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Urinary Prophylaxis with Trimethoprim and Trimethoprim-Sulfamethoxazole: Efficacy, Influence on the Natural History of Recurrent Bacteriuria, and Cost Control

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Low-dose trimethoprim (TMP), trimethoprim-sulfamethoxazole (TMP-SMZ), and nitrofurantoin macrocrystals were found to be safe and effective as prophylaxis against recurrent urinary tract infections. Women given placebo had 2.8 infections per patient-year during the six-month study period, while women given TMP, TMP-SMZ, or nitrofurantoin had significantly lower infection rates (0–0.15 per patient-year). The effect of prophylaxis appeared to be limited to the period when the agents were taken. Only one patient had a TMP-resistant coliform isolated from cultures obtained during prophylaxis and six months afterwards. The sole factor associated with the recurrence of infection after prophylaxis was a history of three or more infections in the year preceding prophylaxis. Thirty-one of the 60 women in the trial were monitored for a mean of 6.1 years before and 3.2 years after they entered the study. Analysis of infection rates indicated that about half these women were experiencing an infection cluster when they entered the study and that the prestudy baseline infection rate correlated with the poststudy rate. Thus, prophylaxis did not appear to exert a long-term effect on the baseline infection rate. Urinary prophylaxis generally appears to become cost-effective when the baseline infection rate exceeds two per patient-year.

Recurrent urinary tract infections can be prevented in most susceptible women with low-dose trimethoprim-sulfamethoxazole (TMP-SMZ) or trimethoprim (TMP) alone given daily or thrice weekly [1–5]. However, several important issues concerning long-term urinary prophylaxis have not been adequately addressed. These include: (*1*) to whom prophylaxis should be given and for how long; (*2*) whether prophylaxis is cost-effective compared with treatment of each individual episode of infection; and (*3*) with what frequency TMP-resistant microorganisms emerge in the urinary, rectal, or vaginal flora of women receiving chronic low-dose TMP or TMP-SMZ. During and after a double-blind, placebo-controlled study of the efficacy of urinary prophylaxis with TMP-SMZ, TMP, and nitrofurantoin macrocrystals, we gathered data relevant to these three issues.

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Materials and Methods

Prophylaxis study. A detailed description of the methods used in our double-blind, placebo-controlled study of prophylaxis has been published previously [3]. In brief, women with acute cystitis and histories of two or more culture-proven urinary tract infections in the preceding 12 months were eligible for the study if they were not pregnant and had no known urologic abnormalities, no previous abnormal iv pyelograms, and no known allergy to the study medications used. Participants entered the prophylaxis study two weeks after completion of successful therapy for their acute urinary tract infections. (Treatment was considered successful if midstream urine cultures yielded negative results.) Patients were assigned in random fashion to three groups of 15 patients each and received TMP-SMZ (40 mg of TMP plus 200 mg of SMZ daily), nitrofurantoin macrocrystals (100 mg daily), or placebo (one tablet daily). Women allergic to SMZ were given TMP alone (100 mg daily) in a nonrandom fashion. All drugs

and the placebo were given by mouth. Patients were given drug or placebo for six months or until a urinary tract infection (either symptomatic or asymptomatic) was documented. After the period of drug administration or documentation of infection, all patients were monitored for another six months. Throughout the study and the follow-up period, patients were seen monthly or whenever symptoms occurred; cultures of midstream urine and urinalysis were done, and rectal, urethral, and vaginal swabs were obtained at each visit. Halfway through the study, testing for antibody-coated bacteria in any urine specimen containing $>10^3$ microorganisms/ml was instituted [3].

Long-term follow-up analysis. Thirty-one of the 60 women enrolled in the prophylaxis study were monitored in our urinary tract infection clinic for more than two years before and two years after the study. These women received essentially all care related to their urinary symptoms and signs at the U.S. Public Health Service Hospital in Seattle. When they were asymptomatic, they were seen routinely at the clinic at four-month intervals; at these visits the patients were examined, midstream urine was cultured, and urinalysis was performed. If symptomatic episodes occurred, the patients were asked to return to the clinic or to contact the nurse involved in the study. For purposes of this analysis, all midstream urine cultures containing $\geq 10^5$ typical uropathogens/ml were considered indicative of infection. When atypical organisms or mixed cultures were found, additional midstream urine or catheter specimens were usually collected in order to confirm infection. For each patient, the number of infections, clinic visits, and years of follow-up in the clinic were ascertained from clinic records and from other medical records.

Prevalence of TMP-resistant gram-negative bacilli. During both the six-month study period and the six-month follow-up period, rectal, urethral, and vaginal swabs were collected from all patients and were plated on MacConkey and blood agar plates. From these plates, three separate colonies of each morphologically different colonial type of gram-negative bacillus were screened for TMP resistance. Eighteen-hour cultures grown in trypticase soy broth were diluted to a concentration of 10^8 organisms/ml and were inoculated with a Steers replicator onto Mueller-Hinton agar containing 10 μg of TMP/ml and 0.3 μg of thymidine kinase/ml.

Analysis of cost-effectiveness. To compare the cost of TMP-SMZ prophylaxis with the cost of treatment of acute episodes of urinary tract infection in women with frequent recurrences, we used a decision analysis model that has been described fully elsewhere [6]. Data available from the trial just described—including rates of infection with and without prophylaxis, average intervals to recurrence, and rates of adverse reactions—provided the necessary probabilities for many of the branch points in the decision analysis model. The direct costs of diagnosis and treatment of urinary tract infections at our hospital were determined by retrospective review of the medical charts of 117 consecutive women who came to our outpatient department with dysuria, frequency of urination, pyuria, and bacteriuria. The number and types of laboratory tests, medications, follow-up visits, and X-rays were recorded, along with other factors contributing to costs, for each patient. Direct costs were then calculated by methods previously outlined [6].

Results

Efficacy of prophylaxis. The women in each of the four groups were comparable in terms of the number of infections in the preceding year and the frequency of abnormalities of either the lower or the upper urinary tract, as detected on iv pyelograms. Compared with women given the placebo (rate of urinary tract infection, 2.8 per patient-year), women given TMP-SMZ, TMP alone, or nitrofurantoin macrocrystals had significantly lower rates of infection (0–0.15 per patient-year) while taking their assigned medication (table 1). In the six-month follow-up period after discontinuation of the medication, women who had taken the placebo had a rate of infection of 3.0 per patient-year, while those who had taken an active drug had an infection rate of 1.2–1.7 per patient-year. Thus, each of the three groups of women given an active antimicrobial agent during the study period experienced a significant increase in the rate of infection after the medication was discontinued. Although the follow-up infection rates were lower among women who took an active agent than

among those who took a placebo, the differences were not statistically significant.

We compared patients who had recurrent infections during the six-month follow-up period with those who did not in order to determine whether specific factors were associated with recurrence of infection after prophylaxis. No association was found between the recurrence of infection and age, iv pyelogram abnormalities, the presence of non-*Escherichia coli* infections before prophylaxis, or the carriage of *E. coli* in rectal, urethral, or vaginal cultures before or after prophylaxis. However, a patient's baseline history of urinary tract infection during the 12 months before prophylaxis was related to the likelihood of recurrence after discontinuation of prophylactic medication. Eighteen of 24 women who had experienced three or more infections during the year before prophylaxis had a recurrence during the six months after prophylaxis was discontinued, while only three of 13 women who had had two infections during the year before prophylexis had a recurrence during the six months after prophylaxis ($P = 0.004$).

Long-term follow-up analysis. To examine further the relation of baseline rates of urinary tract infection and the need for continuing prophylaxis, we analyzed the rates of infection for 31 study patients who had been closely followed in our clinic for long periods. These women had been monitored for a mean of 6.1 years before entering the prophylaxis study and had had a mean of 1.1 infections per patient-year. Of the 183 infections they had experienced, 95% were symptomatic. In the year immediately preceding entry into the study, the number of infections per patient-year increased to 2.8 ($P = 0.02$) compared with the prestudy baseline. However, this fact reflected the requirements for participation in the study, i.e., each patient had to have had at least two infections during that year. In the follow-up period (mean, 3.2 years), the infection rate declined to 1.2 patient-year—a figure nearly identical to that in the prestudy period (table 2). When patients were stratified by their prestudy baseline infection rates (table 3), it became evident that the rates of infection during the follow-up period were correlated significantly with those during the prestudy period ($P < 0.05$).

Emergence of TMP-resistant gram-negative bacilli. During the six-month study period and the six-month follow-up period, no patient developed a urinary tract infection caused by TMP-resistant gram-negative bacilli. Of 367 rectal, urethral, and

Table 1. Urinary tract infections in patients given trimethoprim-sulfamethoxazole (TMP-SMZ), trimethoprim alone (TMP), nitrofurantoin macrocrystals (NFM), or placebo.

	Infections during indicated period*	
Regimen	Prophylaxis†	Follow-up‡
TMP-SMZ	1/13 (0.15)	7/13 (1.3)
TMP	0/14 (0)	8/10 (1.7)
NFM	1/13 (0.14)	6/14 (1.2)
Placebo	10/13 (2.8)	10/13 (3.0)

* Results are expressed as the number of infected patients/total number of patients (number of infections per patient-year).

† $P < 0.005$ for each active drug regimen vs. placebo.

‡ $P < 0.005$ for each drug during prophylaxis vs. during six-month follow-up period.

Table 2. Long-term analysis of 31 patients with histories of recurrent urinary tract infection.

Interval	Infections per patient-year (mean)	Patient-years of follow-up (mean)
Prestudy period	1.1	6.1
One year before entry into study	2.8*	1.0
Poststudy period	1.2	3.2

* $P < 0.02$ (Student's t test) one year before entry into study vs. either the prestudy period or the poststudy period.

Table 3. Stratification of patients by rate of urinary tract infection during the prestudy baseline period (mean, 3.2 years), showing correlation of this rate with the rate of recurrent infection during long-term follow-up (mean 6.1 years).

		Infections per patient-year (mean)		
Category*	No. of patients	Prestudy baseline period	One year before entry into study	Poststudy follow-up period
<1	16	0.3	2.7	0.6
≥1-<2	9	1.4	3.2	1.3
≥2	6	2.8	2.3	2.5
Total	31	1.1	2.8	1.2

* Categories are based on the number of infections per patient-year in the prestudy baseline period.

Table 4. Resistance to trimethoprim of gram-negative bacilli isolated from rectal, urethral, and vaginal swabs of patients who participated in the prophylaxis study.

Organism	No. of strains resistant/no. tested
Escherichia coli	1/313
Klebsiella	0/16
Pseudomonas aeruginosa	14/14
Enterobacter	0/10
Proteus	0/9
Citrobacter	0/5
Total	15/367

vaginal isolates obtained from patients during these periods, 15 were TMP-resistant gram-negative bacilli (14 stains of *Pseudomonas aeruginosa* and one strain of *E. coli*) (table 4). The MICs for the *E. coli* strain were 0.15 μg of TMP/ml and 2.85 μg of SMZ/ml. After one month of prophylaxis, patients given TMP or TMP-SMZ had significantly fewer gram-negative bacilli isolated from rectal, urethral, or vaginal swabs than did patients given the placebo ($P < 0.02$) or nitrofurantoin ($P < 0.02$). Analysis of the patients with TMP-resistant strains in terms of drug studied and time of isolation suggested that *P. aeruginosa* was most often found in patients given TMP, that carriage was persistent as long as TMP treatment was continued, but that the organism tended to disappear when prophylactic TMP was discontinued (table 5). Among patients in whom carriage of *P. aeruginosa* began during TMP treatment, the organism generally was isolated continually until the drug was stopped (table 6).

Cost-effectiveness of urinary prophylaxis. Using a decision analysis model, we found the cost of prophylaxis to be $85.82 per patient-year. In contrast, the cost of treatment of acute infection for patients averaging three infections per year was $392.20 per patient-year. Sensitivity analysis (figure 1) indicated that the cost of prophylaxis was never lower than the cost of treating one infection per patient-year, regardless of the average cost per episode of infection. However, for women with baseline infection rates of two or three per patient-year, prophylaxis became cost-effective at approximately $60 and $40, respectively.

Discussion

These studies indicate that urinary prophylaxis with TMP and TMP-SMZ is highly effective in preventing infections in women who have baseline infection rates of two or more per patient-year. Over long periods, the baseline frequency with which a woman has recurrent infections may be a useful indicator of whether she will benefit from continuous long-term prophylaxis. Many authorities recommend that women with more than two infections per year be considered candidates for prophylaxis, but data addressing the question of how long such women should be given a prophylactic drug are not yet available [1–4]. Our long-term follow-up data suggest that at least 50% of women with two or more infections in a given year actually have baseline infection rates of less than one per patient-year when longer periods are considered. These women may be better off with three to six months of prophylaxis during a period of heightened susceptibility or a cluster of infections. As Kraft and Stamey [7] have reported, monitor-

Table 5. Isolation of trimethoprim (TMP)-resistant gram-negative bacilli analyzed by drug regimen and time of isolation.

Regimen*	Time of isolation				
	Before study	1 month into study	6 months into study	1 month after study	6 months after study
TMP	1/35	3/8	3/5	2/19	1/19
TMP-SMZ	0/20	0/5	1/15	0/10	1/31
NFM	0/27	1/30	1/24	0/15	0/10
Placebo	0/30	0/23	0/17	1/17	0/6

NOTE. Results are expressed as the number of patients with TMP-resistant isolates/total number of isolates.
* TMP-SMZ = trimethoprim-sulfamethoxazole; NFM = nitrofurantoin macrocrystals.

Table 6. Time and site of isolation of trimethoprim (TMP)-resistant gram-negative bacilli.

Regimen*	Frequency of isolation†	Site of isolation at indicated time‡				
		Before study	1 month into study	6 months into study	1 month after study	6 months after study
TMP	3/12	–	R+	R+	R+	R+
		V+	V+	V+	–	–
		–	–	R+	R+	–
TMP-SMZ	2/14	–	–	–	–	R+
		–	–	R+§	–	–
NFM	2/13	–	–	V+	–	–
		–	R+	–	–	–
Placebo	1/13	–	–	–	V+	–

* TMP-SMZ = trimethoprim-sulfamethoxazole; NFM = nitrofurantoin macrocrystals.
† Results are expressed as the number of patients with TMP-resistant gram-negative bacilli/total number of patients.
‡ Abbreviations: – = no organisms isolated; R+ = rectum; V+ = vagina.
§ This was the sole TMP-resistant isolate of *Escherichia coli*. All other isolates were *Pseudomonas aeruginosa*.

ing of patients for many years often reveals a cluster of infections in a given patient. Unfortunately, it is not possible at present to predict when susceptibility to infection may increase. Our data suggest that women with a baseline rate of more than two infections per year over many years continue to suffer infections at that rate and may benefit from long-term prophylaxis.

TMP-resistant *E. coli* did not emerge frequently in either the urinary or the fecal flora of women given prophylactic TMP for six months. These patients did frequently carry *P. aeruginosa* in their stools, but this organism disappeared when TMP prophylaxis was discontinued. The methodology we used was not optimal for the specific isolation of TMP-resistant gram-negative bacilli because we did not plate rectal, urethral, and vaginal swabs directly onto a selective medium containing TMP. Instead, the selective medium was used secondarily in screening three morphologically different colony types of gram-negative bacilli. Hence, we may have underestimated the true incidence of carriage of TMP-resistant Enterobacteriaceae, particularly if the quantity of such organisms was small. However, both Hyams et al. [8] and Guerrant et al. [9] monitored women given TMP for two to four weeks and only rarely isolated TMP-resistant coliforms from the fecal flora of their patients. As we did, Guerrant and associates found transient carriage of *P. aeruginosa* in many patients [9].

Assessment of the cost-effectiveness of urinary prophylaxis in one clinical setting may not be easily extrapolated to other settings. However, in our hospital, urinary prophylaxis with TMP-SMZ, TMP alone, or nitrofurantoin was quite clearly cost effective in women regularly experiencing three infections per patient-year and was probably cost effective in women regularly experiencing two infections per patient-year. In women with recurrences at a rate of one per patient-year, prophylaxis does not appear to be cost-effective, and treatment of individual episodes of infection may be preferable. Because single-dose therapy was not being used in our hospital at the time of this analysis, no information on single-dose therapy was included in the cost-effectiveness study. However, since pharmaceutical costs per se constitute only a

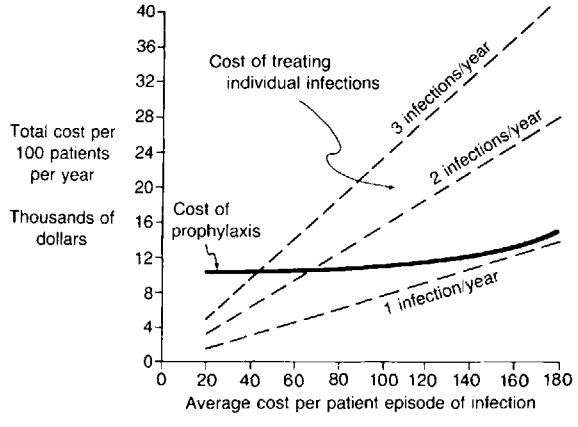

Figure 1. Cost of prophylaxis vs. cost of treatment of individual infections at different baseline infection rates and costs per episode [3].

small portion of the total cost of treatment of a urinary tract infection, our results do not change greatly if the cost of single-dose therapy is substituted for the cost of 7–10 days of therapy.

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