Treatment of Lower Urinary Tract Infections With Single-Dose Trimethoprim-Sulfamethoxazole

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Two hundred three women from a primary care medical practice with symptoms of lower urinary tract infection and positive urine cultures were treated with trimethoprim-sulfamethoxazole. One hundred eleven women received a single dose and 92 were treated for ten days. Cure rates were 87 percent and 89 percent, respectively, one week after therapy. A narrow 95 percent confidence interval for the difference between the two cure rates ($.02 \pm .09$) suggests the treatments are equally effective. Patients were followed by chart audit and a self-reporting questionnaire. No difference in recurrence rates was found between the two groups six months after therapy. Single-dose trimethoprim-sulfamethoxazole is as effective as ten-day treatment in women with symptoms suggestive of lower urinary tract infection and has no greater relapse rate.

Urinary tract infection is among the most common problems for which patients consult primary care physicians. Traditional therapy for uncomplicated infections has been 5 to 14 days of oral antibiotic treatment. Recent studies, however, have demonstrated the effectiveness of single doses of several antibiotics, principally amoxicillin and trimethoprim-sulfamethoxazole,[1-15] leading to a consensus that many patients with urinary tract infection can be treated more simply and at a lower cost.[16-22]

Despite evidence of success, unresolved questions appear to have prevented wide acceptance of single-dose therapy. There are three major areas of concern:

1. Confusion exists over the need to test for antibody-coated bacteria to predict those patients who will respond to single-dose therapy.
2. Small patient samples investigated in previous studies leave the possibility that a clinically important difference in therapeutic response rates has been missed.
3. Suggestions that the use of single-dose therapy may lead to an increased incidence of relapse or reinfection.

Antibody-coated bacteria testing has been suggested as a prerequisite to single-dose therapy because it differentiates patients with cystitis from those with upper urinary tract disease.[23-26] In a number of studies[1,2,7] failure of single-dose treatment has been higher in groups of women with

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antibody-coated bacteria. Lack of access to this test for most primary care providers may have limited their use of single-dose therapy. The incidence of antibody-coated bacteria has varied widely in patients studied, ranging from 60 percent in referral centers to 10 percent in primary care populations.[2] Some have suggested that for unselected, primary care patients, antibody-coated bacteria testing is unnecessary.[2,14,16]

Previous studies have evaluated small numbers of patients. Several commentators have noted that a true difference between treatments may have gone undetected (a type II error made).[16,17,27]

There has also been a question whether single-dose therapy leads to increased relapses or reinfections after the initial episode has resolved.[2,15,16]

The study to be reported here compares single-dose trimethoprim-sulfamethoxazole with a ten-day course of the same antibiotic for presumed lower urinary tract infections in women. The objectives of the study were to (1) compare single-dose with ten-day therapy in an unselected patient population using the resources available to a typical primary care physician, (2) involve sufficient number of patients to be reasonably certain of not missing a clinically significant therapeutic difference, and (3) follow up over six months to establish whether there was any difference in relapse or reinfection rates between the two groups.

Methods

Patient Selection

Subjects of this trial were self-referred, nonpregnant women aged between 18 and 65 years who presented with symptoms of frequency, urgency, or dysuria to two family practice clinics of the Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina. These two clinics are training sites for medical students and family medicine residents, offering primary care to patients from the Durham community and Duke University students and employees. Each clinic has 25,000 annual patient visits; the patient population is 30 percent black and 18 percent are on Medicaid.

A patient was entered into the study by her provider if, based on the assessment of symptoms and urinalysis, a lower urinary tract infection seemed likely. Informed consent was obtained, and the patient was allocated to one of two treatment groups (described in Treatment below). Allocation was made from a sequential list that was generated from a table of random numbers and balanced every 20 entries. Most patients were treated before urine culture results were available. Patients were ultimately retained in the trial only if they had a bacteria colony count of greater than 100,000/mL of urine. A patient was excluded if she had any of the following: sulfa allergy, pregnancy, glucose-6-phosphate dehydrogenase deficiency, temperature greater than 38°C, chills, costovertebral tenderness, Foley catheter, breast feeding, known renal or urologic abnormality, current antibiotic therapy, a urinary tract infection within 30 days, or more than two urinary tract infections within 12 months prior to entering the study.

Bacteriologic Methods

All urine samples were collected by the midstream clean-catch method described by Kunin.[28] Cultures were grown on a urine dipslide (manufactured by Oxoid United)[29] on MacConkey and CLED media. Slides were initially interpreted by certified laboratory technicians at each clinic who were unaware of the treatment allocation. Dipslides read as containing bacterial colonies numbering more than or equal to 50,000/mL were sent to an independent reference laboratory, where bacterial counts and bacterial identification were confirmed by a blinded observer. Sensitivity tests to antibiotics were performed by the Kirby-Bauer technique.

Treatment

Subjects were randomized to either (1) single-dose treatment with three double-strength tablets of trimethoprim-sulfamethoxazole (each tablet containing 160 mg of trimethoprim and 800 mg of sulfamethoxazole) taken in one dose at the time of presentation, or (2) a ten-day treatment consisting of one double-strength tablet of trimethoprim-sulfamethoxazole twice a day for the ensuing ten days.

Follow-up

Seven days after the completion of therapy (day

Table 1. Characteristics of 226 Women Receiving Single-Dose or Ten-Day Treatment

	Single-Dose (n = 119)	Ten-Day (n = 107)	Total
Characteristics			
Age (mean, years)	26.5	28.0	27.2
Previous urinary tract infections (mean)	2.0	2.0	2.0
Duration of symptoms (mean, days)	5.0	5.0	5.0
Symptoms (%)			
Frequency	90	87	88
Dysuria	91	90	90
Urgency	86	83	84

8 for single-dose and day 17 for ten-day), a repeat urine culture was obtained, and the patient was interviewed for symptoms and side effects. A bacteria colony count greater than 50,000/mL of urine on the culture was considered a treatment failure. Among failures, a relapse was defined as a culture that grew the same bacterium with the same antibiotic sensitivities as the initial infection; reinfection was a culture that grew a different bacterium or the initial bacterial strain with different antibiotic sensitivities. Any patient not submitting a follow-up urine culture within three to 14 days following the completion of treatment was considered lost to follow-up. Patients with negative initial urine cultures were dropped from the study and followed by their personal physicians.

The chart of each subject was audited to determine the incidence of recurrent urinary tract infections by an observer who was masked to the mode of initial treatment. A recurrent urinary tract infection was defined as a clinical episode suggestive of a urinary tract infection within six months after initial treatment and associated with any of the following:

1. Bacterial colony count on urine culture of greater than or equal to 100,000/mL
2. Urinalysis with greater than or equal to 10 white blood cells per high-power field (WBC/HPF) or a bacteria count of 2+/HPF
3. Symptoms of cystitis followed by treatment when no laboratory studies were performed

The follow-up was supplemented by a questionnaire sent to subjects at the completion of the six-month follow-up. Patients were asked to recall the number of urinary tract infections they experienced during the preceding six months and whether any of these were treated at a health center other than the study clinics. Those who failed to return the questionnaire were asked the same questions by telephone interview.

Statistical comparisons were performed using the *t* test, analysis of variance, and chi-square statistics. An alpha level of .05 was taken as the point at which statistical significance was inferred.

Results

A total of 332 women was eligible for the study and randomized to receive either single-dose or ten-day therapy with trimethoprim-sulfamethoxazole. Of these, 106 had negative initial cultures, leaving 226 women eligible for follow-up. One hundred nineteen women were given single-dose treatment, and 107, ten-day therapy. The average age of these women was 27 years. They had on average two previous urinary tract infections, with 40 percent experiencing their first episode.

The mean duration of current symptoms was five days, although the median was three days. Eighty-eight percent of women presented with frequency, 90 percent had dysuria, and 84 percent complained of urgency. There was no significant difference in these characteristics between treatment groups (Table 1). Pyuria of greater than 10

Table 2. Percentage of Bacteria Isolated From Urine of 226 Women Receiving Single-Dose or Ten-Day Treatment

	Single-Dose (n = 119)	Ten-Day (n = 107)	Total
Escherichia coli	85	82	83
Staphylococcus (coagulase negative)	4	7	6
Proteus mirabilis	4	4	4
Enterococcus species	2	2	2
Other	5	5	5

WBC/HPF in the urine sediment was present in 94 percent of single-dose recipients compared with 85 percent of those receiving ten-day treatment.

The bacteria isolated from initial urine cultures are shown in Table 2. Escherichia coli was isolated from 83 percent of women; coagulase-negative Staphylococcus, Proteus mirabilus, and Enterococcus made up most of the remaining isolates. There was no significant difference in the distribution of bacteria between single-dose and ten-day recipients. Table 3 presents the sensitivities of the commonly isolated organisms to trimethoprim-sulfamethoxazole, sulfisoxazole, and ampicillin.

Twenty-three of the 226 women or 10 percent eligible for follow-up failed to return within three to 14 days of completing therapy and were considered lost to follow-up. Comparison of characteristics of the 203 women completing follow-up and the 23 women lost to follow-up showed that those lost to follow-up were significantly younger (23.8 vs 27.6 years, $P < .05$). There were no statistically significant differences in mean number of past urinary tract infections, mean duration of symptoms, or reported urinary frequency, dysuria, or urgency between the groups. Comparison of the bacterial isolates between these two groups showed no statistically significant differences.

The 23 patients who were lost to follow-up were not equally distributed between the single-dose and ten-day therapy groups; eight had received single-dose and 15 had been given ten-day treatment. This twofold higher loss to follow-up among women receiving ten-day therapy approaches statistical significance (chi-square = 3.2, $P = .07$).

Response to Treatment

Bacteriologic cure was achieved for 97 of the 111 women (87 percent) receiving single-dose therapy and 82 of the 92 women (89 percent) who received ten days of treatment. Constructing a 95 percent confidence interval for the difference between the two cure rates gives a value of $.02 \pm .09$. This translates to a reasonable certainty that the true difference in effectiveness between single-dose and ten-day treatment is no greater than 11 percent.

Of the 14 treatment failures in the single-dose group, 5 were classified as relapses and 9 as reinfections. There was one relapse and nine reinfections among the ten-day course failures. There were no significant differences between patients who were bacteriologically cured and those considered failures in either duration of symptoms prior to treatment or previous number of urinary tract infections.

For both groups prior duration of symptoms was shorter for women who were treatment failures, but this trend was not statistically significant. Distribution of bacterial isolates was similar for treatment successes and failures; Escherichia coli accounted for over 80 percent of the organisms among successes and failures in both groups.

To assess the possible impact of loss to follow-up on treatment outcome, cure rates were recalculated using a "worse case" illustration. Assuming all eight women given single-dose treatment were dissatisfied because the therapy failed and did not return to follow-up, and all 15 lost from the ten-day treatment group were cured and saw no reason to return, the cure rates are 82 percent and 91 percent for single-dose and ten-day treatment, respectively. This difference is still neither statistically significant nor clinically important.

Follow-up

Symptoms recorded at the follow-up visit showed that women receiving single-dose treatment had more urinary frequency than those receiving ten-day treatment (18 percent vs 8 percent, $P < .05$). Women on the ten-day regimen reported a significantly higher incidence of rash (8 percent vs 1 percent, $P = .02$). One patient in the ten-day group was instructed to stop her medicine by her

Table 3. Percentage of Sensitive Bacteria Isolated From Initial Urine Cultures to Trimethoprim/Sulfamethoxazole, Sulfisoxazole, and Ampicillin

	Trimethoprim/ Sulfamethoxazole	Sulfisoxazole	Ampicillin
Escherichia coli	97 (188)*	88 (184)	81 (188)
Staphylococcus	82 (11)	85 (13)	83 (12)
Proteus mirabilis	100 (9)	78 (9)	100 (9)
Enterococcus species	100 (4)	75 (4)	0 (4)
Other	82 (11)	78 (9)	0 (11)

*Numbers in parentheses are isolates tested

Table 4. Recurrent Urinary Tract Infections During Six Months Following Initial Treatment From Chart Audit (n = 310) and From Self-Report Treatment Outside Study Clinics (n = 250)

	Number of Episodes		
	Percentage with None	Percentage with One	Percentage with Two or More
	Chart Audit		
Single-dose (n = 110)	65	25	10
Ten-day (n = 100)	67	22	11
Initial culture <100,000 (n = 100)	80	19	1
	Self-Report		
Single-dose (n = 87)	80	13	7
Ten-day (n = 78)	79	13	8
Initial culture <100,000 (n = 85)	85	12	3

physician when she developed urticaria. There were no statistically significant differences in reported urgency, dysuria, flank pain, fever, nausea, vomiting, diarrhea, headache, or vaginitis symptoms between the two treatment groups.

Chart audit follow-up was completed for 310 of the 332 subjects initially randomized (94 percent). The results shown in Table 4 indicate that women whose initial cultures were negative were significantly less likely to have a urinary tract infection in the follow-up period than those with positive cultures. There was no difference in recurrence rates between single-dose and ten-day therapy subjects. Follow-up questionnaires were completed on 250 women (76 percent of the initial sample). Only 46 women reported one or more episodes of urinary tract infection symptoms for which they sought treatment outside the study clinics or self-treated. Recurrence rates were similar for single-dose and ten-day groups.

Discussion

Results of this study show that single-dose treatment with trimethoprim-sulfamethoxazole is

as effective as ten-day treatment for nonpregnant women with symptoms of lower urinary tract infections. This study evaluated a primary care patient population and used resources and techniques available on a routine basis to primary care physicians. Sufficient numbers of patients were studied to give 95 percent confidence that a difference between treatment groups as small as 11 percent was not missed.

It is likely that the use of the antibody-coated bacteria assay in many single-dose studies has adversely affected acceptance of this treatment. Cure rates as low as 33 percent have been reported when single-dose treatment was given and the antibody-coated bacteria test was positive. In some studies patients positive for antibody-coated bacteria have been excluded from consideration as single-dose candidates.[5] Studies of Savard-Fenton et al[7] and Buchwold et al,[5] however, which demonstrated single-dose cure rates of 59 percent and 69 percent, respectively, for patients with antibody-coated bacteria, included patients from medical center clinics. Rubin et al[2] have suggested that infections caused by antibody-coated bacteria are more likely in referral populations, perhaps because these people lack easy access to care and wait longer before seeking care. In primary care practices, infections caused by antibody-coated bacteria are much less common, and such tests as the antibody-coated bacteria assay may be unnecessary.[14,16] The high cure rates found in this reported study, which was performed without attempting to "localize" the infection, support this notion.

The choice of trimethoprim-sulfamethoxazole for this study was based on several factors. Trimethoprim-sulfamethoxazole has a long half-life and a broader antibacterial spectrum of activity than agents such as sulfisoxazole and ampicillin.[33-35] Data in Table 3 show that a greater percentage of bacterial isolates were susceptible to trimethoprim-sulfamethoxazole than sulfisoxazole or ampicillin. Some data suggest that patients with positive antibody-coated bacteria tests have better response to trimethoprim-sulfamethoxazole than ampicillin[2] or sulfisoxazole.[5]

The data reported here show that single-dose trimethoprim-sulfamethoxazole is well tolerated, which is consistent with other reports of single-dose therapy.[1-5] Specifically, a significantly lower incidence of skin rashes was reported in the single-dose group.

This study used a dipslide culture technique to establish diagnosis. This technique is accurate,[29] inexpensive, and ideally suited for use in the primary care office setting. All positive dipslides were checked by standard bacteriological culture and sensitivity methods. At the time the study was begun, a bacteria colony count of greater than 100,000/mL was accepted as a standard definition of a positive culture. This definition has since been questioned as too strict a criterion.[17,30-32] However, using a conservative criterion is a more rigorous test of single-dose therapy, assuming that lower numbers of bacteria would be at least equally sensitive to the treatment.

The study was not double blinded, but a placebo effect on the urine cultures that were used as test of cure is unlikely. A double-blinded study may have been useful to eliminate bias in the evaluation of symptoms and side effects, but symptoms and side effects were not found to differ consistently between treatment groups.

Patients were followed for symptoms and bacteriologic cure one week after therapy and then up to six months by self-report and chart audit. The audit and questionnaire criteria for recurrent urinary tract infection are liberal. Treated episodes of cystitis-like symptoms without confirmatory cultures and patient self-reports of episodes treated outside the study clinic facilities were accepted as recurrences in urinary tract infections. These inclusions probably overestimate recurrences. Of interest, however, were the differences reported in the two treatment groups. It was expected that any reporting bias would favor ten-day treatment. Patients who received single-dose were aware that their treatment was innovative and might have thought the single-dose seemed inadequate. The data strongly suggest that the therapies were equivalent, since the recurrence rates obtained were similar for both the chart audit and questionnaire follow-up.

Addendum

Two recent papers have been published. Schultz et al[36] reported the efficacy of single-dose vs ten-day therapy with trimethoprim-sulfamethoxazole in a single-blind randomized trial involving 136 women with acute cystitis. They reported a higher rate of relapses in women taking single-dose therapy and a higher cure rate in women tak-

ing ten-day therapy. They used different criteria to define infections and relapses, however, and their single-dose relapse group contained several patients with urologic abnormalities. These factors may be responsible in part for the differences in the results of the two studies.

Hooton et al[37] reported a single-blind randomized comparison of the effectiveness of single-dose regimens of trimethoprim-sulfamethoxazole, amoxicillin, and cyclacillin for treatment of cystitis in 38 adult women. They prematurely stopped the study due to a low cure rate in the amoxicillin and cyclacillin treatment groups (50 percent and 30 percent, respectively) in comparison to the trimethoprim-sulfamethoxazole treatment group (85 percent). This paper lends further support to the use of single-dose trimethoprim-sulfamethoxazole as the agent of choice for uncomplicated cystitis in women.

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