Empiric Use of Trimethoprim-Sulfamethoxazole (TMP-SMX) in the Treatment of Women with Uncomplicated Urinary Tract Infections, in a Geographical Area with a High Prevalence of TMP-SMX–Resistant Uropathogens

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This study evaluated whether trimethoprim-sulfamethoxazole (TMP-SMX) is effective for treatment of uncomplicated urinary tract infections (UTIs) due to TMP-SMX–resistant (TMP-SMX–R) pathogens. Healthy nonpregnant premenopausal women with symptomatic lower UTI were assessed for the presence of pyuria and bacteriuria; if either was present, a urine sample was cultured and TMP-SMX was prescribed. Clinical and microbiologic cure was assessed at days 5–9 and 28–42 after cessation of therapy. For 71% of patients, cultures grew TMP-SMX–susceptible (TMP-SMX–S) microorganisms, and for 29%, cultures grew TMP-SMX–R organisms. Escherichia coli remained the predominant bacteria in both groups of cultures. At visit 2, microbiological cure had been achieved in 86% of the patients in the TMP-SMX–S group and 42% of those in the TMP-SMX–R group. Similar differences were found at visit 3 by clinical evaluation. Treatment with TMP-SMX of uncomplicated UTI caused by TMP-SMX–R microorganisms results in microbiologic and clinical failure. In high-resistance areas, TMP-SMX should not be the empiric drug of choice for uncomplicated UTI.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for the treatment of uncomplicated community-acquired urinary tract infections (UTIs) in areas where the prevalence of TMP-SMX–resistant pathogens is <10% [1]. Talan et al. [2] showed that, in women with uncomplicated pyelonephritis, in vitro resistance of isolates to TMP-SMX was strongly associated with bacteriologic and clinical failure. However, the effect of infection with pathogens that demonstrate in vitro resistance to TMP-SMX among women with uncomplicated cystitis has not been extensively evaluated to date. In Israel, 30%–50% of uropathogens (mainly Escherichia coli) recovered from women with community-acquired cystitis are resistant to TMP-SMX. However, doctors continue to prescribe TMP-SMX, arguing that in vitro resistance does not necessarily reflect in vivo resistance, especially with a drug such as TMP-SMX that achieves high levels in urine [3]. Therefore, we decided to evaluate whether TMP-SMX is effective for the treatment of uncomplicated cystitis in women infected with TMP-SMX–resistant pathogens.
PATIENTS AND METHODS

Study population. Healthy premenopausal women ≥18 years old with a clinical diagnosis of uncomplicated lower UTI were enrolled at 12 outpatient clinics (11 in northern Israel and 1 in the central part of the country) from January 1997 through December 2000. A lower UTI was defined by dysuria, frequency, urgency, and suprapubic tenderness without associated fever and loin pain. Pregnant women and women with a history of pyelonephritis, sensitivity to sulfa drugs, or glucose-6-phosphatase dehydrogenase deficiency were excluded. The study was approved by the local ethics committee of each participating institution.

Study procedures. Women who had a clinical diagnosis of lower UTI were assessed for pyuria and bacteriuria by use of a leukocyte esterase dipstick. If pyuria and/or bacteriuria were present, a urine sample was sent to the laboratory for culture and analysis; after written informed consent was obtained, TMP-SMX (160 mg/800 mg b.i.d. for 5 days) was prescribed. Demographic data, such as the patient’s age and any previous episodes of UTI, were also recorded. This constituted visit 1. If urine cultures were negative for all pathogens, the women were excluded from the study. We subsequently defined 2 groups of patients: one group of women with uncomplicated lower UTI caused by TMP-SMX–susceptible organisms, and a second group with infections caused by TMP-SMX–resistant organisms.

Clinical and microbiological follow-up was done at 5–9 days (visit 2) and at 28–42 days (visit 3) after cessation of therapy. Women with asymptomatic bacteriuria were observed without being prescribed a new course of antimicrobial agents. Adverse events were also recorded.

Microbiologic methods. For all women, a urine sample was obtained for quantitative culture before the start of therapy and 5–9 days and 28–42 days after cessation of therapy or if symptoms of UTI appeared at any time during the follow-up period. Organisms that grew to a concentration of ≥10^3 cfu/mL of urine were identified by use of standard microbiologic techniques. Antimicrobial susceptibility testing was performed according to National Committee for Clinical Laboratory standards [4] with Microscan Urine Combo 2 panels (Dade Microscan).

Main outcome measures. The primary measure of efficacy was bacteriologic cure at visit 1 among all enrolled women whose data were suitable for efficacy analysis. The efficacy evaluation was performed if the following criteria were met: (1) the patient met the enrollment criteria for uncomplicated lower UTI; (2) the pretreatment urine culture grew a uropathogen at a concentration of ≥10^3 cfu/mL of urine, (3) the patient had taken the study drug for 5 full days, (4) no other antimicrobial agents had been prescribed, and (5) the patient had had ≥1 follow-up visit after the cessation of therapy. Uropathogens are listed in table 1. Bacteriologic failure at visit 1 was defined as persistence of the original infecting agent or agents, as assessed by standard microbiologic identification techniques, or as a superinfection with a new uropathogen. Secondary criteria for efficacy were sterile cultures at 28–42 days after the cessation of therapy (at visit 2) and clinical cure (absence of all signs and symptoms related to UTI) at visit 3.

Statistical methods. Data analysis was performed with the SPSS statistical package (SPSS). The relationships between clinical and bacteriologic findings and TMP-SMX resistance were examined by use of the χ² test. We calculated 95% CIs for proportions of interest. We estimated, on the basis of previous epidemiologic studies, that 30%–40% of the uropathogens in our geographical area are resistant to TMP-SMX. On the basis of previous studies, we expected that the cure rates for women with uncomplicated cystitis who were infected with TMP-SMX–susceptible pathogens would be ~85%, and the cure rate for women infected with TMP-SMX–resistant pathogens would be 40%–50%.

To obtain differences of 20% with P ≤ .05 and a power of 90%, we estimated that we would need a sample size of ~120 women in the TMP-SMX–resistant group and 280 women in the TMP-SMX–susceptible group. Because we expected a drop-out rate of 20%, we estimated that a total sample size of ≥550 women would be required.

RESULTS

Study population. A total of 618 women with clinical symptoms of lower UTI and pyuria and/or bacteriuria were enrolled (figure 1). Of these, 544 had urine cultures positive for uropathogens; 74 women with sterile culture were excluded from the study. A total of 384 (71%) of 544 samples yielded a TMP-SMX–susceptible organism, and 160 (29%) yielded a TMP-SMX–resistant uropathogen. In the TMP-SMX–susceptible and

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. (%) of isolates</th>
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<tbody>
<tr>
<td>Escherichia coli</td>
<td>296 (77)</td>
</tr>
<tr>
<td>Klebsiella species</td>
<td>49 (13)</td>
</tr>
<tr>
<td>Proteus species</td>
<td>20 (5)</td>
</tr>
<tr>
<td>Morganella species</td>
<td>16 (4)</td>
</tr>
<tr>
<td>Others</td>
<td>19 (5)</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>10 (3)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>Group B β-hemolytic streptococcus</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>384 (71)</td>
</tr>
</tbody>
</table>
Table 2. Bacteriologic and clinical response of women with urinary tract infections treated with trimethoprim-sulfamethoxazole (TMP-SMX).

<table>
<thead>
<tr>
<th>Efficacy criterion</th>
<th>Infection with TMP-SMX–susceptible pathogens</th>
<th>Infection with TMP-SMX–resistant pathogens</th>
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<tbody>
<tr>
<td></td>
<td>Proportion of patients (%)</td>
<td>Percentage of patients (95% CI)</td>
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<tr>
<td>Primary: microbiologic cure at visit 2</td>
<td>288/353</td>
<td>82 (81–92)</td>
</tr>
<tr>
<td>Secondary Microbiologic cure at visit 3</td>
<td>265/280</td>
<td>93 (88–97)</td>
</tr>
<tr>
<td>Clinical cure at visit 2</td>
<td>293/333</td>
<td>88 (84–91)</td>
</tr>
<tr>
<td>Clinical cure at visit 3</td>
<td>265/285</td>
<td>93 (90–96)</td>
</tr>
</tbody>
</table>

* No. of patients with finding/no. of evaluable patients.

TMP-SMX–resistant groups, 49 and 9 women were excluded, respectively; 19 and 4 women, respectively, were dropped from the study because they were lost to follow-up, and 30 and 5 women, respectively, had adverse events. The mean age (± SD) of the women in the TMP-SMX–susceptible group was 33.1 ± 7.9 years, and it was 34.0 ± 7.6 years for the women in the TMP-SMX–resistant group. TMP-SMX–resistant bacteria were recovered from 98 (65%) of 151 of the women with recurrent UTIs and from 62 (41%) of the women without a history of recurrences (P = .001).

Table 1 summarizes the susceptibilities of the uropathogens to TMP-SMX. E. coli was the most common infecting organism in both the TMP-SMX–susceptible and TMP-SMX–resistant groups (77% and 81% of isolates, respectively). In addition, the TMP-SMX–resistant uropathogens had a higher rate of resistance than did the TMP-SMX–susceptible pathogens to amoxicillin-clavulanate (88% vs. 75% of isolates; P < .001) and cephalexin (57% vs. 45%; P = .009), but not to nitrofurantoin, ciprofloxacin, and ofloxacin.

**Bacteriologic response.** The rate of bacteriologic cure 5–9 days after the cessation of therapy (our primary efficacy parameter) was significantly different in the 2 groups: 288 (86%) of 333 women infected with TMP-SMX–susceptible bacteria had sterile cultures, compared with only 64 (42%) of 151 women infected with TMP-SMX–resistant strains (P < .001) (table 2). At visit 3 (at which the secondary efficacy criteria were assessed), 265 (93%) of 285 of women infected with TMP-SMX–susceptible strains still had sterile cultures, compared with 53 (70%) of 76 women infected with a TMP-SMX–resistant uropathogen (P < .001).

**Clinical outcomes.** Clinical cure rates were significantly higher among women infected with TMP-SMX–susceptible strains: at visit 2, 293 (88%) of 333 women infected with TMP-SMX–susceptible strains had clinical cure, compared with 81 (54%) of 151 women infected with TMP-SMX–resistant strains (P < .001). At visit 3, clinical cure rates were 265 (93%) of 285 women in the TMP-SMX–susceptible group and 53 (70%) of 76 women in the TMP-SMX–resistant group (P < .001). Mild to moderate adverse events were recorded in 145 (25%) of 590 women, but treatment was discontinued as a result of adverse events for only 61 (10%) of the women (table 3).

**DISCUSSION**

TMP-SMX is considered the drug of choice for the treatment of community-acquired acute uncomplicated cystitis in women. Reported bacteriologic eradication and clinical cure rates have generally been >85%–90% [1]. Shortly after the introduction of TMP-SMX, however, bacterial resistance to this combination was first identified in clinical isolates. In the past decade, an increasing prevalence of community-acquired infections due to uropathogens resistant to TMP-SMX was reported worldwide [5]. Chomarat [6] summarized the susceptibilities of urinary isolates from different countries during the last 10 years, and the percentage of TMP-SMX–resistant pathogens ranged from 70% in Latin America to 9% in the United States. The prevalence of resistance is especially high in developing countries and has been associated with frequent use of the drug in human or veterinary treatment [5–7]. In the United States, Gupta et al. [8] showed that the prevalence of resistance...
to TMP-SMX among *E. coli* strains isolated from women with acute uncomplicated UTI increased from 9% in 1992 to >18% in 1996. We have been monitoring the susceptibility of uropathogens in northern Israel since 1991 [9] and have seen the rate of TMP-SMX resistance increase to 49%. Weber et al. [10] have published a surveillance study conducted in southern Israel that also shows that the prevalence of TMP-SMX resistance is high.

Most of these previously cited studies used microbiologic data obtained from clinical laboratories and did not differentiate susceptibility patterns by age, sex, recent receipt of antibiotics, history of recurrence of UTIs, or other factors that would be likely to influence the prevalence of resistance. In addition, young women, postmenopausal women, and women with recurrent UTIs were not specifically identified. Therefore, we conducted a survey in which we identified young women who had acute uncomplicated cystitis, anticipating that the prevalence of infection with TMP-SMX–resistant organisms would be lower than that found in previous studies [3]. Unfortunately, although young women aged 16–49 years with uncomplicated cystitis had a lower rate of infection with TMP-SMX–resistant pathogens than did elderly women (39% vs. 50% of women), the rate of infection with resistant uropathogens was high among all of these patients.

In the present study, the overall prevalence of TMP-SMX resistance among 544 uropathogen isolates was 29%. We did not determine the actual MICs of the TMP-SMX–resistant strains of *E. coli* isolated from the women in the study, nor did we ascertain the mechanism of resistance. Chromosomal mutations generally result in low-level resistance to TMP-SMX (MIC of TMP, 5–512 μg/mL), whereas plasmid-mediated resistance generally results in very high levels of resistance (MIC of TMP, ≥2000 μg/mL) and has accounted for most resistant strains in other studies [11]. One might speculate that the high concentration in urine achieved by TMP-SMX would allow for successful treatment of women with acute uncomplicated cystitis who have chromosomally mediated resistance. TMP-SMX is primarily excreted unchanged in the urine and achieves concentrations in urine of ~100 μg of TMP per milliliter of urine after the usual orally administered dose. The high bacteriologic failure rates we observed among patients infected with resistant strains are consistent with high-level, most likely plasmid-mediated, resistance.

Surprisingly, there are few other studies with which to compare our data [12, 13]. McCarthy et al. [12] observed that only 5 out of 10 women with cystitis due to TMP-SMX–resistant strains of *E. coli* achieved bacteriologic eradication, and only 1 had clinical cure after treatment with TMP-SMX. Our results, based on data from a much larger sample and with correspondingly smaller confidence intervals around the outcomes of interest, are similar. Talan et al. [2] compared 7 days of ciprofloxacin therapy with 14 days of TMP-SMX therapy in
women with uncomplicated pyelonephritis. They observed that for women treated with TMP-SMX who were infected with a TMP-SMX–resistant uropathogen, the bacteriologic failure rate was 50%, as compared with only 4% for the women infected with TMP-SMX–susceptible microorganisms \( P < .001 \). The results of the study of Talan et al. [2] and of the present study indicate that in women with either pyelonephritis or cystitis, infection with a TMP-SMX-R organism predicts clinical failure if TMP-SMX is used for treatment.

In conclusion, the administration of TMP-SMX to women with uncomplicated UTIs caused by TMP-SMX–resistant pathogens is accompanied by unacceptably high rates of bacteriologic and clinical failure, and TMP-SMX is not recommended as the empiric drug for UTI treatment in areas where >10%–20% of strains demonstrate resistance. In selecting an alternative agent, one must be aware that TMP-SMX–resistant organisms are generally resistant to multiple drugs, often demonstrating simultaneous resistance to orally administered cephalosporins and amoxicillin-clavulanate. Resistance to fluoroquinolones and nitrofurantoin remain uncommon among strains of uropathogens that cause cystitis, and these drugs are the main alternative choices at present.

ISRAELI UTI GROUP MEMBERS

The members of the study group are Y. Rohana, N. Fainlaid, L. Bennet, M. Cantarell, and A. Gvidolin.

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