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A Bacterial Interference Strategy for Prevention of UTI in Persons Practicing Intermittent Catheterization

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Abstract

Study Design—Non-randomized pilot trial

Objectives—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 1 UTI, and had documented bacteruria within the past year. All subjects received a urinary catheter that had been pre-inoculated with *E. coli* 83972. The catheter was left in place for 3 days then removed. Subjects 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 ($> 10^2$ cfu/ml) of *E. coli* 83972 in urine cultures for > 3 days after catheter removal and (2) the rate of symptomatic UTI while colonized with *E. coli* 83972.

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Results—Thirteen subjects underwent 19 insertions of study catheters. Eight subjects (62%) became successfully colonized for > 3 days after catheter removal. In these 8 subjects, the rate of UTI while colonized was 0.77 per patient-year, in comparison to the rate of 2.27 UTI per patient-year prior to enrollment.

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

Keywords

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

Introduction

Each year more than 30 million bladder catheters are used in the United States.¹ Urinary catheters bypass normal host defenses to allow bacterial entry at a rate of approximately 3% to 10% per day, and they encourage bacterial persistence in the bladder.² The majority (98%) of individuals who are catheterized for 30 days or longer will have bacteriuria with one or more species of uropathogens.³ 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.^{4, 5} Although most episodes of catheter-associated bacteriuria are asymptomatic, asymptomatic bacteriuria in many cases progresses to symptomatic urinary tract infection (UTI) and even bacteremia.⁶ Individuals with spinal cord injury (SCI) who rely on bladder catheters for urinary drainage are predisposed to recurrent UTI.⁷ Currently few, if any, measures are effective at prevention of UTI in persons with neurogenic bladders secondary to SCI.

Bacterial interference, or using benign bacteria to prevent infection with virulent pathogens,^{8, 9} may offer a solution to the significant problem of recurrent UTI in persons with 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.^{10, 11} Our previous work in vivo with individuals with SCI using long-term, indwelling catheters also supports our hypothesis that *E. coli*-coated urinary catheters may help prevent catheter and bladder colonization by uropathogens and thus prevent UTI. Since the preferred method of bladder management in persons with SCI is an intermittent catheterization program (ICP),^{12, 13} we studied short-term use of *E. coli* 83972-coated urinary catheters as a means to achieve 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

Subjects

This prospective clinical trial was approved by the institutional review board of Baylor College of Medicine and by the Research & Development Committee of the Michael E.

DeBakey Veterans Affairs Medical Center. Subjects were recruited from the outpatient SCI clinic at this facility. Adults with SCI of 1 year duration with neurogenic bladders managed by ICP were eligible for enrollment if they (1) had experienced at least 1 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, subjects 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 subject 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 then removed and cultured by sonication.¹⁴ Three days was chosen as the dwell time, as this brief period of catheterization was convenient to subjects (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. Subjects were also called at these time intervals, to remind them to collect urine for the study and to question them about symptoms of UTI. Subjects 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. Subjects who did not have the *E. coli* 83972 in their urine or on their catheter on the day of study catheter removal could undergo another inoculation attempt, up to 3 attempts total.

As we were interested in simplifying the inoculation protocol for the subjects, 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. Since the rate of colonization was low in comparison to our previous studies that had used pre-insertion antibiotics, the next 9 inoculation attempts incorporated pre-insertion antibiotics. Per this protocol modification, subjects who had detectable bacteriuria (10^2 cfu/ml) were treated for 7 days with antibiotics targeted at the organism(s) in the enrollment urine culture. Subjects then had a 3-4 day washout period prior to 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).¹⁵ Subjects 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) in

trypticase soy broth (TSB; Becton Dickinson, Sparks, MD) were each inoculated with a single colony of *E. coli* 83972 then incubated at 37°C static for 48 hours. 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 hours the broth was tested for contamination by dilution plating. After 48 hours of incubation, the catheter was inserted into the subject's bladder under otherwise sterile conditions. Subjects 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 while colonized with *E. coli* 83972. Successful bladder colonization was defined as the detection (10^2 cfu/ml) 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 prior to catheter insertion grew 10^2 cfu/ml organisms.

For each subject, we documented the incidence of symptomatic UTI while colonized with *E. coli* 83972. Symptomatic UTI was defined as significant bacteriuria (10^5 cfu/ml) and pyuria (>10 WBC/hpf) plus 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.^{16, 17} The determination of symptomatic UTI was made by the research team together with the primary care provider based upon subjects' self-reported symptoms. The rate of UTI per subject per year while colonized was calculated by extrapolating the total number of subject days of colonization to 1 year. Only subjects who became colonized for >3 days were included in this calculation. In order to have a baseline for comparison, we also recorded the number of UTI occurring during the year prior to study enrollment and during the year after bladder colonization (including the time period of colonization). These UTIs were determined by 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 administration of antibiotics to treat UTI. Since 2 subjects only had 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 subjects were male, 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%), while 6 were black (46%). Nineteen inoculation attempts were made in these 13 subjects, resulting in 8 bladder colonizations lasting > 3 days. Thus, 62% of subjects became colonized. The overall success rate of a single inoculation attempt was 42%.

Prior to the use of pre-insertion antibiotics, 10 inoculation attempts resulted in 3 bladder colonizations. Subsequently, 8 subjects underwent 9 inoculation attempts under the pre-insertion antibiotic protocol, resulting in 5 successful colonizations. Of note, 2 subjects (#6

and #7) underwent 2 inoculations attempts each, 1 without and 1 with pre-insertion antibiotics. The success rate of inoculation after pre-insertion antibiotics was 55%, in comparison to 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 7 subjects who received antibiotics under the pre-insertion antibiotics protocol (1 subject had sterile urine at enrollment), 6 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 subjects was 2.27 UTI/subject-year and was 2.29 UTI/subject-year for subjects who subsequently became successfully colonized (excluding the subjects for whom UTI/year were unknown). For the 8 subjects who became successfully colonized, the rate of symptomatic UTI requiring treatment while colonized 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 subjects was 1.98 UTI/subject-year. Only 1 subject (#2) experienced a symptomatic UTI while potentially colonized 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 prior to 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.¹⁸ We have also previously observed that *Proteus* tends to eliminate *E. coli* 83972 in the catheterized human bladder.¹⁹

The case of subject #12 is illustrative of a potential protective effect of bladder colonization by *E. coli* 83972. While colonized with *E. coli* 83972, he did not experience urinary symptoms despite the presence of *Pseudomonas* in his urine. Inappropriate treatment was given for this asymptomatic bacteriuria (ABU) on day 39 after catheter removal. These antibiotics eradicated the *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 subjects experienced adverse effects: groin pain during colonization that resolved spontaneously, dysreflexia during inflation of the catheter balloon, and symptomatic UTI in a subject 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 subjects 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 subjects.¹⁹

Our study confirms the futility of treating ABU in persons with SCI. When we treated subjects' baseline ABU in order to facilitate bladder colonization, only 1 of 7 treated subjects 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.²⁰

Our data suggest that subjects have protection from symptomatic UTI while colonized 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 while subjects were colonized with *E. coli* 83972 in comparison to the year prior to the study and to 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 subjects for the occurrence of UTI while colonized, while determination of UTI during other time periods was based on chart review. Since the pre-study rate of UTI (2.27 UTI/year) is similar to the rate of UTI after loss of colonization with *E. coli* 83972 (1.98 UTI/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* 83792-coated urinary catheter was likely to make a strong impression on the research subjects and could have influenced their reporting of symptoms of UTI. The research team also knew of the subjects' colonization status. This study was designed as a pilot and will help us plan the appropriate randomized, placebo-controlled trial. All of our subjects were male, as the SCI population at our facility is 99% male, 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. Subjects may have a decreased risk of symptomatic UTI while colonized 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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Table 1

Colonization Success and UTI Outcomes

Subject	Pre-Study UTI/year	Pre-insertion Antibiotics	Colonization Attempts	Organisms Present at Insertion	Days Colonized	Successful Colonization?	# UTI while colonized	Reason for Loss of 83972	Post study UTI/year
1	1	No	1	<i>Enterococcus</i>	197	Yes	0	Spontaneous	1
2	2	No	3	<i>Proteus</i>	97	Yes	1*	Antibiotics	3
3	Unknown [§]	No	1	<i>Serratia Enterococcus</i>	0	No	0	N/A	Unknown [§]
4	0	No	2	<i>Pseudomonas Klebsiella</i>	11	Yes	0	Spontaneous	2
5	0	No	1	<i>Klebsiella</i>	0	No	0	N/A	0
6	1	No	1	<i>E. coli</i>	0	No	N/A	N/A	2
		Yes	1	<i>E. coli</i>	0	No			
7	Unknown [§]	No	1	<i>E. coli</i>	0	No	N/A	N/A	Unknown [§]
		Yes	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	N/A	N/A	0
12	5	Yes	1	<i>Pseudomonas and Enterococcus</i>	39	Yes	0	Antibiotics	4 [#]
13	4	Yes	1	<i>Klebsiella</i>	0	No	N/A	N/A	2 [#]

* 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 prior.

[§]Unknown means that the subject received the majority of their care at an outside facility, so the number of UTIs could not be documented accurately.

[#]These subjects had 8 months of follow-up after inoculation.