

## ORIGINAL ARTICLE

# A bacterial interference strategy for prevention of UTI in persons practicing intermittent catheterization

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**Study design:** Non-randomized pilot trial.

**Objectives:** To determine whether *Escherichia coli* 83972-coated urinary catheters in persons with spinal cord injury (SCI) practicing an intermittent catheterization program (ICP) could (1) achieve bladder colonization with this benign organism and (2) decrease the rate of symptomatic urinary tract infection (UTI).

**Setting:** Outpatient SCI clinic in a Veterans Affairs hospital (USA).

**Methods:** Participants had neurogenic bladders secondary to SCI, were practicing ICP, had experienced at least one UTI and had documented bacteruria within the past year. All participants received a urinary catheter that had been pre-inoculated with *E. coli* 83972. The catheter was left in place for 3 days and then removed. Participants were followed with urine cultures and telephone calls weekly for 28 days and then monthly until *E. coli* 83972 was lost from the urine. Outcome measures were (1) the rate of successful bladder colonization, defined as the detection ( $\geq 10^2$  cfu ml<sup>-1</sup>) of *E. coli* 83972 in urine cultures for > 3 days after catheter removal and (2) the rate of symptomatic UTI during colonization with *E. coli* 83972.

**Results:** Thirteen participants underwent 19 insertions of study catheters. Eight participants (62%) became successfully colonized for > 3 days after catheter removal. In these 8 participants, the rate of UTI during colonization was 0.77 per patient-year, in comparison with the rate of 2.27 UTI per patient-year before enrollment.

**Conclusions:** *E. coli* 83972-coated urinary catheters are a viable means of achieving bladder colonization with this potentially protective strain in persons practicing ICP.

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**Keywords:** urinary tract infection; spinal cord injury; *Escherichia coli*

## Introduction

Each year, more than 30 million bladder catheters are used in the United States.<sup>1</sup> Urinary catheters bypass normal host defenses to allow bacterial entry at a rate of approximately 3–10% per day, and they encourage bacterial persistence in the bladder.<sup>2</sup> The majority (98%) of individuals who are catheterized for 30 days or longer will have bacteriuria with one or more species of uropathogens.<sup>3</sup> Individuals practicing an intermittent catheterization program (ICP) become colonized at a lower but still significant rate, with 51–61% of urine samples from persons practicing ICP containing bacteria.<sup>4,5</sup> Although most episodes of catheter-associated bacteriuria are asymptomatic, asymptomatic bacteriuria

(ABU) in many cases progresses to symptomatic urinary tract infection (UTI) and even bacteremia.<sup>6</sup> Individuals with spinal cord injury (SCI) who rely on bladder catheters for urinary drainage are predisposed to recurrent UTI.<sup>7</sup> Currently few, if any, measures are effective at preventing UTI in persons with neurogenic bladders secondary to SCI.

Bacterial interference, or using benign bacteria to prevent infection with virulent pathogens,<sup>8,9</sup> may offer a solution to the significant problem of recurrent UTI in persons who require urinary catheters for bladder drainage. Urinary catheters which have been pre-inoculated with benign *Escherichia coli* 83972 may prevent UTI by interfering with either catheter colonization or bladder invasion by uropathogens. *In vitro*, we found that coating urinary catheters with *E. coli* 83972 impeded subsequent catheter colonization by a wide variety of uropathogens.<sup>10,11</sup> Our earlier study *in vivo* with individuals with SCI using long-term, indwelling

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catheters also supports our hypothesis that *E. coli*-coated urinary catheters may help prevent catheter and bladder colonization by uropathogens and thus prevent UTI. As the preferred method of bladder management in persons with SCI is ICP,<sup>12,13</sup> we studied the short-term use of *E. coli* 83972-coated urinary catheters as a means of achieving bladder colonization in persons with SCI practicing ICP. We also assessed the effect of bladder colonization with *E. coli* 83972 upon the incidence of symptomatic UTI.

## Methods

### Participants

This prospective clinical trial was approved by the institutional review board of Baylor College of Medicine and by the Research and Development Committee of the Michael E DeBaakey Veterans Affairs Medical Center. Participants were recruited from the outpatient SCI clinic at this facility. Adults with SCI of  $\geq 1$  year duration with neurogenic bladders managed by ICP were eligible for enrollment if they (1) had experienced at least one UTI in the past 10 years and (2) had documented bacteriuria within the past 1 year. Exclusion criteria included supraventricular urinary diversion, vesicoureteral reflux, obstructing urolithiasis, nephrostomy catheters, ongoing requirement for antibiotic therapy, poorly controlled diabetes mellitus, vascular or valvular prosthetic material, and immunosuppression. After providing informed consent, participants underwent either renal ultrasound or urodynamics to rule out obstructive urolithiasis and/or vesicoureteral reflux, and they submitted urine specimens for baseline cultures.

### Study design

Each participant received an *E. coli* 83972-coated study catheter. Placement of a study catheter in the bladder was defined as an inoculation attempt. The catheter was left in place for 3 days and then removed and cultured by sonication.<sup>14</sup> Three days was chosen as the dwell time, as this brief period of catheterization was convenient to participants (generally over the weekend) and also acceptable to health-care providers, as such a short dwell time was unlikely to change voiding dynamics. Urine cultures were performed on days 0, 1, 3, 7, 21, 28, and then monthly after catheter removal, until *E. coli* 83972 was lost from the urine. Participants were also called at these time intervals, to remind them to collect urine for the study and to question them about symptoms of UTI. Participants reporting symptoms that could be related to UTI were requested to come to the outpatient SCI clinic for evaluation by either the principal investigator or by their primary care physician. Participants who did not have *E. coli* 83972 in their urine or on their catheter on the day of study catheter removal could undergo another inoculation attempt, up to three attempts in total.

As we were interested in simplifying the inoculation protocol for the participants, we experimented with whether pre-inoculation antibiotics to clear the bladder of other flora were necessary to achieve successful bladder colonization

with *E. coli* 83972. Pre-insertion antibiotics were not used for the first 10 inoculation attempts. As the rate of colonization was low in comparison with our earlier studies that had used pre-insertion antibiotics, the next nine inoculation attempts incorporated pre-insertion antibiotics. As per this protocol modification, participants who had detectable bacteriuria ( $\geq 10^2$  cfu ml<sup>-1</sup>) were treated for 7 days with antibiotics targeted at the organism(s) in the enrollment urine culture. Participants then had a 3- to 4-day washout period before study catheter insertion to allow antibiotics to clear from the urine.

### Catheter preparation and insertion

To ensure patient safety, a *pap* deletion of wild-type *E. coli* 83972 was used to inoculate study catheters (Hu2117).<sup>15</sup> Participants who required antibiotics to sterilize their bladder received study catheters prepared with a derivative strain of *E. coli* 83972 carrying short-term resistance to the appropriate antibiotic class (strains Hu2140, Hu2207, Hu2209, Hu2293 and Hu2194). In these derivative strains, the antibiotic resistance genes are carried on 'suicide' plasmids that are rapidly lost in the absence of selective pressure from antibiotics. Lubricious coated latex catheters (Bardex Lubricath, Covington, GA, USA) in trypticase soy broth (TSB; Becton Dickinson, Sparks, MD, USA) were each inoculated with a single colony of *E. coli* 83972 and then incubated at 37 °C static for 48 h. The composition of the lubricious coating is proprietary, but this hydrophilic surface became slippery during the catheter preparation process, thus facilitating insertion. At 24 and 48 h, the broth was tested for contamination by dilution plating. After 48 h of incubation, the catheter was inserted into the participant's bladder under otherwise sterile conditions. Participants generally placed their own catheters.

### Outcomes

The outcomes of interest were (1) the rate of successful bladder colonization and (2) the rate of symptomatic UTI during colonization with *E. coli* 83972. Successful bladder colonization was defined as the detection ( $\geq 10^2$  cfu ml<sup>-1</sup>) of *E. coli* 83972 in urine cultures for >3 days after catheter removal. Pre-insertion antibiotics were considered to have been effective if the urine culture collected immediately before catheter insertion grew  $\leq 10^2$  cfu ml<sup>-1</sup> organisms.

For each participant, we documented the incidence of symptomatic UTI during colonization with *E. coli* 83972. Symptomatic UTI was defined as significant bacteriuria ( $\geq 10^5$  cfu ml<sup>-1</sup>) and pyuria (> 10 WBC per high power field) plus  $\geq 1$  of the following signs and symptoms for which no other etiology could be identified: fever (oral temperature > 100 °F), suprapubic or flank discomfort, bladder spasm, change in voiding habits, increased spasticity or worsening dysreflexia.<sup>16,17</sup> The determination of symptomatic UTI was made by the research team together with the primary care provider based upon participants' self-reported symptoms. The rate of UTI per participant per year during colonization was calculated by extrapolating the total number of participant days of colonization to 1 year. Only participants

who became colonized for >3 days were included in this calculation. To have a baseline for comparison, we also recorded the number of UTI occurring during the year before study enrollment and during the year after bladder colonization (including the time period of colonization). These UTIs were determined by a retrospective chart review by the principal investigator. The definition of UTI used for retrospective ascertainment of UTI was the presence of symptoms attributable to the urinary tract, documented bacteriuria and the administration of antibiotics to treat UTI. As two participants had only 8 months of follow-up data, the overall UTI incidence was calculated per available months of follow-up and converted to the patient-year measurement.

## Results

All 13 participants were men, had neurogenic bladder secondary to SCI and were using ICP for bladder management. Their average age was 56 years (range 37–73 years), and the average time since injury was 15 years (range 1.3–35 years). Seven were white (54%), whereas six were black (46%). Nineteen inoculation attempts were made in these 13 participants, resulting in eight bladder colonizations lasting for >3 days. Thus, 62% of participants became colonized. The overall success rate of a single inoculation attempt was 42%.

Before the use of pre-insertion antibiotics, 10 inoculation attempts resulted in three bladder colonizations. Subsequently, eight participants underwent nine inoculation attempts under the pre-insertion antibiotic protocol, resulting in five successful colonizations. It is worth noting that two participants (nos. 6 and 7) underwent two inoculation attempts each, one without and one with pre-insertion antibiotics. The success rate of inoculation after pre-insertion antibiotics was 55%, in comparison with the success rate without pre-insertion antibiotics of 33% ( $P=0.26$ , Fisher's

Exact Test). Pre-insertion antibiotics were ineffective at sterilizing the urine despite the fact that we chose antibiotics based on the antimicrobial susceptibilities of the organisms in an enrollment urine culture. Specifically, of the seven participants who received antibiotics under the pre-insertion antibiotics protocol (one participant had sterile urine at enrollment), six had bacteriuria at the time of study catheter insertion, usually with one or more new species (Table 1).

The pre-study rate of UTI for all participants was 2.27 UTI per subject-year and was 2.29 UTI per subject-year for participants who subsequently became successfully colonized (excluding the participants for whom UTI per year was unknown). For the eight participants who became successfully colonized, the rate of symptomatic UTI requiring treatment during colonization with *E. coli* 83972 was 0.77 per patient-year. During the year after the insertion of study catheters (excluding the time period of colonization with *E. coli* 83972), the rate of UTI for all participants was 1.98 UTI per subject-year. Only one participant (no. 2) experienced a symptomatic UTI during potential colonization with *E. coli* 83972. On day 97 after study catheter removal, his urine culture contained *Proteus* and *E. coli* 83972. He inserted an indwelling foley catheter the next day for convenience in bladder management. Two days later he developed fever, chills and hematuria. Urine collected on this day before initiation of antibiotics grew *Proteus* and a pathogenic *E. coli* strain. No *E. coli* 83972 was present in this urine culture, but we included this UTI as an event occurring during colonization in the interest of avoiding bias. It is likely that his UTI was related to the change in his bladder management, as a urinary catheter provides an excellent substrate for *Proteus* growth.<sup>18</sup> We have also observed earlier that *Proteus* tends to eliminate *E. coli* 83972 in the catheterized human bladder.<sup>19</sup>

The case of participant no. 12 is illustrative of a potential protective effect of bladder colonization by *E. coli* 83972.

**Table 1** Colonization success and UTI outcomes

Subject	Pre-study UTI per year	Pre-insertion antibiotics	Colonization attempts	Organisms present at insertion	Days colonized	Successful colonization?	No. of UTI while colonized	Reason for loss of 83972	Post-study UTI per year
1	1	No	1	<i>Enterococcus</i>	197	Yes	0	Spontaneous	1
2	2	No	3	<i>Proteus</i>	97	Yes	1 <sup>a</sup>	Antibiotics	3
3	Unknown <sup>b</sup>	No	1	<i>Serratia Enterococcus</i>	0	No	0	NA	Unknown <sup>b</sup>
4	0	No	2	<i>Pseudomonas Klebsiella</i>	11	Yes	0	Spontaneous	2
5	0	No	1	<i>Klebsiella</i>	0	No	0	NA	0
6	1	No	1	<i>Escherichia coli</i>	0	No	NA	NA	2
7	Unknown <sup>b</sup>	Yes	1	<i>E. coli</i>	0	No	NA	NA	Unknown <sup>b</sup>
		No	1	<i>Klebsiella and Providencia</i>	28	Yes	0	Spontaneous	
8	2	Yes	1	None	21	Yes	0	Spontaneous	2
9	1	None indicated	1	None	10	Yes	0	Antibiotics	2
10	5	Yes	1	<i>Pseudomonas</i>	71	Yes	0	Spontaneous	0
11	4	Yes	2	<i>Citrobacter</i> (both times)	0	No	NA	NA	0
12	5	Yes	1	<i>Pseudomonas and Enterococcus</i>	39	Yes	0	Antibiotics	4 <sup>c</sup>
13	4	Yes	1	<i>Klebsiella</i>	0	No	NA	NA	2 <sup>c</sup>

Abbreviations: NA, not applicable; UTI, urinary tract infection.

<sup>a</sup>This subject did not have *E. coli* 83972 in his urine on the day of UTI diagnosis, but had been colonized with *E. coli* 83972 2 days before.

<sup>b</sup>Unknown means that the subject received the majority of his care at an outside facility, so the number of UTIs could not be documented accurately.

<sup>c</sup>These subjects had 8 months of follow-up after inoculation.

During colonization with *E. coli* 83972, he did not experience urinary symptoms despite the presence of *Pseudomonas* in his urine. This ABU was inappropriately treated with antibiotics on day 39 after catheter removal. These antibiotics eradicated *E. coli* 83972 but not the *Pseudomonas*. He subsequently developed bladder spasms and required targeted therapy to eradicate the *Pseudomonas*.

Our bladder colonization protocol was well tolerated. Three participants experienced adverse effects: groin pain during colonization that resolved spontaneously, dysreflexia during inflation of the catheter balloon and symptomatic UTI in a participant who failed to become colonized.

## Discussion

*E. coli* 83972-coated urinary catheters are a viable means to achieve bladder colonization with this benign organism. This study is too small to determine which factors predicted successful colonization, but pre-inoculation antibiotics tended to increase the colonization success rate. Although these antibiotics did not clear the bladder of other flora, we suspect that they suppressed the quantity of other organisms and helped *E. coli* 83972 become established. However, overall, only 8 of 19 inoculation attempts resulted in successful colonization. We would expect a higher success rate of colonization if participants underwent successive placement of study catheters, or possibly if we increased the dwell time of the catheters as in our study in the long-term catheterized SCI participants.<sup>19</sup>

Our study confirms the futility of treating ABU in persons with SCI. When we treated participants' baseline ABU to facilitate bladder colonization, only one of seven treated participants had sterile urine following a course of antibiotics to which the organisms cultured from their urine were susceptible. Thus, we agree with guidelines that advise non-treatment of ABU in the SCI population.<sup>20</sup>

Our data suggest that participants have protection from symptomatic UTI during colonization with *E. coli* 83972, although the use of a retrospective, historical control is a potential source of bias. Over diagnosis of UTI in the preceding year may give an appearance of efficacy when in fact none is present. We can definitively report that the number of treated episodes of UTI decreased when participants were colonized with *E. coli* 83972 in comparison with the year before the study and with the year after inoculation (excluding the time of colonization with *E. coli* 83972). However, this difference may be attributed to differences in case ascertainment, as we actively followed participants for the occurrence of UTI during colonization, while determination of UTI during other time periods was based on chart review. As the pre-study rate of UTI (2.27 UTI per year) is similar to the rate of UTI after loss of colonization with *E. coli* 83972 (1.98 UTI per year), we believe that we successfully applied the same case definitions throughout.

Another potential weakness in our study is the lack of placebo control. Bladder inoculation with an *E. coli* 83972-coated urinary catheter was likely to make a strong impression on the research participants and could have

influenced their reporting of symptoms of UTI. The research team also knew of the participants' colonization status. This work was designed as a pilot study and will help us plan the appropriate randomized, placebo-controlled trial. All of our participants were men, as 99% of the SCI population at our facility are men, so whether our results are applicable to women with SCI is undetermined.

Overall, short-term use of *E. coli* 83972-coated urinary catheters was an effective, safe and well-tolerated means to achieve bladder colonization with *E. coli* 83972. Participants may have a decreased risk of symptomatic UTI during colonization with this organism. The possible protective effect against UTI encourages us to perform further trials with *E. coli* 83972-coated urinary catheters in the SCI population, including persons practicing ICP.

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