent antibiotic use, and prior estrogen use (either OCs or estrogen-replacement therapy) as independent risk factors for infection with TMP- or TMP-SMX–resistant uropathogens [24, 25]. We found no evidence of an association between OCs or estrogen-replacement therapy and risk of infection with a TMP-SMX–resistant isolate. Women who had diabetes and who had recently been hospitalized were excluded from our studies; thus, we cannot comment on the effects of these variables.

Our data clearly show that recent antibiotic use is an important risk factor for infection with an isolate that is resistant to first-line therapy for UTI. Women who took TMP-SMX in the 2 weeks preceding the diagnosis of their infection were significantly more likely to be infected with an isolate that was resistant not only to this antimicrobial but also to other agents used for the treatment of UTI (ciprofloxacin and nitrofurantoin). Although the mechanisms of resistance to these agents are quite different, it is possible that resistance to a first-line UTI agent is a marker for more extensive past exposure to other antimicrobials used frequently in the management of UTI. In the logistic-regression model, however, antibiotic use during the 2 weeks before presentation had a strong, statistically significant association with infection due to a TMP-SMX–resistant isolate, but a history of frequent, recurrent UTI did not. This suggests that recentness of antibiotic use, rather than extensiveness of past exposure, is important with regard to the resistance status of the current isolate.

To fully understand the impact that data regarding the prevalence of antibiotic resistance should have on clinical practice, more information is needed regarding the impact of in vitro resistance on clinical treatment failure in women with acute uncomplicated cystitis. In our study, the clinical success rate of TMP-SMX treatment for women infected with a resistant
isolate was 55.5%. During the study period, treatment decisions were left to the discretion of the attending physician, and patients did not receive a uniform duration of prescribed therapy. Among women infected with a TMP-SMX-resistant isolate who received TMP-SMX therapy, we found a significant difference in the mean duration of prescribed therapy between the patients who experienced clinical failure and those who did not; however, this difference did not reach statistical significance in the logistic-regression model. It is possible that some isolates classified as “resistant” may be near the conventional breakpoints for susceptibility, and that more prolonged courses of therapy with agents that achieve high peak concentrations in the urine may be sufficient to successfully eradicate the infection.

Most health care providers do not have access to data about the prevalence of resistance in the geographic area in which they practice. It has been suggested that mechanisms be established for the periodic assessment of antimicrobial susceptibilities among UTI isolates in communities [16]; however, such mechanisms do not currently exist, and it is unclear who would pay for these studies. In the absence of data regarding resistance rates in the local community, physicians may opt for use of alternative antibiotic therapies. Nitrofurantoin is a reasonable option; however, this agent has not been shown to be effective as short-course (i.e., 3-day) therapy for acute uncomplicated cystitis, so longer (i.e., 7-day) durations of therapy would be required [5].

Fluoroquinolones are an attractive alternative, because studies from the United States have shown that resistance to fluoroquinolones has remained uncommon, and these agents are well tolerated and highly effective for use as short-course therapy for acute uncomplicated cystitis, although they are more expensive than other alternatives. Recent studies of resistance among uropathogens from outside the United States have revealed alarmingly high levels of resistance to fluoroquinolones in certain areas, which raises the concern that, if these agents become first-line therapy for common non–life-threatening infections, emerging resistance may limit their usefulness for other, more serious conditions.

The ability to identify, on the basis of clinical history, patients at high risk of infection with a TMP-SMX-resistant uropathogen would allow physicians to reserve alternative antibiotic therapies for those patients who are at the highest risk of clinical failure because of antibiotic resistance. On the basis of our data, women who have recently taken TMP-SMX prior to developing a UTI should probably not be treated with this agent. Although our study showed that use of antibiotics other than TMP-SMX also increased the risk of infection with a TMP-SMX-resistant isolate, the risk was not as great, and empiric therapy with TMP-SMX may still be reasonable. Another option might be to perform a urine culture for those women who are at risk for infection with a resistant isolate, so that therapy could be adjusted on the basis of the results of susceptibility tests if clinical failure occurs—remembering that, in our study, more than one-half of the women infected with a TMP-SMX-resistant isolate who received treatment with this agent did not have clinical treatment failure. Although untreated, uncomplicated cystitis is unlikely to progress to pyelonephritis, treatment failure may be associated with morbidity due to persistent symptoms, as well as with increased costs due to return physician visits and additional testing and treatment.

The possibility that more-prolonged courses of TMP-SMX might be used as a strategy to decrease the rate of clinical failure in women infected with a resistant isolate deserves further study. Increased cost and patient convenience will need to be considered in evaluating management strategies that involve obtaining samples for culture and susceptibility data and more-prolonged courses of therapy. Additional prospective studies to more clearly define risk factors for TMP-SMX resistance are needed.

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References


