Bacterial Interference for Prevention of Urinary Tract Infection: A Prospective, Randomized, Placebo-Controlled, Double-Blind Pilot Trial

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(See the editorial commentary by Ronald on pages 1535–6)

This prospective, randomized, placebo-controlled, double-blind pilot trial examined the efficacy of bacterial interference in preventing urinary tract infection (UTI) in 27 patients with spinal cord injury. Patients whose bladders became colonized with Escherichia coli 83972 were half as likely (P = .01) than noncolonized patients to develop UTI during the subsequent year.

Approximately 247,000 persons currently live with complications of spinal cord injury (SCI) in the United States [1]. Urinary tract infection (UTI), the most common infection in this population, is associated with major medical and economic sequelae and is difficult to prevent [2–4]. Moreover, systemic antibiotic prophylaxis [5, 6], local antimicrobial-utilizing approaches (including daily care of the urethral meatus) [7, 8], disinfection of the collection bag [9, 10], and irrigation of the catheter and bladder [11, 12] have not been demonstrated to adequately prevent catheter-related UTI in either patients with SCI or able-bodied persons. The limited success of such traditional approaches prompted our interest in exploring the potential preventive efficacy of bacterial interference.

Earlier investigations have indicated that inoculation of the neurogenic bladder of patients with SCI with a nonpathogenic strain (i.e., although it has the genes for 4 fimbriae types [fim, foc, and uca] and hemolysin [hly], it does not express any) of Escherichia coli 83972 can result in long-term asymptomatic bladder colonization [13–15]. Although a small, prospective clinical trial has shown that patients with SCI had significantly lower rates of symptomatic UTI while their bladders were colonized with E. coli 83972, compared with their baseline prestudy rates [16], that initial study was limited by its nonrandomized, single-arm, open-label design. The objective of this pilot clinical trial was to examine in a more scientifically robust fashion the efficacy and safety of this approach with bacterial interference.

Patients and methods. This prospective, randomized, double-blind, placebo-controlled trial was approved by the institutional review board. Patients were randomly assigned in a 3:1 ratio to have their bladders inoculated with either E. coli 83972 (experimental group) or sterile normal saline (control group).

Adult patients with SCI for a duration of ≥1 year who had a neurogenic bladder that required indwelling (transurethral or suprapubic) or intermittent catheter drainage and experienced frequent, symptomatic episodes of UTI (≥2 episodes during the preceding year) were eligible for enrollment. Exclusion criteria included supravesical urinary diversion, vesicoureteral reflux, obstructing urolithiasis, an indwelling nephrostomy catheter, extraurogenital infections that require prolonged antibiotic therapy, uncontrolled diabetes mellitus, and immunosuppression. After obtaining informed consent, a medical history was obtained, and physical examination, urine culture, radiologic evaluation with plain radiography of the abdomen, renal ultrasound, and urodynamic study were performed to check for urolithiasis and vesicoureteral reflux.

Because previous experience indicated that successful colonization with E. coli 83972 was more likely achieved by inoculating sterile rather than nonsterile bladders [13, 16], patients with positive baseline urine culture results completed a 1-week course of properly selected antibiotics 2–3 days before inoculation. After inserting a new catheter and emptying the bladder, a 30-mL aliquot of either E. coli 83972 suspension (106 cfu/mL of saline) or sterile saline was instilled into the bladder and allowed to dwell for 2 h. Each cycle of inoculations consisted of bladder instillations twice per day for 3 consecutive days. Patients were successfully kept unaware of the nature of solutions instilled into their bladders.

Urine samples for culture were obtained by means of freshly inserted catheters at 1 week after bladder inoculation, then monthly thereafter for 1 year. Successful bladder colonization was defined by the growth (≥104 cfu/mL) of E. coli 83972 in
Table 1. Clinical characteristics of patients inoculated with *Escherichia coli* 83972 or sterile normal saline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Experimental group</th>
<th>Control group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (range)</td>
<td>52 (27–71)</td>
<td>52 (28–74)</td>
<td>NS</td>
</tr>
<tr>
<td>Level of spinal cord injury</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Quadriplegia</td>
<td>10</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Paraplegia</td>
<td>11</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Type of bladder catheter</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Indwelling transurethral</td>
<td>12</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Indwelling suprapubic</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Intermittent catheterization</td>
<td>7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mean no. of UTIs in the past year (range)</td>
<td>3 (2–5)</td>
<td>3 (2–5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. of patients, unless otherwise indicated. NS, not significant; UTI, urinary tract infection.

urine cultures for ≥1 month. To distinguish *E. coli* 83972 from other *E. coli* strains, we relied on both antibiotic susceptibility patterns and restriction fragment-length polymorphism analysis that used PFGE. Patients who became initially colonized with *E. coli* 83972 and then cleared this organism from their bladders did not undergo further inoculations.

The primary outcome of UTI was diagnosed by a blinded evaluator (R.O.D.) for patients who were unaware of their randomization group by the presence of significant bacteriuria (≥10^5 cfu/mL) and pyuria (≥10 WBCs/high power field) plus ≥1 of the following signs and symptoms, for which no other etiology could be identified: fever (oral temperature, >37.8°C), suprapubic or flank discomfort, bladder spasm, increased spasticity, and worsening dysreflexia [17, 18].

The clinical characteristics of patients were compared by using Fisher’s exact test or the χ² test for categorical variables and Student’s *t* test for continuous variables. Fisher’s exact test was used to compare the proportions of patients in different groups who developed ≥1 episode of UTI. The numbers of episodes of UTI were compared using the Wilcoxon rank sum test. The proportions of patients who were free of UTI as a function of the time elapsed between bladder inoculation and the first episode of UTI were compared between patients who became colonized with *E. coli* 83972 and noncolonized patients, using the log-rank test on the Kaplan-Meier estimates. All *P* values were based on 2-tailed tests of significance.

**Results.** A total of 27 male patients were randomized to the experimental group (21 patients) or placebo group (6 patients). The 2 groups of patients had similar clinical characteristics (table 1). Thirteen (62%) of 21 patients in the experimental group became colonized with *E. coli* 83972 and then cleared this organism from their bladders after an average of 3.5 months. Repeated urine cultures performed during periods of colonization revealed 3 growth patterns: *E. coli* 83972 that always grew alone (3 patients); *E. coli* 83972 that initially grew alone, then in

![Figure 1. Kaplan-Meier estimates of the risk of urinary tract infection (UTI), by time elapsed since bladder inoculation in colonized and noncolonized patients. Colonized patients are patients who became initially colonized with *Escherichia coli* 83972 but did not necessarily remain colonized throughout the 1-year follow-up period.](https://academic.oup.com/cid/article-abstract/41/10/1531/347478)
combination with other organisms (5 patients); and *E. coli* 83972 that always grew in combination with other organisms (5 patients). Regardless, *E. coli* 83972 that usually grew at a concentration higher than or similar to concentrations of co-colonizing organisms.

Overall, 13 (62%) of 21 patients in the experimental group and all 6 patients in the control group developed at least 1 episode of UTI during the 1-year follow-up period (\( P = .07 \)). The number of UTI episodes that occurred during the follow-up period was significantly lower (\( P = .036 \)) in the experimental group (mean, 1.6 episodes) than in the control group (mean, 3.5 episodes).

Because there were no differences in the clinical characteristics and the incidence of UTI among the 8 patients in the experimental group who could not be colonized with *E. coli* 83972 and the 6 patients in the control group, all 14 patients were considered to be noncolonized for statistical comparisons. Patients colonized with *E. coli* 83972 were significantly less likely than noncolonized patients to develop at least 1 episode of UTI during the 1-year follow-up period (6 [46%] of 13 patients vs. 13 [93%] of 14 patients; \( P = .01 \)). Figure 1 shows the Kaplan-Meier estimates of the risk of UTI, by time elapsed since bladder inoculation in colonized versus noncolonized patients and illustrates that bladder colonization with *E. coli* 83972 was protective against infection (\( P = .002 \), by the log-rank test).

A single patient developed autonomic dysreflexia 30 min after instillation of placebo solution and recovered completely after the catheter was unclamped and the inoculum was drained from the bladder. None of the 27 patients had clinical evidence of septicemia following bladder inoculations. Only 1 of 13 colonized patients developed UTI while *E. coli* 93972 still existed in the bladder; however, because that episode of UTI was characterized by polymicrobial growth of other organisms (including *Pseudomonas aeruginosa* that had previously caused UTI) in urine cultures, the patient was diagnosed and treated for UTI due to *P. aeruginosa*.

**Discussion.** The results of this controlled pilot study provide the first valid proof that bacterial interference based on deliberate bladder colonization with *E. coli* 83972 protects against UTI in patients with SCI. The observed 2-fold reduction (46% vs. 93%) in the likelihood of UTI developing in colonized versus noncolonized patients surpasses the magnitude of protection afforded by all other potentially preventive approaches, including antimicrobial-coated catheters, whose activity can be overwhelmed by the high concentration of urinary pathogens [19]. Because only 1 of 13 colonized patients developed UTI while *E. coli* 93972 still existed in the bladder, we have embarked on genetic alteration of *E. coli* 83972 in an effort to prolong the duration of bladder colonization (1 patient remained colonized for almost 3 years) and, we hope, to further augment protection against infection. Although the exact mechanism(s) by which *E. coli* 83972 exerts its protective impact is still unclear, possibilities include secretion of substances that can kill or inhibit growth of other pathogens, physical blockage of binding sites on the uroepithelium, and alteration of the nutritional or pH level in the surrounding environment.

The lack of evidence in this study of septicemia and UTI attributed to *E. coli* 83972 after bladder inoculations, coupled with our previous finding of no adverse impact of chronic *E. coli* 83972 colonization on renal function, support the safety of this preventive approach [17]. Potential limitations of this small-sized study include the inclusion of adult men only, the nonblinding of the nurse who performed bladder inoculations, and the inability to perform cost-benefit analysis. Regardless, these promising results have allowed us to initiate a large National Institutes of Health-sponsored, prospective, randomized, placebo-controlled, double-blind, multicenter clinical trial to confirm the efficacy and safety and assess the cost-benefit of bacterial interference in more diverse SCI populations.

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