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Treatment of Uncomplicated Urinary Tract Infections with Trimethoprim Versus Sulfisoxazole, with Special Reference to Antibody-Coated Bacteria and Fecal Flora

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A total of 331 college-age women with urinary tract infections were studied. These women were assigned randomly to the following groups: 50 patients treated with 400 mg of trimethoprim (TMP) per day for 14 days (designated the TMP400/14d group); 50 treated with 2.0 g of sulfisoxazole (SZ) per day for 14 days (SZ/14d group); 120 treated with 200 mg of TMP per day for 10 days (TMP200/10d group); and 111 treated with 2.0 g of SZ per day for 10 days (SZ/10d group). By the last day of therapy, clinical and bacteriological cure rates were 100% in the TMP400/14d, SZ/14d, and TMP200/10d groups and 97.1% in the SZ/10d group. At 1 week after therapy ended, the initial urinary pathogens remained eradicated in 100% of the TMP400/14d group, 98.2% of the TMP200/10d group, 95.6% of the SZ/14d group, and 98.0% of the SZ/10d group. At 4 weeks after therapy ended, the clinical cure rates were 92.0% in the TMP400/14d group, 92.0% in the SZ/14d group, 89.0% in the TMP200/10d group, and 90.0% in the SZ/10d group. At 4 and 24 weeks after therapy ended, the recurrence rates in the four treatment groups did not differ significantly. The antibody-coated bacteria test localized 39.5% of the infections to kidneys and 56.8% of the infections to bladders. Neither symptoms nor responses to therapy were correlated with the antibody-coated bacteria test results. Both TMP at a dose of 200 mg/day and SZ were tolerated well. TMP at a dose of 400 mg/day was associated with a skin rash in 24% of the patients receiving this therapy. TMP suppressed fecal *Escherichia coli*. SZ increased the number of sulfa-resistant fecal isolates; however, this phenomenon did not affect the rate of sulfa-resistant recurrences.

Trimethoprim (TMP), a 2,4-diaminopyrimidine, is an antimicrobial agent which acts against a wide variety of bacterial species by selectively inhibiting microbial folate metabolism. TMP competitively inhibits bacterial dihydrofolate reductase and consequently blocks the formation of tetrahydrofolate and deoxyribonucleic acid synthesis. The inhibitory activity of TMP is enhanced by adding a sulfonamide, which acts in a prior step to prevent the formation of dihydrofolate (5, 6). Furthermore, Darrell et al. reported that the presence of a sulfonamide could reduce the emergence of TMP resistance when bacteria were exposed in vitro to low levels of TMP, provided that they were initially sulfa sensitive (11). Consequently, TMP has been used extensively in combination with sulfamethoxazole for the treatment of a variety of infections, including urinary tract infections (UTIs) (7, 9, 26). Interest in the synergistic effects of TMP and the sulfonamides diverted attention from the activity of TMP as an antibacterial agent in its own right. Preliminary descriptions of TMP as the sole therapeutic agent against adult UTIs have been encouraging (4, 17, 21, 23).

In this study the efficacy and safety of TMP were compared with the efficacy and safety of sulfisoxazole (SZ) in the treatment of acute uncomplicated UTIs in young women. The antibody-coated bacteria test (ACBT) (31) was used to localize the sites of infections. The effects of these two drugs on the ecology of the bowel flora were also evaluated to detect the emergence of resistant organisms which might be potential urinary pathogens.

MATERIALS AND METHODS

Patient criteria. The patient population consisted of college-age women with uncomplicated UTIs who came to the University of Florida Student Health Services Outpatient Kidney Clinic. Patients with uncomplicated UTIs were defined as those patients

having had two or fewer infections in the preceding 12 months and did not have known abnormalities of the urinary tract. One of the major criteria for inclusion in the study was the isolation of more than 10^5 colonies of the same bacterium per ml in each of three consecutive urine samples collected within 24 h. Treatment was initiated immediately after the last urine sample was obtained. During the first 3 days of therapy, the time of each voiding and the severity of lower urinary tract symptoms were recorded in a patient diary. Patients with asymptomatic infections were also included in the study. These patients were selected from a group of students who were performing monthly urine cultures as part of follow-up evaluations for previous UTIs.

Patients were excluded from the study if they were allergic to sulfonamide or TMP or both, had gonorrheal infections, were pregnant, or had catheter-induced UTIs, renal calculi, renal failure (serum creatinine levels twice the normal level), radiologically proven obstructive uropathies, hepatic disease, or known or suspected glucose 6-phosphate dehydrogenase deficiencies.

Bacteriology. The specimens were processed as described by Barry et al. (2). Quantitative urine cultures were performed by previously described methods (12). Antimicrobial susceptibilities were determined by the disk diffusion method of Bauer et al. (3), using 5-μg TMP disks and 300-μg SZ disks. Wellcotest agar and Mueller-Hinton agar (Difco Laboratories, Detroit, Mich.) were used to ensure a low thymidine content in the culture medium. Serotyping of O-antigen was performed with *Escherichia coli* isolates (32).

Before therapy and 1 week after therapy ended, fecal cultures were obtained by using rectal swabs, each of which was placed in a Culturette tube (Scientific Products, Inc., Evanston, Ill.) and immediately refrigerated at 4°C. Within 24 h, these swabs were streaked onto MacConkey and blood agar plates. After overnight incubation at 37°C, the bacterial isolates were identified and tested for antibiotic susceptibility by the method used for the urine cultures (2, 3, 25). A total of 24 age-matched volunteers who had not received any antibacterial agent for the preceding 8 weeks served as controls. A fecal culture was obtained from each volunteer initially and then again 2 weeks later. By using a speculum examination, specimens were obtained from each patient to screen for vaginal *Candida*, *Trichomonas*, and gonococci before therapy, and each patient was reexamined for vaginal *Candida* 1 week after therapy ended.

Measurements of complete blood counts transaminase enzyme levels, alkaline phosphatase levels, serum creatinine levels, and blood urea nitrogen levels were made before therapy and 1 week after therapy ended.

Urinalysis was performed on unspun urine samples. Pyuria was defined as the presence of at least one to five leukocytes in multiple high-power fields.

Test of localization. The site of infection was determined in vitro by the fluorescent ACBT, using a modification of the method of Thomas et al. (31). The sediment from 10 ml of pretherapy urine was examined for antibody-coated bacteria with 0.55 ml of a 1:10 dilution of fluorescence conjugated anti-human globulin of goat origin (Hayland Diagnostics, Dearfield, Ill.). The test was considered positive when at least two fluorescent bacteria were found in each of 10 high-power fields (×400). The test was considered negative if no antibody-coated bacteria were observed after multiple fields were examined for approximately 5 min. We assumed that a positive ACBT indicated a kidney infection, and a negative ACBT indicated a bladder infection (15, 19, 30). Each positive ACBT specimen was examined for nonspecific fluorescence by testing a washed subculture of the bacterial isolates. The test was considered nonspecific if the positive antibody-coated bacteria persisted in the subcultured isolates.

Treatment. Patients were assigned randomly to an oral treatment schedule of either 200 mg of TMP every 12 h for 14 days (designated the TMP400/14d group) or 500 mg of SZ every 6 h for 14 days (SZ/14d group). A skin rash occurred in 12 of the initial 50 patients who received this dose of TMP. Consequently, the treatment schedules were revised to 100 mg of TMP every 12 h for 10 days (TMP200/10d group) and 500 mg of SZ every 6 h for 10 days (SZ/10d group). Patients with concurrent vaginal *Candida* and *Trichomonas* infections were treated simultaneously with miconazole nitrate (2%) vaginal cream and metrodiazole oral tablets, respectively.

Assessment of treatment. Clinical and bacteriological follow-up evaluations were conducted 2 days after therapy was begun and on the last day of therapy. Similar studies were repeated 1, 2, and 4 weeks after therapy ended and thereafter at 4-week intervals. Each patient was observed closely for drug reactions or side effects. Follow-up urine cultures with colony counts of $\leq 10^3$ cells per ml of urine were considered bacteriological cures, cultures with $\geq 10^5$ cells of a single organism per ml were considered bacteriological failures, and cultures with between 10^3 and 10^5 cells per ml were considered bacteriologically suspicious. All of the positive and suspicious specimens were reassessed with two additional urine cultures.

Criteria were established to separate recurrences into relapses and reinfections. A reinfection occurred when any or all of the following criteria were met: (i) recurrence with a different bacterium, (ii) recurrence with a different *E. coli* serotype, (iii) recurrence at or beyond 4 weeks after therapy ended and (iv) recurrence with the same bacteria, but with conversion of a positive ACBT to a negative ACBT. The last type of recurrence was valid if one accepts the premise that a positive ACBT indicated a kidney infection and a negative ACBT indicated a bladder infection. Therefore, if the initial urinary pathogen survived in the kidneys after therapy, causing a recurrence (relapse), the ACBT remained positive, whereas conversion of a positive ACBT to a negative ACBT implied a new infection. A relapse occurred when all the following criteria were met: (i) recurrence with a bacterium of the same species and antibiotic susceptibility, (ii) recurrence with *E. coli* of the same serotype, (iii) recurrence with the same bacteria without conversion of a positive ACBT to a negative ACBT, and (iv) recurrence with the same bacteria within 4 weeks after therapy ended.

This study received prior approval of the University of Florida College of Medicine Human Experimentation Committee. The procedures were fully explained to each patient, and informed consents were obtained.

The data were analyzed in consultation with the Health Center Biostatistician. The life table method (10) was used to determine both the percent cumulative rate of cure and the percent cumulative rate of recurrence. This method incorporated all of the patients studied and took into account those patients on whom follow-up studies were not done, as well as the treatment failures.

RESULTS

A total of 331 patients were studied; 50 patients were assigned randomly to the TMP400/14d group, 50 were assigned to the SZ/14d group, 120 were assigned to the TMP200/10d group, and 111 were assigned to the SZ/10d group. The clinical characteristics of the patients were similar in all four treatment groups (Table 1). The mean age was 22 ± 4.0 years. Radiological and urological studies were limited to those patients with histories of previous UTIs. These studies included 59 intravenous pyelograms, 18 voiding cystourethrograms, and 16 cystoscopic examinations; all produced normal results.

Pretherapy bacteriology. Table 2 shows that the most common pretherapy principal urinary pathogens were *E. coli* (71.9%) and novobiocin-resistant *Staphylococcus saprophyticus* (12.1%) (14, 20). Serotyping of O-antigen was performed for 231 of the 238 strains of *E. coli*. Only 121 *E. coli* strains (52.4%) could be typed. The most common serotypes were *75* (30.6%) and *06* (28.1%).

Of the 331 primary pathogens isolated, 330 (99.7%) were susceptible in vitro to TMP, and 275 (83.1%) were susceptible to SZ. The one TMP-resistant isolate was a beta-hemolytic group B *Streptococcus* strain that was also resistant to SZ. The patient with this bacterial infection responded favorably to TMP therapy. SZ resistance was found in 56 (16.9%) of the 331 pretherapy urinary isolates. The resistant strains included 47 *E. coli* strains, 8 *Klebsiella pneumoniae* strains, and 1 beta-hemolytic group B *Streptococcus* strain. Eradication of bacteria occurred by day 2 of therapy with SZ in 5 of 10 resistant *E. coli* infections treated with this agent. The remaining 37 patients with SZ-resistant *E. coli* infections and the 8 patients with *K. pneumoniae* infections were treated successfully with TMP.

Results after 2 days of therapy. A total of 48 of the 50 patients in the TMP400/14d group, all 50 patients in the SZ/14d group, and 119 of 120 patients in the TMP200/10d group completed 2 days of therapy, and all showed clinical and bacteriological cures. Two patients in the TMP400/14d group and one patient in the TMP200/10d group did not return. In the SZ/10d group, 109 of 111 patients completed 2 days

Table 1. *Clinical characteristics of the patients*

Treatment group	Total no. of patients	Age (yrs)		No. of patients symptomatic	No. of patients asymptomatic	No. of symptom days before therapy		No. of patients with:						No. with the following no. of UTIs in the preceding 12 months:		
		Mean ± standard deviation	Range			Mean ± standard deviation	Range	CVAT[a]	Fever	Pyuria	Vaginal *Candida*	*Trichomonas*	Gonorrhea	0	1	2	3
Combined TMP	170	21.7 ± 3.9	17–45	169	1	2.7 ± 1.6	1–7	22	6	94	12	1	0	98	54	19	3
Combined SZ	161	21.8 ± 3.8	17–40	159	2	2.5 ± 1.6	1–7	22	15	91	18	0	0	112	38	8	3
All patients	331	21.8 ± 3.8	17–45	328(99.1)[b]	3(0.9)	2.6 ± 1.6	1–7	44(13.3)	21(6.3)	185(55.9)	40(12.1)	1(0.3)	0	206(62.2)	92(27.8)	27(8.2)	6(1.8)

[a] CVAT, Costovertebral angle tenderness.
[b] Numbers in parentheses are percentages.

TABLE 2. *Principal pretherapy urinary pathogens*

Bacterium	No. of patients infected in:		% of total	No. resistant to:	
	Combined TMP groups (n = 170)	Combined SZ groups (n = 161)		TMP	SZ
E. coli	129	109	71.9	0	47 (19.7)[a]
S. saprophyticus	15	25	12.1	0	0
Proteus sp.	12	13	7.6	0	0
K. pneumoniae	10	11	6.3	0	8 (38.1)
Enterobacter sp.	2	1	0.9	0	0
Citrobacter sp.	1	2	0.9	0	0
Beta-hemolytic *Streptococcus* group B	1	0	0.3	1	1

[a] Numbers in parentheses are percentages.

of therapy, and 2 did not return. Of these 109 patients, 103 showed clinical and bacteriological cures, and 6 remained infected. Five of these failures were due to *E. coli* that had been initially resistant to SZ, and one was a superinfection with a resistant *E. coli* strain. According to our study protocol, the five cases with SZ-resistant *E. coli* infections were considered non-evaluable rather than treatment failures.

Results on last day of therapy. In the TMP400/14d group, 38 of 48 patients completed therapy and showed 100% clinical and bacteriological cures. Of the remaining 10 patients, TMP treatment was discontinued in 8 because of a skin rash, and 2 failed to return.

A total of 46 of the 50 patients in the SZ/14d group and 114 of 119 patients in the TMP200/10d group completed therapy and showed 100% clinical and bacteriological cures. The remaining nine patients did not return.

In the SZ/10d group, 101 of 103 patients completed therapy, and 2 did not return. Of 101 patients, 99 were cured clinically and bacteriologically, and 2 had persistent infections.

Posttherapy follow-up. (i) Results 1 week after therapy ended. In the TMP400/14d group, all 38 patients remained clinically and bacteriologically cured. In the SZ/14d group, 44 of the 46 patients remained free of infection, and 2 developed relapses. In the TMP200/10d group, 110 of 114 patients were cured, 2 were reinfected, and 2 developed relapses. In the SZ/10d group, 98 of 99 patients were cured, and 1 was reinfected.

(ii) Results 4 weeks after therapy ended. The initial urinary pathogens remained eradicated in 100% of the TMP400/14d group, 98.2% of the TMP200/10d group, 93.5% of the SZ/14d group, and 96.1% of the SZ/10d group.

The cumulative clinical and bacteriological responses through 4 weeks after therapy ended are shown in Table 3. In the TMP400/14d group, 35 patients (92.0%) remained clinically and bacteriologically cured, and there were 3 reinfections (8.0%) (Table 3). In the SZ/14d group, 42 patients (91.3%) remained clinically and bacteriologically cured, and there were 3 relapses (6.5%) and 1 reinfection (2.2%). In the TMP200/10d group, 102 patients (89.5%) remained free of infection, 10 became reinfected (8.8%), and 2 relapsed (1.7%). In the SZ/10d group, 92 patients (90.2%) remained clinically and bacteriologically cured, 6 became reinfected (5.8%), 2 relapsed (2.0%), and two had persistent infections or were failures (2.0%).

(iii) Results 24 weeks after therapy ended. By 24 weeks after therapy ended there were 11 recurrences (32.0%) in the TMP400/14d group, 16 recurrences (36.0%) in the SZ/14d group, 27 recurrences (24.0%) in the TMP200/10d group, and 28 recurrences (29.0%) in the SZ/10d group (Fig. 1). The rates of cure, reinfection, and relapse were not significantly different in the four treatment groups.

In the patients who received TMP, recurrent infections were all due to organisms susceptible to the drug, whereas in the patients treated with SZ, 7 (15.9%) of 44 recurrences were caused by sulfa-resistant bacteria.

Localization of the site of infection. The ACBT was performed on samples from 324 patients; of these 324 tests, 128 (39.5%) were positive, 184 (56.8%) were negative, and 12 (3.7%) were nonspecific. The results of the ACBT did not correlate with the symptoms of the UTIs. Samples from patients with symptoms suggestive of upper urinary tract involvement, such as fever or flank pain or both, produced a distribution of 61.8% negative ACBT and 38.2% positive ACBT. Similarly, samples from patients with lower urinary tract symptoms produced 60.4% negative ACBT and 39.6% positive ACBT.

All 71 ACBT-positive and 86 ACBT-negative patients treated with TMP manifested clinical and bacteriological cures after 2 days of therapy and on the last day of therapy. Of 57 ACBT-

TABLE 3. *Cumulative clinical and bacteriological responses through 4 weeks after therapy ended*

Treatment group	No. (%) of patients				
	Evaluable	Cured	Reinfected	Relapsed	Failures
TMP400/14d	38	35 (92.0)	3 (8.0)	0	0
SZ/14d	46	42 (91.3)	1 (2.2)	3 (6.5)	0
TMP200/10d	114	102 (89.5)	10 (8.8)	2 (1.7)	0
SZ/10d	102	92 (90.2)	6 (5.8)	2 (2.0)	2 (2.0)

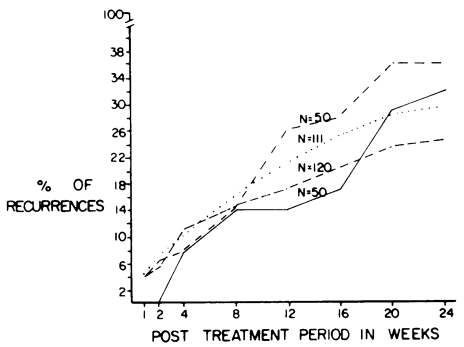

FIG. 1. *Percent cumulative rates of recurrence in the four treatment groups. N, Number of patients in each treatment group. (——) TMP400/14d; (---) TMP200/10d; (-·-) SZ/14d; (····) SZ/10d.*

positive patients treated with SZ, 56 showed clinical and bacteriological cures after 2 days of therapy, and 55 showed cures on the last day of therapy. A total of 98 ACBT-negative patients treated with SZ were cured clinically and bacteriologically after 2 days of therapy, and 97 were cured on the last day of therapy. The ACBT-positive patients did not show persistence of infection or a propensity for higher recurrences than patients who were ACBT negative. By 4 weeks after therapy ended, reinfections in ACBT-negative patients accounted for seven (77.8%) of nine recurrences in the combined TMP treatment groups and four (57.1%) of seven recurrences in the combined SZ treatment groups. However, in the ACBT-positive patients, reinfections accounted for five (100%) of five recurrences in the combined TMP treatment groups and three (50.0%) of six recurrences in the combined SZ treatment groups. The percent cumulative rates of recurrence for ACBT-positive and ACBT-negative patients through 24 weeks after therapy ended were not statistically different (Fig. 2 and 3).

Hematology and blood chemistry. Blood chemistries and alkaline phosphatase and transaminase levels remained normal in all of the treatment groups. Reductions in the numbers of leukocytes in the patients checked after therapy ended were observed in 19 (12.7%) of 150 patients in the combined TMP treatment groups and in 18 (12.5%) of 144 patients in the combined SZ treatment groups. These reductions were generally the result of a return to normal of the initially elevated leukocyte levels that occurred during acute infections.

Fecal flora. Fecal cultures from 24 uninfected volunteers showed no apparent changes in the types of *Enterobacteriaceae* colonizing the bowels during 2 weeks of observation (Fig. 4). Occasionally, an individual had more than one strain of *E. coli* or other *Enterobacteriaceae*. Of 25 *E. coli* isolates, 4 (16.0%) remained resistant to sulfonamides in the initial and repeated fecal cultures. Non-*E. coli* sulfonamide-resistant *Enterobacteriaceae* were found in only 1 (9.1%) of 11 initial isolates. TMP-resistant *Enterobacteriaceae* were not observed in the fecal flora of the volunteer group.

Before antibiotic therapy, 72 (22.3%) of the 322 *E. coli* strains and 7 (7.9%) of the 89 other *Enterobacteriaceae* strains isolated from fecal cultures showed resistance to SZ, whereas only 1 (0.31%) of the 322 *E. coli* strains and 3 (3.4%) of the 89 other *Enterobacteriaceae* strains were resistant to TMP. TMP and SZ produced different effects on the fecal flora, but the effects of the two dosage regimens of each drug were not different from one another. All *Enterobacteriaceae*, including *E. coli*, were cleared from the fecal flora in 8 (21.6%) of 37 patients in the TMP400/14d group, in 21 (18.6%) of 113 patients in the TMP200/10d group, in 2 (4.4%) of 45 patients in the SZ/14d group, and in 2 (2.0%) of 99 patients in the SZ/10d group. Figure 5 shows the effects of treatments with the two TMP and two SZ schedules on the fecal flora. In contrast to SZ, TMP caused a significant reduction in the number of *E. coli* cells colonizing the rectum. In those patients who received SZ, 26 (16.6%) of 157 of *E. coli* strains and 1 (3.1%) of 32 other *Enterobacteriaceae* strains were sulfa resistant initially. After treatment with SZ, the number of resistant strains increased to 58 (39.7%) of 146 *E. coli* strains and 8 (20.0%) of 40 other *Enterobacteriaceae* strains. Pretherapy fecal cultures

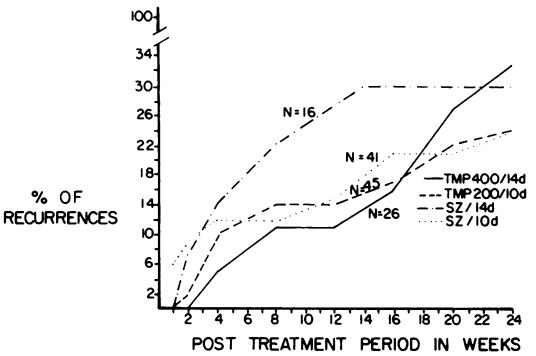

FIG. 2. *Percent cumulative rates of recurrence in ACBT-positive patients. N, Number of patients in each treatment group.*

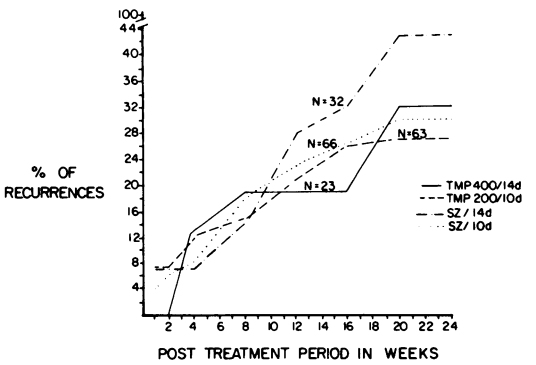

FIG. 3. *Percent cumulative rates of recurrence in ACBT-negative patients. N, Number of patients in each treatment group.*

in the two TMP treatment groups showed that all of the 165 *E. coli* isolates were susceptible to TMP and that only 1 (1.8%) of 57 other *Enterobacteriaceae* isolates was resistant. After treatment with TMP, the number of resistant strains increased to 3 (2.8%) of 106 *E. coli* strains and 8 (10.4%) of 77 other *Enterobacteriaceae* strains.

TMP was associated with the emergence of 8 (10.4%) of 77 resistant *Enterobacteriaceae* strains other than *E. coli* in the fecal flora, but this was not significantly different from the TMP resistance observed in 5 (12.5%) of 40 *Enterobacteriaceae* strains other than *E. coli* in fecal cultures from patients who received SZ. In addition, TMP appeared to decrease the number of SZ-resistant *E. coli* strains colonizing the rectum from 45 (27.3%) of 165 isolates before therapy to 24 (22.6%) of 106 after therapy.

Drug reactions. In the TMP400/14d group, 12 (24%) of 50 patients experienced drug reactions after 5 to 13 days of therapy. TMP treatment was discontinued in eight of these patients. The reactions consisted of generalized mild to moderate maculopapular or morbilliform rashes. This was an isolated finding and was not associated with any increase in the transaminase enzyme levels or any significant change in hematological values. The rashes were self-limited and resolved within 2 to 3 days after the medication was discontinued. To attempt to verify the cause of the skin rash, seven of the patients who had the reaction were tested by separate sublingual challenges of TMP and yellow dye no. 10, an ingredient of the 200-mg TMP pills. Five patients had allergic reactions to TMP, and none had a reaction to the dye. Subsequent treatment with 200 mg of TMP per day for 10 days in 120 patients caused no skin rashes or other adverse reactions.

One patient receiving SZ developed malaise, depression, and a persistent headache. The symptoms disappeared after the drug was discontinued. Vaginal *Candida* occurred in 5 (2.9%) of 170 patients treated with TMP and in 4 (2.5%) of 161 patients treated with SZ.

DISCUSSION

In this study initial in vitro susceptibility tests showed that TMP had a broader antibacterial spectrum than SZ. Both of the TMP treatment schedules used (200 mg/day for 10 days and 400 mg/day for 14 days) were effective in eradicating primary urinary pathogens. Clinical and bacteriological failures with SZ treatment in 5 (50%)

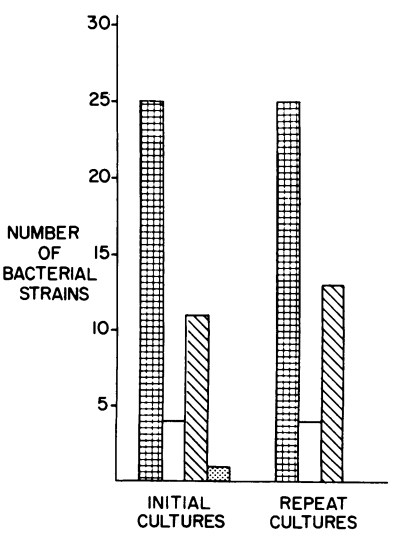

FIG. 4. *Fecal flora obtained from 24 noninfected controls initially and again 2 weeks later. Frequently, more than one bacterial isolate was obtained from a culture. ■, E. coli; □, SZ-resistant E. coli; ▨, non-E. coli Enterobacteriaceae; ⊞, SZ-resistant Enterobacteriaceae.*

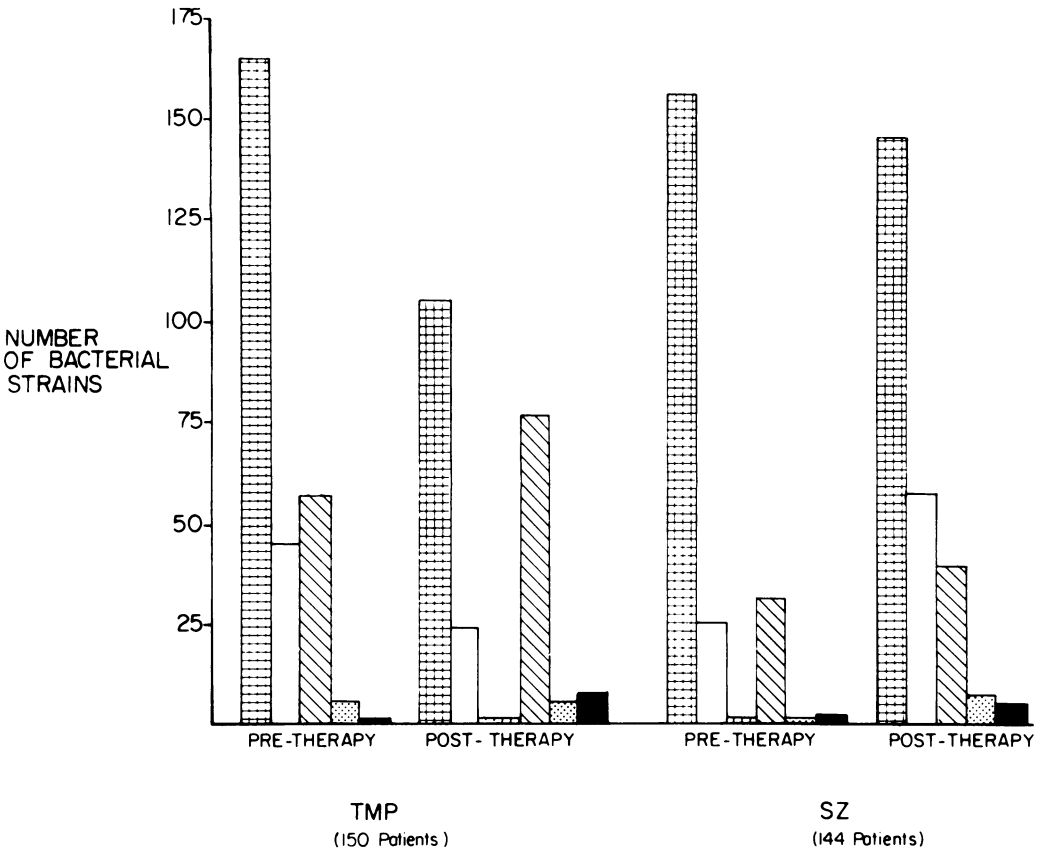

FIG. 5. *Comparison of pre- and posttherapy fecal floras in combined TMP and SZ groups. The numbers of patients indicated on the figure were the numbers of patients from whom pre- and posttherapy fecal cultures were taken. Frequently, more than one bacterial isolate was obtained from a culture.* ▩, *E. coli;* □, *SZ-resistant E. coli;* ▥, *TMP-resistant E. coli;* ▧, *non-E. coli Enterobacteriaceae;* ⊡, *SZ-resistant Enterobacteriaceae;* ■, *TMP-resistant Enterobacteriaceae.*

of 10 patients who were infected with sulfa-resistant primary pathogens. Failures did not occur with TMP (that is, the remaining 37 patients with SZ-resistant infections were all treated successfully with TMP). Therefore, before urine cultures and susceptibility data are available, TMP may be used with a greater degree of confidence than SZ. Also, the dosage schedule of TMP (twice a day) is easier and more practical to take than the dosage schedule of SZ (four times a day).

Throughout the 24 weeks after therapy ended, the rates of recurrence were not different in the SZ-treated groups and the TMP-treated groups. The organisms responsible for recurrences in the TMP-treated groups remained susceptible to this drug, whereas in the SZ-treated groups only 84.1% of the organisms remained susceptible to sulfa. Thus, there was no emergence of resistant urinary pathogens after TMP therapy. Bach et al. (1) reported that the high efficacy of orally administered TMP in the treatment of acute UTIs occurs because the serum and urinary concentrations exceed the minimal inhibitory concentrations for most urinary pathogens. Therefore, the combination of TMP and a sulfonamide seems to have little advantage over TMP alone in the treatment of acute uncomplicated UTIs (16). Clinical trials by European investigators have shown that a combination of TMP and sulfamethoxazole is not superior to TMP alone for the treatment of such infections (21, 23). Brumfitt and Pursell (4) and Kasanen et al. (21) reported that TMP was as effective as TMP plus sulfamethoxazole, nitrofurantoin, ampicillin, and cephalexin for the treatment of acute uncomplicated UTIs. On the other hand, in patients with complicated chronic infections, the cure rate for TMP plus sulfamethoxazole was higher than that for TMP alone and was considerably higher than the cure rate for sulfamethoxazole alone (4, 17).

Our results show that pretherapy sulfa-resistant *E. coli* concentrations in the fecal flora (16.6%) increased significantly after SZ treatment (39.7%); however, this effect did not cause an increase in the number of SZ-resistant recurrent infections (15.9%) compared with the number of initial SZ-resistant infections (16.9%). In contrast, Winberg et al. (33) found an average of 60% sulfa resistance in fecal isolates after SZ therapy. The changes of the fecal flora in the patients of these workers were very important in determining the resistance patterns of the subsequent recurrences. The reason for the difference between their findings and ours is not clear.

After TMP treatment, the emergence of TMP-resistant *E. coli* strains in the fecal flora was minimal (2.5%) compared with the emergence after SZ treatment (38.7%). The TMP-resistant strains did not cause recurrent UTIs. This finding agrees with previous reports that a few TMP-resistant bacteria may emerge in the fecal floras of normal individuals, but they do not appear to be responsible for recurrent UTIs (14, 21, 22, 28). This may be because the resistant isolates are frequently at an adaptive disadvantage, grow poorly, and disappear from the bowels within several weeks after TMP treatment is discontinued. To suppress chronic UTIs, a number of patients have received TMP for long periods (in one case, for several years) without emergence of resistant bacteria in the fecal flora (8, 29). However, there is evidence indicating that prolonged use of TMP may be associated with an increase in the number of resistant organisms in the fecal flora (J. Sander, H. Fellner, S. Kalstad et al., Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 59, 1979), particularly in hospital environments, where cross-contamination is a very common problem.

In this study, negative fecal cultures were observed in 19.3% of the patients after treatment with TMP and in 2.7% of the patients after treatment with SZ. In the remaining patients, TMP significantly suppressed the number of fecal *E. coli* strains, whereas SZ did not. Thus, TMP either effectively eradicated potential urinary pathogens from the fecal flora or decreased their concentrations. Considering these different effects of TMP and SZ on the fecal flora, one may expect to find fewer UTIs after treatment with TMP than after treatment with SZ. However, the percentages of recurrence through the 24 weeks after therapy ended were not significantly different in the TMP treatment groups and the SZ treatment groups. This lack of correlation between the changes in the fecal flora and the patterns of recurrence may have been due to a more important role played by host factors in the pathogenesis of UTIs (8).

Another interesting aspect of this study was the apparent lack of agreement between the ACBT results and the symptoms of lower and upper urinary tract infections. The relevance and significance of this test have been the subject of several reports (13, 27, 29, 32; D. Hyams, S. J. Pancost, J. A. Jabre, and H. C. Neu, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 295, 1978). Asymptomatic patients have been reported to be ACBT positive (18, 29). On the other hand, in this study we found a considerable number of patients who were ACBT negative and had upper tract symptoms. Since these patients were seen early in the course of the illness, it is possible that there was insufficient time for antibodies to develop. Until further studies clarify the cause of these false-negative results, caution must be exercised in interpreting ACBT results.

When given at a dose of 200 mg/day for 10 days, TMP was tolerated well, and there was no evidence of adverse effects on kidneys, livers, or bone marrow. Higher doses of TMP (400 mg/day) were associated with an increased incidence of maculopapular skin rashes. This observation had been reported previously from Scandinavia (Sander et al., 19th ICAAC, abstr. no. 59). Skin rashes were not reported in a number of other studies in which similar or even higher doses of TMP were used (4, 17, 21, 23). It is not clear whether the occurrence of skin rashes is a dose-related phenomenon. However, it did not appear to be related to dyes or fillers in the tablets, changes in phenylalanine-tyrosine metabolism, or exposure to sunlight (K. H. Pattishall, unpublished data). This reaction may have had an immunological basis, since several patients developed rashes within several hours after sublingual challenge of purified TMP powder without a concomitant change in pulmonary function. Since 100 mg of TMP given twice a day was not associated with any adverse reactions, this is the dose which should be used for uncomplicated UTIs.

Although TMP showed a broader antibacterial activity and resulted in fewer fecal resistant isolates than SZ, the overall treatment results and recurrence rates were not statistically different for the two drugs.

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