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Coating Urinary Catheters with an Avirulent Strain of *Escherichia coli* as a Means to Establish Asymptomatic Colonization

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Abstract

We investigated whether insertion of urinary catheters that had been coated with *Escherichia coli* HU2117 could establish bladder colonization with this nonvirulent organism. Ten of 12 subjects were successfully colonized for 14 days or more. The rate of symptomatic UTI during colonization was 0.15 per 100 patient-days.

Bacteriuria and pyuria are uniformly present in patients who have indwelling urinary catheters.^{1–3} Antimicrobial therapy may transiently eradicate the bacteria, but bacteriuria promptly recurs, and the infecting bacteria become progressively resistant to antibiotics.^{4,5} No mode of treatment is known to eliminate chronic, subclinical infection or to prevent intercurrent, clinically important infections.

Escherichia coli HU2117 is a nonpathogenic organism that reduces the in vitro incidence of urinary catheter colonization by a wide variety of uropathogens.^{6,7} We report initial data on introduction of this bacterial strain into the human bladder via insertion of an indwelling urinary catheter coated with *E. coli* HU2117, the lack of related complications, the persistence of colonization, and the reduction of the incidence of symptomatic urinary infection in these subjects.

METHODS

Subjects

This prospective clinical trial was approved by the institutional review board of our institution. Adult inpatients with spinal cord injury (SCI) with a duration of 1 year or more who had neurogenic bladders that required indwelling (transurethral or suprapubic) catheter drainage and who had had at least 1 clinically recognized UTI in the past were eligible for enrollment. Exclusion criteria included vesicoureteral reflux and immunosuppression.

Study design

Subjects were treated with 1 week of antibiotic therapy on the basis of enrollment urine culture results. After completion of antibiotic therapy, a urinary catheter (Bardex; Lubricath) that had been incubated in broth with *E. coli* HU2117 for 48 hours was inserted. Urine samples for semiquantitative culture were collected immediately before insertion, after insertion, and then

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weekly. Study catheters were removed after 28 days and cultured using a sonication technique.⁸ After catheter removal, colonized subjects submitted urine specimens monthly until *E. coli* HU2117 was no longer detected in their urine.

Bacterial strain

E. coli HU2117 is a genetically engineered strain created from wild-type *E. coli* 83972, a strain that caused persistent colonization without symptomatic infection in a prepubertal girl during a 3-year period of observation.⁹ *E. coli* HU2117 has an 800-base pair deletion mutation in the chromosomal *papG* gene; as a result, it cannot make P fimbriae, which are associated with pyelonephritis and bacteremia.^{10,11}

RESULTS

Twelve subjects received an *E. coli* HU2117-coated urinary catheter. None of these subjects had sterile urine at the time of study catheter insertion despite having received targeted antibiotic therapy during the preceding week. Ten (83%) of 12 subjects (95% confidence interval, 52%-98%) were successfully colonized with *E. coli* HU2117 for 14 days or more after inoculation by insertion of a study catheter. The median duration of successful colonization was 48.5 days (range, 15-165 days). One failure to colonize was attributed to residual antibiotics in the patient. The other failure to colonize was attributed to catheter encrustation by *Proteus mirabilis*, because the catheter became obstructed and required removal. All subjects remained colonized with other species while colonized with *E. coli* HU2117.

Study catheters from 8 of the 10 colonized patients were cultured after removal; all of them had *E. coli* HU2117 on the surface (median concentration, 4×10^5 cfu/cm of catheter length). At the time the study catheters were inserted, the median concentration of *E. coli* HU2117 was 6.1×10^4 cfu/cm of catheter length. In all cases, the removed study catheter was also colonized by other species (median, 2 other species [range 2-4 other species]). In many cases, the species co-colonizing the catheter and the urine were potential uropathogens, such as *Proteus* and *Pseudomonas* species, which the preinsertion course of antibiotics had failed to eradicate.

No patient experienced UTI symptoms attributable to colonization with *E. coli* HU2117. Subjects tolerated the study catheters and colonization with *E. coli* HU2117 without complaints. Symptomatic UTI appeared in 1 patient during a total of 648 subject-days of colonization. This UTI occurred after the study catheter had been removed to give the subject a trial of intermittent catheterization. The subject developed urinary obstruction while he had more than 10^5 cfu/mL of *Pseudomonas* in his urine in addition to *E. coli* HU2117, and his symptoms did not resolve until the drug-resistant *Pseudomonas* strain had been eradicated with amikacin.

Two factors were significantly associated with colonization success. The absence of *Proteus* species from a subject's urine was associated with a longer duration of colonization with *E. coli* HU2117 ($P = .04$, Wilcoxon rank sum test). (Figure) The presence of *Proteus* species in the subject's urine prior to study catheter insertion had a deleterious effect on the biofilm of *E. coli* HU2117 on the study catheter. Specifically, catheters removed from subjects who were co-colonized with *Proteus* species had a median *E. coli* HU2117 concentration of only 3×10^1 cfu/cm of catheter length at removal, whereas catheters removed from subjects without *Proteus* co-colonization had a median *E. coli* HU2117 concentration of 5.9×10^5 cfu/cm of catheter length ($P = .02$, Wilcoxon rank sum test). The second factor predictive of colonization success was the duration of catheter insertion; catheters left in place for a longer period resulted in a longer duration of colonization ($R = 0.80$; $P = .002$, Spearman rank correlation) (Figure). A confounding variable was early removal of study catheters that had become occluded by encrustation.

DISCUSSION

Given the difficulty of eradicating bacteriuria in a patient with long-term bladder catheterization,¹² the problem of chronic bacteriuria and recurrent UTI in catheter-dependent persons is not likely to be resolved by the use of antimicrobial agents. Our results suggest that placement of an *E. coli* HU2117-coated catheter is an effective and safe means to colonize the bladders of persons with long-term catheterization. The overall rate of symptomatic UTI in our study, 0.15 cases per 100 patient-days of colonization, compares quite favorably to the reported rate of UTI for subjects with SCI using indwelling urinary catheters (2.72 cases per 100 patient-days).¹³ Our trial was not designed to detect the effect of *E. coli* HU2117 colonization on the incidence of UTI. However, the remarkably low rate of UTI among subjects colonized with *E. coli* HU2117 suggests that this organism may have a protective function in the bladder of catheterized persons.

Our findings are in accord with those from clinical trials of direct bladder inoculation with *E. coli* HU2117.¹⁴⁻¹⁶ A randomized, placebo-controlled trial of direct bladder inoculation with this organism found that subjects colonized with *E. coli* HU2117 were significantly less likely than noncolonized patients to develop UTI (6 [46%] of 13 patients vs 13 [93%] of 14 patients; $P = .01$, Fisher exact test).¹⁵ These findings support our interest in further studies of *E. coli* HU2117-coated catheters.

Unlike standard antimicrobial agents, the concentration of which declines continuously from the time of administration, *E. coli* HU2117 is a living organism that replicates and renews itself. Should these *E. coli* HU2117-coated catheters prove efficacious in preventing UTI, this self-renewing aspect will be particularly convenient. However, the potential pitfall of bacterial interference is that no living organism is truly avirulent in an immunocompromised host.^{17, 18} Immunocompromised subjects were excluded from our study.

The main limitation of our study is its small size, but it was intended as a pilot test of the safety and efficacy of *E. coli* HU2117-coated catheters in a highly problematic population. We plan to assess the safety and efficacy of these catheters in a wider group of subjects. Our ultimate objective is to explore the efficacy of these catheters in preventing symptomatic UTI.

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FIGURE.

Effect of bladder catheterization and the presence or absence of *Proteus* species in the urine prior to catheterization on the duration of bladder colonization with *Escherichia coli* HU2117. *Circles*, Subjects with *Proteus* species in their urine prior to insertion of the study catheter. *Diamonds*, Subjects without detectable *Proteus* species in their urine prior to insertion of the study catheter.