In Vitro Efficacy of Antimicrobial-Coated Bladder Catheters in Inhibiting Bacterial Migration along Catheter Surface

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Most cases of catheter-related urinary tract infection are probably caused by organisms that migrate from the urethral meatus–catheter interface along the external surface of the catheter into the bladder. To examine the ability of bladder catheters coated with minocycline and rifampin to inhibit bacterial migration along the external surface of the catheter, a novel in vitro bladder model was used. Compared with uncoated catheters, antimicrobial-coated bladder catheters significantly impeded the migration of Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Enterococcus faecalis, and Candida albicans (bacteriuria developed at a mean of 2–5 days vs. 9–34 days, respectively, after bacterial contamination of the catheter). Although production of zones of inhibition by coated catheters may provide some protection against infection, there was no correlation between the size of zones of inhibition and level of efficacy in inhibiting bacterial migration in vitro. Examination of the clinical efficacy of these antimicrobial-coated bladder catheters is prudent.

Indwelling bladder catheters are implicated in ~90% of the 1 million episodes of urinary tract infection (UTI) that occur each year in US hospitals [1]. Bacteria introduced to the urinary system of patients with indwelling bladder catheters generally multiply more efficiently and persist for a longer period of time than they do in the noncatheterized urinary tract [2]. Despite the success of an adequately maintained closed drainage system in limiting the intraluminal entry of organisms from both the lumen of the drainage bag and the junction between the bladder catheter and the collection tube, almost all patients with indwelling bladder catheters will eventually become bacteriuric if the catheter remains in place long enough. Most episodes of catheter-related UTI are probably caused by organisms that migrate from the catheter–urethral meatus interface along the external surface of the catheter into the bladder [3, 4]. Attempts to reduce bacterial colonization of the urethral meatus by daily cleansing with antimicrobial agents failed to reduce the frequency of UTI [5]. Coating of bladder catheters with effective antimicrobial agent(s) could theoretically be useful in reducing bacterial migration along the catheter surface.

There is a growing interest in studying the efficacy of coating a variety of indwelling medical catheters with different antimicrobial agents for preventing catheter-related infections. Our understanding of the antiinfective properties of antimicrobial-coated catheters, however, is more advanced with vascular than with urinary catheters. For instance, the size (>9 mm) of the in vitro zone of inhibition of Staphylococcus aureus around chlorhexidine-coated vascular catheters has been demonstrated to correlate well with the antiinfective efficacy of such catheters in a rabbit model of subcutaneous infection [6] and in human subjects [7]. Although different types of antimicrobial-coated urinary catheters, including those coated with nitrofurazone [8] or with minocycline plus rifampin [9], have been demonstrated to produce zones of inhibition in vitro against most urinary pathogens, the clinical impact of this in vitro phenomenon on catheter-related UTI remains to be investigated. The purpose of this in vitro study was to examine the ability of bladder catheters coated with minocycline and rifampin to inhibit bacterial migration along the external surface of the catheter and to investigate the potential relationship between the size of zones of inhibition produced by coated catheters and the level of efficacy in inhibiting bacterial migration along the catheter surface.

Materials and Methods

Bladder model. A novel in vitro bladder model (figure 1) was devised to compare bacterial migration along the external surface of 18 French all-silicone Foley catheters coated with minocycline and rifampin versus uncoated catheters (both catheters were supplied by Cook Urological, Spencer, IN; the only difference be-
into the side outlet of the funnel over the external surface of the catheter at a fixed rate of 0.2 mL/min. The source of infection consisted of a suspension of *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, or *Candida albicans* at a concentration (confirmed by plate counts) of ~10^6 cfu/mL of 5% dextrose solution; bacterial suspensions were prepared by growing a few colonies of the organism in trypsinase soy broth (BBL Microbiology Systems, Cockeysville, MD) overnight at 37°C, adjusting the bacterial concentration in the infected broth to ~5 × 10^7 cfu/mL, then diluting a 1-mL aliquot from the infected broth in 500 mL of 5% dextrose. The urine flowing around the catheter into the funnel was collected in the collection bag, represented by a glass flask with two side outlets; the overflowing urine drained through one side outlet, and the capped end of the catheter was externalized through the other side outlet.

**Antimicrobial efficacy.** For each of the 5 tested organisms, the ability of antimicrobial-coated catheters versus uncoated catheters to impede migration of organisms along the catheter surface was tested twice with this in vitro bladder model. To check for development of bacteriuria, 10^-3 mL aliquots of urine were obtained daily from the “bladder” through the sampling port and inoculated onto trypticase soy agar with 5% sheep blood (BBL Media; Becton Dickinson Microbiology Systems, Cockeysville, MD). As soon as bacteriuria was detected (detectability limit, ~10^3 cfu/mL), the catheter was retrieved from the system in a sterile fashion (generally within 24 h of culturing urine samples). A 4-cm segment of the catheter distal to the balloon was cultured by both the roll-plate and sonication methods, and each of two 1-cm segments was studied for zones of inhibition (see below).

**Zones of inhibition.** By use of a modified Kirby-Bauer technique [10], a total of four determinations of the zones of inhibition produced by catheters against each of the 5 tested organisms were made, both before catheter placement (baseline zone of inhibition) and after catheter removal (residual zone of inhibition) from the bladder system. Organisms were individually grown at 37°C for 18 h in trypticase soy broth to a concentration of 0.5 McFarland units (10^8 cfu/mL). A cotton swab was dipped in the bacterial suspension, then rubbed across the surface of a Mueller-Hinton agar plate (Difco). A 1-cm segment of the catheters was pressed into the center of an agar plate that had been freshly inoculated with the individual organisms and incubated at 37°C for 24 h. The size of the zones of inhibition for each of the 5 tested organisms was assessed by measuring the diameter of the clear zone perpendicular to the long axis of the catheter segment.

**Results**

As figure 2 shows, it took a significantly longer time for each of the 5 tested organisms to cause bacteriuria following bacterial contamination of the external surface of antimicrobial-coated versus uncoated catheters (*P < .05* for all 5 tested organisms; one-tailed *t* test). In all cases, cultures of the catheter yielded the same original contaminating organism that had also caused bacteriuria. As expected, uncoated catheters did not produce any detectable zones of inhibition. The mean baseline zones of inhibition produced by coated catheters ranged from 13 mm (for *P. aeruginosa*) to 29 mm (for *E. faecalis*). There

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**Figure 1.** In vitro bladder model that simulates flow of urine from “kidney” into “bladder,” which contains tip of indwelling Foley catheter. As bacteria originating from source of infection contaminate catheter at level of “urethral meatus,” they migrate along external surface of catheter via “urethra” into “bladder,” resulting in bacteriuria.
was no correlation between the size of baseline zones of inhibition produced by coated catheters and the number of days it took to develop bacteriuria following bacterial contamination of the external surface of coated catheters (Pearson correlation coefficient = .0; P = 1.0). Likewise, there was no correlation between the size of baseline zones of inhibition produced by coated catheters and the difference in the number of days it took to develop bacteriuria following bacterial contamination of coated versus uncoated catheters (Pearson correlation coefficient = −.06; P = .93). Coated catheters did not produce residual zones of inhibition at the time of catheter removal for all tested organisms, except for *E. faecalis*, which had a mean residual zone of inhibition of 10 mm.

### Discussion

The findings of this in vitro study suggest that silicone Foley catheters coated with minocycline and rifampin can impede the migration of urinary pathogens along the external surface of the catheter. Although the leaching of antimicrobial agents off the surface of coated medical devices to produce zones of inhibition is generally thought to provide some protection against bacterial colonization of both vascular [6, 10] and urinary [8, 9] catheters, the results of this in vitro study suggest that the size of the zone of inhibition may not predict the level of antiinfective efficacy of coated bladder catheters. Our in vitro findings regarding the lack of correlation between the size of zones of inhibition and the level of efficacy of antimicrobial-coated bladder catheters in impeding the migration of different organisms along the catheter surface may be explained, at least partially, by the differences between various organisms in their natural ability to adhere to and migrate along the catheter surface.

All cases of bacteriuria that were associated with the use of uncoated catheters occurred within a mean of 2–5 days (range, 2–6) of bacterial contamination of the external surface of the catheter, a finding that supports the reproducibility of inducing catheter-related bacteriuria in this novel in vitro bladder model. This model appears to simulate closely a clinically relevant setting, in terms of such factors as volume of urine produced by the “kidney” per minute and bacterial contamination of the external surface of the catheter. In fact, to the best of our knowledge, this report constitutes the first description of an in vitro bladder model that is intended to evaluate the migration of bacteria along the external surface of bladder catheters. In a recently described physical model of a urinary drainage system, the use of a silver-releasing device located in the drainage tube below the sampling port was reported to protect the catheterized bladder from infection by blocking for at least 10 days the intraluminal migration of bacteria from contaminated urine in the drainage bag [11]. However, migration of bacteria along the external surface of the bladder catheter, which probably constitutes the most important route of acquiring catheter-related UTI in patients with an adequately maintained, closed drainage system [3, 4], was not studied in that physical model [11].

The combination of minocycline and rifampin possesses unique properties that may be considered suitable for coating catheters.
of catheters. This combination has a synergistic and broad-spectrum antimicrobial activity against almost all potential urinary pathogens, including gram-negative bacilli, gram-positive cocci, and *C. albicans* [10, 12]. Since neither minocycline nor rifampin is used as a therapeutic drug for treatment of established UTI, it may seem appropriate to attempt to prevent catheter-related UTI by coating bladder catheters with these two agents. The difference in the mechanisms of antimicrobial action of minocycline (inhibits protein synthesis) and rifampin (inhibits DNA-dependent RNA polymerase) may theoretically reduce the likelihood of developing bacterial resistance to either drug; this issue, however, was not examined in this study.

The results of a recently completed large, multicenter, prospective clinical trial have suggested that short-term (median duration of placement of 7 days) central venous catheters coated with minocycline and rifampin are safe and significantly effective in reducing the rates of catheter colonization and catheter-related bloodstream infection [13]. However, because of the differences in the pathogenesis and microbiology of infections related to vascular catheters (contamination of the vascular catheter by relatively low concentrations of mostly gram-positive bacteria residing on the skin) versus urinary catheters (high-grade contamination of the bladder catheter by mostly gram-negative bowel flora), bladder catheters coated with minocycline and rifampin may not necessarily be clinically effective. Since the true benefit from using any type of antimicrobial-coated bladder catheter can be ascertained only in a clinical trial, we are currently conducting a large multicenter, prospective, randomized study to examine the efficacy of bladder catheters coated with minocycline and rifampin versus uncoated bladder catheters in reducing the rates of catheter-related UTI in post-prostatectomy patients.

References