# ANTIBIOTIC PROPHYLAXIS FOLLOWING LOWER URINARY TRACT INSTRUMENTATION*

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*ABSTRACT—The value of routine antibiotic prophylaxis was assessed in 362 women undergoing lower urinary tract instrumentation. A three-day course of a once-a-day dose of 1 g of cefadroxil was compared with a three-day course of 100 mg of nitrofurantoin three times a day, in a randomized investigator blinded placebo controlled study. Both study drugs were significantly more effective in preventing postinstrumentation urinary tract infections than placebo ($p < 0.003$). Differences in efficacy between the two test drugs were not significant; however, side effects in the nitrofurantoin group were more frequent and severe than those in the cefadroxil group. Cefadroxil also offered the advantage of a once-daily dosing schedule.*

The female is more susceptible to ascending urinary tract infection than the male. This is probably due to an anatomically short urethra and proximity of the external urethral meatus to a large bacterial reservoir within the introital tract and along the vaginal vestibule and distal urethra.[1] Instrumentation of the lower urinary tract for diagnostic or therapeutic purposes may result in an increased risk of initiating urinary tract infection.[1-3] Although numerous articles have addressed the use of prophylactic antibiotics,[2-7] to date no study provides enough evidence to support or refute their routine use following lower urinary tract instrumentation.

This study was undertaken to evaluate, in a prospective double-blinded placebo controlled fashion, the role of chemoprophylaxis following instrumentation of the lower urinary tract, and to compare two commonly used urinary antibiotics, i.e., nitrofurantoin and cefadroxil.

## Material and Methods

A total of 409 women undergoing various lower urinary tract instrumentation procedures, namely urethrocystoscopy, urethral dilatations, or simultaneous urethrocystometric urodynamic studies, were enrolled in the study. The indications for lower urinary tract instrumentation were urinary incontinence, urethral syndrome, or voiding dysfunction. Patients with existing urinary tract infection, history of hypersensitivity to cephalosporins or penicillins, severe renal or hepatic impairment, or patients who had received antibiotics within seventy-two hours prior to study enrollment were excluded from the study. Prospective candidates were screened by one of the study investigators or another qualified member of the study team. All details regarding the study were explained to the patients and each patient signed the informed consent form approved by the Institutional Review Committee.

Preliminary evaluation included a history and physical examination and a urine for culture and sensitivity on the day of transurethral instrumentation. Based on a computer-generated randomization sequence, patients received one of the two study drugs or a placebo. Cefadroxil was given in a single daily dose of 1 g, while nitrofurantoin (100 mg) and placebo were given three times per day. Each regimen

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TABLE I. *Urinary signs/symptoms at baseline (%)*

| Symptom | Cefadroxil | Nitrofurantoin | Placebo |
|---|---|---|---|
| Dysuria | 55.9 | 54.1 | 61.6 |
| Urgency | 72.8 | 71.4 | 81.9 |
| Incontinence | 85.3 | 88.0 | 83.3 |
| Suprapubic pain | 35.3 | 33.8 | 45.7 |
| Voiding difficulty | 11.8 | 3.4 | 1.6 |
| CVA tenderness | 7.4 | 3.0 | 7.2 |

TABLE II. *Diagnoses requiring urinary instrumentation*

| | Cefadroxil | Nitrofurantoin | Placebo |
|---|---|---|---|
| Stress urinary incontinence | 83.7 | 58.0 | 54.3 |
| Urethral syndrome | 19.7 | 22.7 | 35.4 |
| Bladder instability | 5.5 | 16.8 | 7.0 |
| Other | 6.6 | 1.5 | 2.2 |

was given for a total of three days. All patients returned for two follow-up visits at two to eight days and then again at nine to eighteen days following their initial instrumentation. Catheterized urine specimens were obtained prior to instrumentation and again at each of the follow-up visits. All the patients found to have positive urine cultures prior to instrumentation were excluded from the study. Patients with evidence of urinary tract infection following instrumentation were considered prophylactic failures and were treated with appropriate antibiotics based on sensitivity reports. To be considered a prophylactic success, a patient was required to have negative urine cultures at each of the two follow-up visits.

Side effects were collected from patient evaluation forms at each visit and were assessed for severity (mild, moderate, severe), and the relationship to drug therapy (unknown, questionable, yes).

Chi-square tests and Fischer exact test were used for statistical analysis of the data with significance defined as a $p$ value less than 0.05. Except where indicated, all terminology conforms to that proposed by the International Continence Society.[8]

## Results

Of the 409 patients enrolled in this study, 47 were excluded from the analysis, resulting in 362 evaluable cases. Reasons for exclusion were positive cultures prior to instrumentation (cefadroxil 5; nitrofurantoin, 8; placebo, 6); only one follow-up visit (cefadroxil, 6; nitrofurantoin, 7; placebo, 6); and no follow-up visit (cefadroxil, 1; nitrofurantoin, 5; placebo, 3). Six patients who did not return for their second follow-up visit until three to four weeks following instrumentation were included in the efficacy analysis. All patients with any follow-up data were evaluated for safety. The mean ages were comparable among the three groups: 46.7 years, cefadroxil; 44.6 years, nitrofurantoin; and 46.1 years, placebo. There were no significant differences with regard to parity or menopausal status between the three groups.

The common urinary signs and symptoms exhibited by patients at baseline included dysuria, urgency, incontinence, suprapubic pain, voiding difficulty, and tenderness of the costovertebral angle (CVA) (Table I). Diagnoses obtained with the aid of instrumentation most frequently included stress urinary incontinence, urethral syndrome, bladder instability, and voiding difficulty. The incidence of these diagnoses in each study group is summarized in Table II.

Bacteriologic efficacy rates in both active prophylaxis groups was significantly greater than in the placebo group ($p < 0.001$ for cefadroxil and $p < 0.003$ for nitrofurantoin). However, the difference between the active groups was not significant. At the first follow-up visit, all patients in the cefadroxil group, 94.7 percent in the nitrofurantoin group, and 81.3 percent in the placebo group had negative urine cultures.

At the second follow-up visit (days 9–18), 96 percent, 92.9 percent, and 77.3 percent of patients in the three respective groups had negative urine cultures (Table III). The organisms

TABLE III. *Efficacy of antimicrobial prophylaxis*

| | Cefadroxil | Nitrofurantoin | Placebo |
|---|---|---|---|
| Patients enrolled | 138 | 133 | 138 |
| Evaluable cases | 126 | 113 | 123 |
| Positive cultures | | | |
| (Days 2–8) (%) | 0 | 6 (5.3) | 23 (18.7) |
| (Days 9–18) (%) | 5 (4.0) | 8 (7.1) | 28 (22.7) |
| $p$-value* | <0.001 | <0.003 | |

*$p$-value when compared with placebo.

TABLE IV. *Organisms isolated from positive urine cultures*

| Organism | Cefadroxil | Nitrofurantoin | Placebo |
|---|---|---|---|
| Escherichia coli | 1 | 6 | 17 |
| Klebsiella | . . | . . | 7 |
| Proteus | . . | 1 | 2 |
| Streptococcus | 2 | . . | 1 |
| Other | 2 | 1 | 0 |

TABLE V. *Adverse effects*

| Drug | No. of Pts. (%) | Symptoms | Severity | Relationship to Drug |
|---|---|---|---|---|
| Cefadroxil | 2 (1.5) | Nausea | Mild | Questionable |
| Nitrofurantoin | 6 (5.3) | Nausea (N = 2) | Severe | Yes |
| | | Dizziness | Severe | Yes |
| | | Headache | Severe | Yes |
| | | Pruritus | Severe | Yes |
| | | Vomiting | Severe | Yes |
| Placebo | 5 (4.8) | Nausea (N = 3) | Mild | Questionable |
| | | Nausea | Moderate | Questionable |
| | | Nausea | Severe | Unknown |
| | | Vomiting | Severe | Unknown |

isolated from positive urine cultures are summarized in Table IV. The colony size of organisms in urine cultures was at least 100,000 in most cases (80.6%).

Varying degrees of nausea was the most frequently reported adverse reaction. All six adverse events reported in the nitrofurantoin group were severe and appeared to be drug related (Table V).

## Comment

This study demonstrates that transurethral instrumentation is associated with a significantly increased risk of urinary tract infection if antibiotic prophylaxis is not employed. The results in these 362 patients suggest that both cefadroxil and nitrofurantoin offer efficacious prophylaxis for infection following urinary tract instrumentation. A 40 percent incidence of significant bacteriuria in the placebo group certainly indicates that patients undergoing transurethral instrumentation, whether it be an endoscopic evaluation, a urodynamic evaluation, or urethral dilatation are at high risk of a urinary tract infection developing.

The other finding in this study corroborates earlier studies on the utility of a once-a-day dosing regimen of cefadroxil.[9-11] Cefadroxil is a cephalosporin which is stable in gastric pH range and will be absorbed following oral administration.[12] Bioavailability of cefadroxil is not affected by food, and a substantially slower elimination rate and a significantly longer serum half-life have been demonstrated in comparison with other cephalosporins.[12] Hausman[9] described the efficacy of once-a-day cefadroxil in urinary tract infections. Ballantyne[10] has reported on the utility of the same regimen in the treatment of skin and skin structure infections, and more recently Gerber *et al.*[11] described the effectiveness of once-daily cefadroxil in the treatment of streptococcal pharyngitis. A once-a-day regimen is generally accepted to offer the best solution to the problem of patients not complying with their prescribed medications and also as demonstrated in this study is associated with less adverse effects.

Use of antibiotic prophylaxis following lower urinary tract instrumentation significantly decreased the risk of urinary tract infection in this study. Because of the low incidence of side effects, the benefits obtained with antibiotic prophylaxis outweigh the risks associated with urinary tract infection in the absence of antibiotic prophylaxis. We conclude that routine antibiotic prophylaxis should be employed following lower urinary tract instrumentation.

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## References

1. Cox LE, Lacy SS, and Hinman F: The urethra and its relationship to urinary tract infection, J Urol **99**: 632 (1968).
2. Kunin CM: Urinary tract infections, JAMA **233**: 458 (1975).
3. Kunin CM: New developments in the diagnosis and treatment of urinary tract infections, J Urol **113**: 585 (1975).
4. Kaiser AB: Antimicrobial prophylaxis in surgery, N Engl J Med **315**: 1129 (1986).
5. Korbel EL, and Maher PO: Use of prophylactic antibiotics in urethral instrumentation, J Urol **116**: 744 (1976).
6. MacDermott JP, Ewing RE, Somerville JFS, and Gray BK: Cephradine prophylaxis in transurethral procedures for carcinoma of the bladder, Br J Urol **62**: 136 (1988).
7. Bergman A, and McCarthy TA: Antibiotic prophylaxis after instrumentation for urodynamic testing, Br J Urol **55**: 568 (1983).
8. Bates P, *et al*: The standardization of terminology of lower urinary tract function, J Urol **121**: 551 (1979).
9. Hausman MS: Treatment of urinary tract infections with cefadroxil, Urology **15**: 40 (1980).
10. Ballantyne F: Cefadroxil in the treatment of skin and soft tissue infections, J Antimicrob Chemother (Suppl B) **10**: 143 (1982).
11. Gerber MA, *et al*: Once daily therapy for streptococcal pharyngitis with cefadroxil, J Pediatr **109**: 531 (1986).
12. Buck RE, and Price KE: Cefadroxil, a new broad-spectrum cephalosporin, Antimicrob Agents Chemother **11**: 331 (1977).