Short-Course Nitrofurantoin for the Treatment of Acute Uncomplicated Cystitis in Women

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Background: There is a paucity of data on the efficacy of nitrofurantoin for the treatment of acute uncomplicated cystitis in regimens shorter than 7 days. Evidence-based use of this drug is increasingly important as trimethoprim-sulfamethoxazole resistance among uropathogens increases.

Methods: To assess the efficacy of nitrofurantoin vs trimethoprim-sulfamethoxazole, 338 women aged 18 to 45 years with acute uncomplicated cystitis were randomized to open-label treatment with either trimethoprim-sulfamethoxazole, 1 double-strength tablet twice daily for 3 days, or nitrofurantoin, 100 mg twice daily for 5 days. Clinical cure 30 days after therapy was the main outcome measure. Secondary outcomes included clinical and microbiological cure rates 5 to 9 days after therapy and, for trimethoprim-sulfamethoxazole–treated women, clinical cure stratified by the trimethoprim-sulfamethoxazole susceptibility of the uropathogen.

Results: Clinical cure was achieved in 79% of the trimethoprim-sulfamethoxazole group and in 84% of the nitrofurantoin group, for a difference of −5% (95% confidence interval, −13% to 4%). Clinical and microbiological cure rates at the first follow-up visit were also equivalent between the 2 groups. In the trimethoprim-sulfamethoxazole arm, 7 of 17 women (41%) with a trimethoprim-sulfamethoxazole–nonsusceptible isolate had a clinical cure compared with 84% of women with a trimethoprim-sulfamethoxazole–susceptible isolate (P < .001).

Conclusion: A 5-day course of nitrofurantoin is equivalent clinically and microbiologically to a 3-day course of trimethoprim-sulfamethoxazole and should be considered an effective fluoroquinolone-sparing alternative for the treatment of acute cystitis in women.

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See also page 2201

Alternatives to trimethoprim-sulfamethoxazole need to be considered in a variety of clinical settings, including the presence of a history of allergy to sulfas, drugs, a known high prevalence of antimicrobial resistance to trimethoprim-sulfamethoxazole among outpatient Escherichia coli isolates in the community, and a high clinical suspicion of a trimethoprim-sulfamethoxazole–resistant infection based on individual patient factors. Fluoroquinolones are a popular alternative to trimethoprim-sulfamethoxazole and have very high rates of efficacy, high rates of susceptibility among pathogens that cause uncomplicated urinary tract infection (UTI), and minimal adverse effects when used in a 3-day regimen as recommended. A recent survey found that fluoroquinolones have replaced trimethoprim-sulfamethoxazole as the most common class of antibiotic prescribed in the United States for uncomplicated UTI in women. However, increasing rates of fluoroquinolone-resistant Escherichia coli are being reported worldwide, including in some areas in the United States. To prevent further emergence of fluoroquinolone resistance, many experts recommend limiting their use to more serious infections, preferring instead fluoroquinolone-sparing agents as second-line therapy for UTI when trimethoprim-sulfamethoxazole cannot be used. Such agents include nitrofurantoin, fosfomycin, and β-lactams. Fosfomycin has the advantage of single-dose therapy but has relatively low efficacy. Although some β-lactams, such as extended-spectrum...
cephalosporins, may have good activity against UTI pathogens, the expected efficacy with this class of drugs has also, in general, been low.\textsuperscript{1,8,9} Nitrofurantoin has been used for more than 5 decades for the treatment of uncomplicated cystitis and remains active against most uropathogens, but its popularity is hampered by a recommended 7-day dosing regimen and concerns about efficacy and tolerance.\textsuperscript{1,3,8}

Few studies have evaluated the efficacy and tolerance of nitrofurantoin, especially in a regimen shorter than 7 days, as is now more commonly preferred for the treatment of UTI.\textsuperscript{1,2} The purpose of this study was thus to assess the efficacy and tolerance of a 5-day course of nitrofurantoin compared with a standard 3-day regimen of trimethoprim-sulfamethoxazole for the treatment of acute uncomplicated cystitis. The effects of trimethoprim-sulfamethoxazole resistance on efficacy were also assessed.

**STUDY METHODS**

This study was conducted at the Hall Health Primary Care Center, an outpatient clinic that offers care to students, faculty, and staff at the University of Washington and to the general public of Seattle. Women 18 to 45 years of age who were not pregnant, who were in good general health, and who had symptoms of acute cystitis (dysuria, frequency, and/or urgency) and a urine culture with at least $10^3$ CFU/mL of a uropathogen were eligible for participation. Women who were pregnant, lactating, or not regularly using contraception or who had diabetes mellitus, known anatomical abnormalities of the urinary tract, allergy to any of the study drugs, or recent (<2 weeks) exposure to an oral or parenteral antimicrobial agent or who were currently using prophylactic antibiotic drugs were not eligible.

**STUDY PROCEDURES**

Flyers and newspaper advertisements were the main methods of recruitment. Interested women were screened via a checklist of inclusion and exclusion criteria. Eligible individuals signed written informed consent forms and then completed a baseline questionnaire and provided a clean-catch midstream urine sample for urinalysis and culture. Participants were then randomized to open-label treatment with trimethoprim-sulfamethoxazole, 1 double-strength tablet twice daily for 3 days, or nitrofurantoin (Macrobid; Procter & Gamble Pharmaceuticals, Cincinnati, Ohio), 100 mg twice daily for 5 days. Treatment assignments were generated by the study statistician (P.L.R.) using a computerized random-number generator and were placed in individual, sequentially numbered opaque envelopes to be opened by study personnel at the time of enrollment.

Participants were contacted by telephone or e-mail on day 3 of therapy to assess clinical cure. Women randomized to the nitrofurantoin arm also collected a midstream urine specimen after taking their sixth dose (after 3 days of therapy). All the participants were scheduled for follow-up visits at 5 to 9 and 28 to 30 days after completion of therapy. At each follow-up visit a questionnaire regarding UTI symptoms was administered, and urine specimens for urinalysis and culture were collected. Patients who returned to the clinic at any time during the study period with recurrence of symptoms ( recurrent UTI) or without resolution of symptoms (persistent UTI) had another urinalysis and culture performed and were treated with an alternative agent depending on the organism and its susceptibility profile. Patients with a uropathogen that was not susceptible to the drug to which they were randomized continued taking the initial agent unless they had persistent symptoms, in which case they were discontinued from the study and were retreated with an agent active against the causative uropathogen.

**LABORATORY PROCEDURES**

Urine samples were refrigerated and transported to the laboratory within 24 hours of collection. Standard urine culture and susceptibility testing were performed using the standards of the Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards).\textsuperscript{10} *Escherichia coli* isolates found to be resistant to trimethoprim-sulfamethoxazole were further tested for minimum inhibitory concentration (MIC) by means of broth dilution.

**SAMPLE SIZE**

The sample size was based on the hypothesis that the clinical cure rate with nitrofurantoin would be equivalent to that with trimethoprim-sulfamethoxazole within a 10% margin, with the expected cure rate for trimethoprim-sulfamethoxazole being 90%. Using the method proposed by Blackwelder\textsuperscript{11} as implemented using UnifyPow,\textsuperscript{12} and aiming for a significance level of 5% and power of 80%, a sample size estimate was set for 143 patients per treatment group. The target enrollment was inflated to 160 patients per group to allow for an anticipated 10% dropout or unenrollable rate among enrollees.

**MAIN OUTCOME MEASURES**

The clinical cure rate at the end of the entire study period (30 days after therapy) was the primary outcome of interest. Women who required antimicrobial drug treatment for lack of resolution of initial UTI symptoms or for new UTI symptoms of dysuria, frequency, and/or urgency or signs of pyelonephritis (costovertebral angle tenderness—with or without fever) during follow-up were defined as having a clinical failure. All others were designated a clinical cure. The clinical and microbiological cure rates at the early follow-up visit (5-9 days after therapy) were secondary outcomes. In addition, the primary outcome was stratified by the antimicrobial susceptibility of the initially infecting strains.

In asymptomatic women, microbiological cure was defined as having less than $10^2$ CFU/mL of all uropathogens and at least a 1-log decrease in colony count of the causative uropathogen compared with the urine culture at enrollment. In women who had persistent or recurrent symptoms of UTI, microbiological cure was defined as having less than $10^2$ CFU/mL of a uropathogen. Possible uropathogens included enteric gram-negative rods, *Staphylococcus saprophyticus*, enterococci, and group B streptococci. Coagulase-negative staphylococci, *α*-hemolytic streptococci, lactobacilli, diphtheroids, and mixed gram-positive flora were categorized as nonuropathogens. If more than 1 organism was identified, the predominant organism (highest colony count) was considered the causative pathogen. Multiple pathogens present in equal quantities were considered copathogens unless more than 3 pathogens were present, in which case the culture was considered contaminated and not eligible for analysis.

**STATISTICAL ANALYSIS**

A case-available analysis was performed on all participants who attended at least 1 follow-up visit. The 95% confidence intervals were constructed about the difference in binomial out-
comes between the 2 treatment groups for evaluation of the hypotheses of equivalence in major outcomes. An absolute value less than 10% in the upper bound was considered equivalent. A Kaplan-Meier curve depicting time to clinical failure was constructed to display clinical outcomes by treatment assignment and antibiotic susceptibility (for the trimethoprim-sulfamethoxazole group only). A log-rank test was used to evaluate differences in time to clinical failure.13

RESULTS

All participant enrollment and follow-up took place between January 1, 2002, and December 31, 2005. A total of 338 women were enrolled and randomized to receive either trimethoprim-sulfamethoxazole (n = 167) or nitrofurantoin (n = 171) (Figure 1). After randomization, 23 women (14 taking trimethoprim-sulfamethoxazole and 9 taking nitrofurantoin) were deemed ineligible for the study based on negative urine culture results. An additional 7 women (5 taking trimethoprim-sulfamethoxazole and 2 taking nitrofurantoin) did not attend any follow-up visits, leaving 308 women (148 taking trimethoprim-sulfamethoxazole and 160 taking nitrofurantoin) available for analyses. The demographics, UTI history, and sexual history were similar between the 2 treatment groups (Table 1). Approximately 30% of the women in each group had less than $10^{5}$ CFU/mL but at least $10^{2}$ CFU/mL of a uropathogen at enrollment. Most enrollment UTIs were caused by E coli alone (82%) or in combination with another uropathogen (4%). The remaining enrollment UTIs were caused by S saprophyticus (8%) or by enterococci, Klebsiella species, Proteus mirabilis, Enterobacter species, or group B streptococci (1%-3% each). The susceptibility profiles of the infecting uropathogens are given in Table 2. Overall, 14% of isolates (12% of E coli and 23% of non–E coli isolates) were intermediate or resistant to trimethoprim-sulfamethoxazole. Of the 13 resistant E coli isolates available for MIC testing to trimethoprim-sulfamethoxazole, all had an MIC greater than 160/3040 µg/mL.

CLINICAL AND MICROBIOLOGICAL OUTCOMES

The overall clinical cure rate (the percentage of women not having a persistent or recurrent UTI throughout the study period) was 79% (117/148) in the trimethoprim-sulfamethoxazole arm and 84% (134/160) in the nitrofurantoin arm, for a nonsignificant difference of −5% (95% confidence interval, −13% to 4%). All of the women with clinical failure had symptoms of cystitis except 2 women in the trimethoprim-sulfamethoxazole group who were diagnosed as having pyelonephritis. An intention-to-treat approach assigning clinical failure to any woman without outcome data (including women who had negative urine culture results at enrollment and women who did not attend any follow-up visits) also demonstrated that the 2 drugs were equivalent within the prespecified margin of 10%. The clinical cure rate for the duration of the study is shown in Figure 2A (P = .25, log-rank test). Clinical and microbiological cure rates at the early follow-up visit were also statistically equivalent (Table 3). Microbiological cure on day 3 of nitrofurantoin therapy was achieved in 127 of 130 women (98%) who were tested.

Among women treated with trimethoprim-sulfamethoxazole, there was a statistically significant decrease in clinical cure in women who had a trimethoprim-sulfamethoxazole–nonsusceptible (intermediate or resistant) uropathogen compared with women who had a susceptible isolate (Figure 2B). Overall, 110 of 131 trimethoprim-sulfamethoxazole–treated women (84%) with a trimethoprim-sulfamethoxazole–susceptible uropathogen had a clinical cure compared with 7 of 17 women (41%) with a trimethoprim-sulfamethoxazole–nonsusceptible uropathogen (P < .001, log-rank test). Microbiological cure was achieved in 123 of 127 trimethoprim-sulfamethoxazole–treated women (97%) vs 11 of 17 women with a trimethoprim-sulfamethoxazole–susceptible isolate (97%) vs 11 of 17 women with a trimethoprim-sulfamethoxazole–nonsusceptible isolate (65%) (P < .001, $\chi^2$ test).

Only 3 women in the nitrofurantoin arm had a nitrofurantoin-nonsusceptible isolate; 2 of these women (67%)

![Figure 1](https://www.archinternmed.com/960847/1672209a.png)

**Figure 1.** Flow diagram of women enrolled, randomized, and included in this case-available analysis. TMP-SMX indicates trimethoprim-sulfamethoxazole.

| Table 1. Demographic Characteristics of 308 Women With Acute UTI by Treatment Group |
|---------------------------------|---------------------------------|---------------------------------|
| **Characteristic**               | **Trimethoprim-Sulfamethoxazole** | **Nitrofurantoin** |
| **Group (n = 148)**              | **Group (n = 160)**               |
| Age, median (range), y           | 31 (18-40)                       | 29 (18-39)                    |
| Never married, No. (%)           | 126 (86)                         | 131 (82)                      |
| Race, No. (%)                    |                                 |                               |
| White                            | 109 (74)                         | 115 (72)                      |
| Asian                            | 27 (18)                          | 29 (18)                       |
| Other                            | 10 (7)                           | 16 (10)                       |
| Hispanic ethnicity, No. (%)      | 4 (3)                            | 7 (4)                         |
| ≥3 lifetime UTIs, No. (%)        | 38 (26)                          | 39 (24)                       |
| Sexually active in past month, No. (%) | 144 (87) | 149 (93) |
| Spermicide use in past month, No. (%) | 36 (24) | 33 (21) |

Abbreviation: UTI, urinary tract infection.
were clinically and microbiologically cured (1 with *E coli* and 1 with *P mirabilis*). The third woman had a *P mirabilis* UTI and met the criteria for clinical and microbiological failure.

**TOLERANCE AND COMPLIANCE**

Similar proportions of women in the trimethoprim-sulfamethoxazole and nitrofurantoin arms (31% and 28%, respectively) reported an adverse effect related to the study medication in response to an open-ended question. On direct questioning about specific symptoms, 41% of women in the trimethoprim-sulfamethoxazole group and 39% in the nitrofurantoin group reported at least 1 adverse effect. Most adverse effects were related to the gastrointestinal system (nausea or diarrhea), central nervous system (headache or lightheadedness), and urogenital system (vaginal itching). Discontinuation of the study due to adverse effects occurred in 1% and 2% of women in the trimethoprim-sulfamethoxazole and nitrofurantoin groups, respectively. Fewer women in the nitrofurantoin group (6%) than in the trimethoprim-sulfamethoxazole group (11%) required treatment (primarily over-the-counter medications) for adverse effects.

Excluding women who stopped taking their study drug early because of a clinical failure requiring repeated treatment with another agent (2 taking trimethoprim-sulfamethoxazole and 3 taking nitrofurantoin), 100% of women in the trimethoprim-sulfamethoxazole arm reported taking all 6 doses of the drug and 97% of women in the nitrofurantoin arm reported taking all 10 doses of their drug. All the women in the nitrofurantoin arm took at least 6 of the prescribed 10 doses.

This is one of the largest studies evaluating the efficacy and tolerance of a 5-day regimen of nitrofurantoin for the treatment of acute uncomplicated cystitis in adult women. Aside from the adequacy of the sample size to establish equivalence as outlined by CONSORT (Consolidated Standards of Reporting Trials) guidelines, this study has the added advantage of evaluating outcomes stratified by susceptibility of the original infecting pathogen to the treatment drug. The latter issue is important in a clinical setting where treatment is chosen empirically (either without a urine culture or before the infecting pathogen and its susceptibility are known if a urine culture is performed). Despite recommendations for a 3-day course of therapy with trimethoprim-sulfamethoxazole for uncomplicated cystitis, many health care professionals still prescribe a 5-day course of this drug. This study provides evidence of an additional treatment choice using the same duration in settings in which trimethoprim-sulfamethoxazole cannot be used, which has the potential to result in decreased use of fluoroquinolones for the treatment of acute uncomplicated cystitis.

Although the study was not designed to specifically evaluate a 3-day regimen of nitrofurantoin, it does demonstrate that most women (98%) had microbiological cure by 3 days of therapy. This is in contrast to a study performed in a similar population in which a 3-day course of macrocrystalline nitrofurantoin (Macrodantin; Procter & Gamble Pharmaceuticals) resulted in early microbiological cure in only 32 of 38 women (84%) and overall cure in only 22 of 36 women (61%). A smaller sample size, a different formulation of nitrofurantoin requiring 4 daily doses, a low rate of trimethoprim-sulfamethoxazole resistance (5%), and a different composite outcome combining bacterial and clinical response may account for some of the discrepancies between the earlier study and the present data. Nonetheless, a well-powered randomized trial specifically aimed at evaluating a 3-day course of nitrofurantoin is needed, and we do not recommend use of a 3-day regimen until such efficacy data are available. A recent pharmacy database study found that a 3-day course of nitrofurantoin was frequently used (presumably for uncomplicated UTI) and resulted in another antibiotic prescription more often than longer courses.

Most previous clinical trials of nitrofurantoin have evaluated a 7-day course of a twice-daily regimen. One of the largest studies is a randomized trial of ciprofloxacin, 100 mg twice daily for 3 days, vs nitrofurantoin or trimethoprim-sulfamethoxazole for 7 days. The primary efficacy measure, microbiological cure 4 to 10 days after therapy, was similar among the 3 treatment groups and was achieved in 86% of 177 evaluable women treated with nitrofurantoin. Clinical cure rates with the 7-day regimen of nitro-

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Table 2. Susceptibility of Uropathogens in Women With Acute UTI

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Nitrofurantoin</th>
<th>Trimethoprim-Sulfamethoxazole</th>
<th>Ciprofloxacin</th>
<th>Amoxicillin-Clavulanate</th>
<th>Cefotaxime</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>99.6</td>
<td>99.6</td>
<td>96.4</td>
<td>82</td>
<td>100b</td>
</tr>
<tr>
<td>Susceptible</td>
<td>99.6</td>
<td></td>
<td>96.4</td>
<td>82</td>
<td>100b</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistant</td>
<td>0.4</td>
<td>12</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-<em>E coli</em></td>
<td>90</td>
<td>77</td>
<td>76</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Susceptible</td>
<td>90</td>
<td></td>
<td>76</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4</td>
<td>2</td>
<td>22</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Resistant</td>
<td>6</td>
<td>21</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviation: UTI, urinary tract infection.

a There were 337 isolates from 308 women with UTI.

b Percentage has been rounded.
furantoin (93%) were similar to what we report herein with a 5-day regimen (90%). A more recent randomized trial comparing nitrofurantoin, 100 mg twice daily for 7 days, with single-dose fosfomycin for uncomplicated cystitis found a microbiological cure rate of 81% 5 to 11 days after nitrofurantoin therapy. Another study of a 7-day regimen of nitrofurantoin found an 82% microbiological cure rate with a twice daily formulation and an 83% microbiological cure rate with trimethoprim-sulfamethoxazole, both lower than those reported herein.

The impact of antimicrobial resistance has been postulated as being of lesser significance in UTI because of the high urinary concentrations achieved by most antimicrobial agents used to treat UTI. Although previous studies have evaluated the clinical and bacterial cure rates with trimethoprim-sulfamethoxazole stratified by trimethoprim-sulfamethoxazole susceptibility, few of these have prospectively studied a 3-day regimen of trimethoprim-sulfamethoxazole in a large cohort and also measured MICs of the resistant organisms. We found that all of the trimethoprim-sulfamethoxazole–resistant isolates tested had MICs greater than the achievable concentration of trimethoprim-sulfamethoxazole in the urine. Given this finding, it is not surprising that the clinical failure rate in women with a trimethoprim-sulfamethoxazole–resistant organism was very high (59%). A previous prospective study in Israel found a 50% clinical failure rate with a 5-day regimen of trimethoprim-sulfamethoxazole in women with a trimethoprim-sulfamethoxazole–resistant E.coli UTI but did not report MIC data. A clinical failure rate of 50% to 60% dictates that alternative agents need to be used when a uropathogen with high-level trimethoprim-sulfamethoxazole resistance is suspected.

This study adheres to many of the guidelines for clinical trials designed to test equivalence recently published by the CONSORT group. One exception to the guideline is that this was an unblinded study, and it is possible that open-label therapy led to a bias in the evaluation of clinical response to therapy. However, because trimethoprim-sulfamethoxazole is the gold standard regimen and the one expected to have higher efficacy based on previous studies, it would be more likely that any bias would favor finding clinical failures in nitrofurantoin-treated participants. In addition, the secondary outcome of microbiological cure is objective and thus is unlikely to be affected by the lack of masking. Although some experts may consider a case-available analysis rather than an intention-to-treat analysis to be a limitation, it is reassuring that both methods produced consistent results. Finally, the participants were primarily a highly compliant, white student population, and therefore, these findings may not be generalizable to settings where these characteristics differ.

An important question raised by this study is whether demonstration of efficacy with a 5-day regimen of nitrofurantoin will provide enough impetus for health care pro-
fessionals to switch from choosing a fluoroquinolone as the second-line (or first-line in some cases) agent for uncomplicated cystitis to nitrofurantoin. The efficacy, tolerability, and availability of once-daily dosing regimens are factors that may still lead to preferred prescribing of fluoroquinolones. However, as the need for preservation of the fluoroquinolones is increasingly recognized, the strong evidence presented herein for excellent efficacy and tolerance of a 5-day regimen of nitrofurantoin may facilitate prescribing that optimizes the care of patients with cystitis while minimizing the propagation of resistance.²

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Author Contributions: Dr Gupta had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gupta, Hooton, and Stamm. Acquisition of data: Gupta and Stamm. Analysis and interpretation of data: Gupta, Hooton, Roberts, and Stamm. Drafting of the manuscript: Gupta, Hooton, Roberts, and Stamm. Critical revision of the manuscript for important intellectual content: Gupta, Hooton, and Stamm. Statistical analysis: Roberts. Obtained funding: Gupta and Stamm. Administrative, technical, and material support: Gupta and Stamm. Study supervision: Gupta, Hooton, and Stamm.

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Additional Contributions: Ajit Limaye, MD, and Susan Swanzy, BS, RM, performed and interpreted the MIC tests; Marsha Cox, BS, and Sheila Manuguid, BS, performed microbiological processing and testing; and Niki Deshaw, MA, and Ellen Cassen, APRN, performed participant enrollment and follow-up (all at the University of Washington).

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