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Novel Antiseptic Urinary Catheters for Prevention of Urinary Tract Infections: Correlation of In Vivo and In Vitro Test Results▽

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Urinary catheters are widely used for hospitalized patients and are often associated with high rates of urinary tract infection. We evaluated in vitro the antiadherence activity of a novel antiseptic Gendine-coated urinary catheter against several multidrug-resistant bacteria. Gendine-coated urinary catheters were compared to silver hydrogel-coated Foley catheters and uncoated catheters. Bacterial biofilm formation was assessed by quantitative culture and scanning electron microscopy. These data were further correlated to an in vivo rabbit model. We challenged 31 rabbits daily for 4 days by inoculating the urethral meatus with 1.0×10^9 CFU streptomycin-resistant *Escherichia coli* per day. In vitro, Gendine-coated urinary catheters reduced the CFU of all organisms tested for biofilm adherence compared with uncoated and silver hydrogel-coated catheters ($P < 0.004$). Scanning electron microscopy analysis showed that a thick biofilm overlaid the control catheter and the silver hydrogel-coated catheters but not the Gendine-coated urinary catheter. Similar results were found with the rabbit model. Bacteriuria was present in 60% of rabbits with uncoated catheters and 71% of those with silver hydrogel-coated catheters ($P < 0.01$) but not in those with Gendine-coated urinary catheters. No rabbits with Gendine-coated urinary catheters had invasive bladder infections. Histopathologic assessment revealed no differences in toxicity or staining. Gendine-coated urinary catheters were more efficacious in preventing catheter-associated colonization and urinary tract infections than were silver hydrogel-coated Foley catheters and uncoated catheters.

In the United States, nosocomial catheter-related urinary tract infections (UTIs) account for almost 1 million cases (24) and approximately 31% of nosocomial infections seen in the intensive care unit each year (16). Approximately 10% to 30% of patients with indwelling bladder catheters develop bacteruria or UTI (24). This contributes not only to increased morbidity and mortality but also to longer hospital stays and increased medical costs (13). Microbiologic cultures of catheter-related UTIs in the intensive care unit reveal several common pathogens. Of these, *Escherichia coli* and *Pseudomonas aeruginosa* account for over 39%.

Several different methods have been used to prevent nosocomial UTIs. Of these, the most common and longest-used method is the sterile closed drainage system, which has substantially reduced the prevalence of catheter-associated UTIs (11). More recently, other preventive methods involving the use of antimicrobial devices, including urinary catheters impregnated with silver, nitrofurazone, and a combination of minocycline and rifampin (rifampicin), have led to a reduced incidence of bacteruria; however, they were not significant at preventing catheter-related UTIs compared to results with uncoated controls (4, 12, 22).

The use of antibiotic (minocycline and rifampin)-impregnated catheters has led to a reduced incidence of gram-positive bacteruria (4). However, given the fact that bacterial resistance to antibiotics has been increasing, this has resulted in a demand for an alternative means of an antiseptic coating that has not been associated with increased resistance. At the M. D. Anderson Cancer Center, we developed a technique of impregnating urinary catheters with Gendine, a novel antiseptic dye consisting of Gentian violet and chlorhexidine, to prevent catheter-related UTIs. In this study, we evaluated Gendine-coated silicone urinary catheters (GND-UCs) for their in vitro antimicrobial efficacy at inhibiting microbial biofilm formation on catheter surfaces and at reducing the incidence of UTIs in an in vivo rabbit model in comparison with results for silver hydrogel-coated catheters and uncoated Foley catheters.

MATERIALS AND METHODS

Catheter coating. Experimental GND-UCs were produced by coating 10-Fr (French) and 12-Fr silicone urinary catheters (Cook Urological, Bloomington, IN) with a novel antiseptic dye, Gendine, based on the modification of a proprietary method (I. Raad, H. Hanna, and N. Nabulsi, August 2001, Novel antiseptic derivatives with broad spectrum antimicrobial activity for the impregnation of surfaces, U.S. patent pending). Uncoated Cook silicone urinary catheters and commercially available Bardex IC silver hydrogel-coated urinary catheters (Bard Medical, Covington, GA) were used as controls.

In vitro adherence. By use of a modified method described by Kuhn et al. (3, 10), GND-UC and silver hydrogel-coated and uncoated catheter segments were tested for the inhibition of biofilm formation. Catheter segments were incubated at 37°C for 24 h in Mueller-Hinton broth inoculated with 5.5×10^5 CFU of various microorganisms. After incubation, the bacterial inoculum was discarded and the segments were washed with shaking in 1 ml of 0.9% sterile saline at 37°C for 30 min. The segments were then carefully removed as to not disrupt the biofilm, placed in 5 ml of 0.9% sterile saline, and sonicated for 15 min. After

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sonication, each sample was vortexed for 5 s and 100 μl of liquid from each segment was serially diluted and spread onto agar plates for quantitative culture. Trypticase soy agar plus 5% sheep blood was used for bacterial organisms, and Sabouraud dextrose agar was used for yeasts (*Candida* spp.). Plates were incubated inverted at 37°C for 24 h, and CFU were counted.

We tested 15 segments in a 3:1:1 catheter ratio (GND-UCs [$n = 9$], silver hydrogel-coated catheters [$n = 3$], and uncoated catheters [$n = 3$]) against seven common microorganisms known to be associated with UTIs, i.e., expanded-spectrum-β-lactamase (ESBL)-positive, multidrug-resistant *E. coli* (strain 2131), multidrug-resistant *P. aeruginosa* (strain 4689), *Klebsiella pneumoniae* (strain 08-025-3696), vancomycin-resistant *Enterococcus* (VRE) (*E. faecium* strain 3836), *Candida albicans* (strain 009-5072), *C. glabrata*, and *C. krusei.* Multidrug-resistant bacteria are defined as organisms that were resistant in vitro to at least two of the active classes of the antimicrobial agents against such organisms.

SEM analysis. Segments from GND-UCs and silver-coated and uncoated control urinary catheters were challenged with multidrug-resistant *E. coli* and VRE, and the subsequent surface architecture was analyzed using scanning electron microscopy (SEM). Urinary catheter segments were fixed with 2% glutaraldehyde, followed by osmium tetroxide, tannic acid, and uranyl acetate. Then, a series of ethanol dehydration steps were performed, and samples were sputter coated with Au-Pd (60:40 ratio) and viewed with a model XL3C SEM Philips microscope scanning the surfaces of catheters for the presence of biofilm and microbial organisms embedding the biofilm matrix.

In vivo animal model. By use of protocols described by Morck et al. (15), 31 male New Zealand White rabbits were surgically implanted with indwelling intravenous catheters to allow continuous infusion of intravenous fluids to maintain normal hydration. In addition, rabbits were catheterized with uncoated 12-Fr Cook silicone Foley catheters (control 1; $n = 9$), Bard hydrogel-uncoated 12-Fr Foley catheters (control 2; $n = 7$), Gendine-coated 12-Fr Cook silicone Foley catheters ($n = 8$), or Bardex IC silver hydrogel-coated 12-Fr Foley catheters ($n = 7$). Rabbits were inoculated with 1.0×10^9 CFU of a streptomycin-resistant *E. coli* (WE 6933) inoculum daily for 4 days (days 1 to 4). This *E. coli* strain was previously shown to cause UTIs in an established rabbit model which is reflective of the clinical setting (15). Each rabbit was inoculated on the prepuce of the penis immediately after catheter placement (day 0) and again daily for 3 days (days 1 to 3). Five to 10 ml of urine was aseptically collected daily from the Foley catheter ports and quantitatively cultured to monitor the infection's progress. Total urine output, consistency, and color were also recorded daily. On day 4, rabbits were euthanized, and the intact urinary tracts were harvested. The tracts were dissected longitudinally to not disturb the biofilm, and the entire catheters were removed. The catheter tips and the segments that were in contact with the urethral meatus were sampled for biofilm formation analysis. Tissue samples from the urethral meatus, bladder neck, and bladder wall were aseptically harvested for microbiologic assessment, and the remaining urinary tracts were fixed in formalin for histopathologic analysis.

Collected catheter segments were placed in 5 ml of 0.9% sterile saline and sonicated for 15 min to disrupt the biofilm. The resulting solution was quantitatively cultured to assess the formation of *E. coli* biofilm on segments. Harvested tissue samples were placed in 5 ml of 0.9% sterile saline and homogenized using a PowerGen 1000 homogenizer (Fisher Scientific, Pittsburgh, PA). The resulting homogenate was quantitatively cultured to determine the incidence of UTIs. All samples collected (urine, tissue, and catheter) were quantitatively cultured in triplicate on Trypticase soy agar plus 5% sheep blood, MacConkey agar, and MacConkey agar plus 100 μg/ml streptomycin, using National Accrediting Agency for Clinical and Laboratory Sciences procedures.

The M. D. Anderson Cancer Center's Institutional Animal Care and Use Committee approved all experimentation involving animals. Animals were maintained in facilities approved by the Association for Assessment and Accreditation of Laboratory Animal Care, International, and in accordance with current U.S. Department of Agriculture, Department of Health and Human Services, and National Institutes of Health regulations and standards.

Statistical methods. The numbers of viable organisms that adhered to catheter segments tested in vitro, as measured in CFU, were compared using a Kruskal-Wallis test (a P value of <0.05 was considered statistically significant). Wilcoxon rank-sum tests were used for pairwise comparisons. The α levels of post-hoc pairwise comparisons were adjusted using a sequential Bonferroni adjustment to control type I errors.

For the statistical analysis of in vivo results, three types of cultures were used to evaluate UTIs in rabbits: urine cultures obtained at 72 to 96 h, tissue cultures from the bladder wall, and catheter cultures from the catheter tip. First, Wilcoxon rank-sum tests were used to compare bacterial burdens between rabbits with GND-UCs and those with silver-coated and uncoated catheters. We used a cutoff of 100 CFU/g (or 100 CFU/ml) and chi-square or Fisher's exact tests to perform categorical data analyses of urine, tissue, and catheter cultures. A P value of ≤ 0.05 was considered statistically significant. All statistical data analyses were performed using SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

TABLE 1. Adherence of microbial biofilm to GND-UCs[a]

Organism	CFU/seg for uncoated catheters	Silver hydrogel-coated catheters		GND-UCs	
		CFU/seg	*P* value	CFU/seg	*P* value
MDR *E. coli* 2131	2.44×10^7	6.50×10^6	0.19	17	0.004
VRE 3836	2.83×10^6	1.32×10^6	0.38	0	0.002
MDR *P. aeruginosa* 4689	8.94×10^7	2.29×10^7	0.19	6	0.004
ESBL *K. pneumoniae*	3.15×10^7	1.84×10^7	0.66	0	0.002
C. albicans	1.38×10^6	2.32×10^5	0.38	0	0.002
C. glabrata	5.05×10^4	7.83×10^4	0.38	0	0.002
C. krusei	6.19×10^4	3.64×10^3	0.08	0	0.002

[a] All values listed are mean CFU per 1-cm catheter segment. *P* values are pairwise comparisons with values for uncoated catheters. MDR, multidrug resistant; seg, segment.

RESULTS

In vitro adherence. We found a significant reduction in the median colony counts of all organisms adhering to biofilm in GND-UCs compared with those in uncoated and Bardex IC silver hydrogel-coated catheters ($P < 0.004$ for all) (Table 1). No statistically significant differences in bacterium or yeast biofilm adherence were found between Bardex IC silver hydrogel-coated and uncoated catheters (Table 1). GND-UCs were highly efficacious compared with Bardex IC silver hydrogel-coated and uncoated catheters, demonstrating at least a 6-log reduction in biofilm adherence when tested against *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and VRE ($P < 0.002$) and at least a 4-log reduction when tested against *C. albicans*, *C. glabrata*, and *C. krusei* ($P < 0.002$). Furthermore, GND-UCs had no detectable CFU for organisms other than *E. coli* and *P. aeruginosa*, which had low counts.

SEM. Ultrastructural morphological differences between GND-UCs and silver hydrogel-coated and uncoated catheters were apparent. As shown in Fig. 1A, VRE cells are present on the surface, with a biofilm matrix seen at some spots covering the cells. In Fig. 1B, organisms are covered with an extensive biofilm, where the biofilm matrix looks like a granular structure with bacterial cells totally embedded within it. GND-UCs resulted in a reduction in biofilm (Fig. 1C).

In vivo adherence. Thirty-one rabbits were included in the data analysis (8 with GND-UCs, 7 with Bardex IC silver hydrogel-coated catheters, and 16 with control, uncoated catheters [9 uncoated silicone and 7 Bardex hydrogel]). Urine cultures and bladder wall tissue cultures were both analyzed continuously and categorically. A culture was considered positive at ≥100 CFU/ml (or CFU/g).

A continuous analysis showed that urine cultures obtained at 72 to 96 h from rabbits with GND-UCs had significantly lower bacterial burdens than did those from rabbits with uncoated catheters (median CFU, 0 versus 1,170; $P = 0.005$) and Bardex IC silver hydrogel-coated catheters (median CFU, 0 versus 340; $P = 0.007$) (Table 2). Rabbits with Bardex IC silver hydrogel-coated catheters had no statistically signifi-

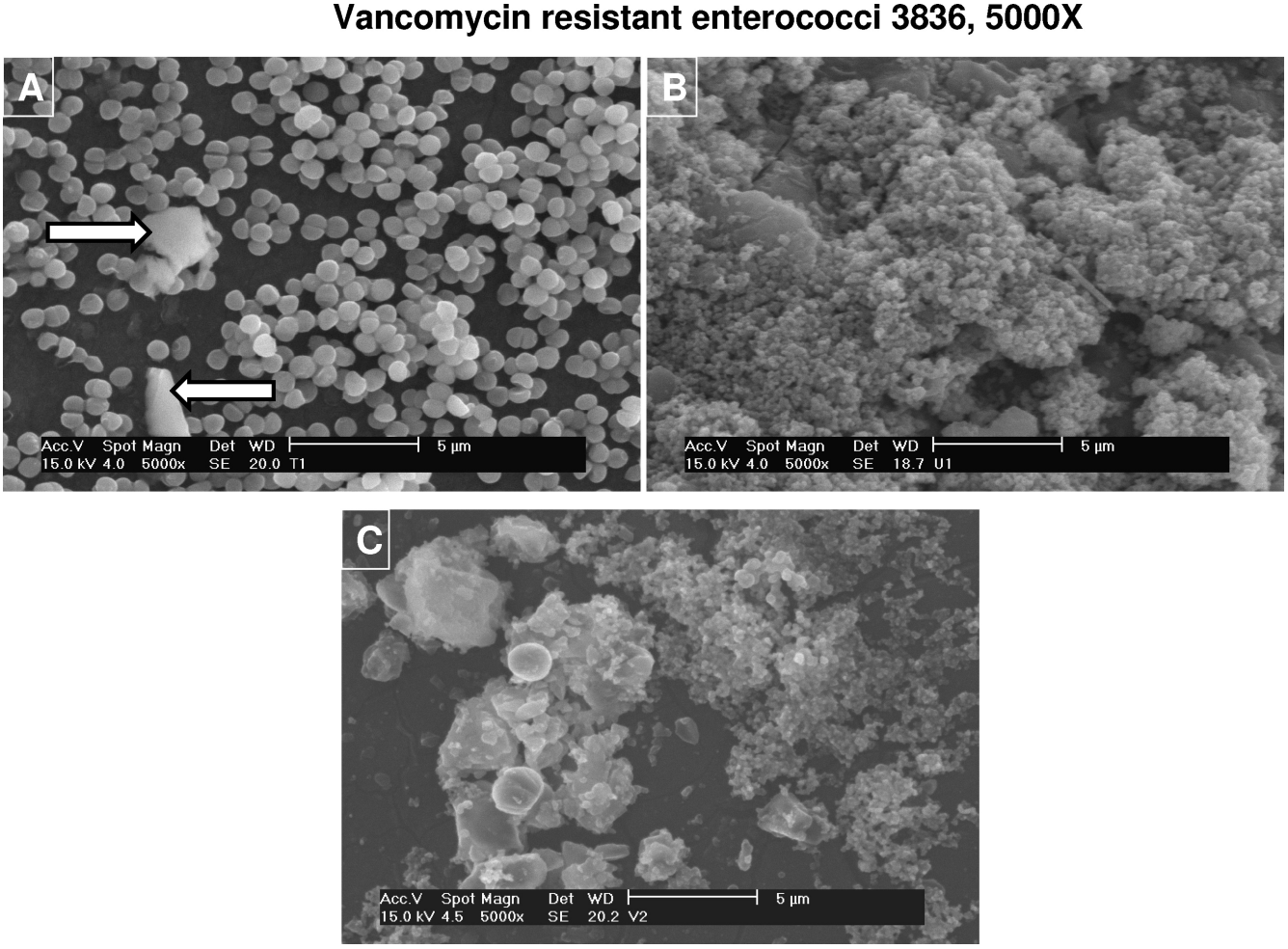

FIG. 1. SEM of bacterial biofilms grown on coated and uncoated urinary catheters. (A) VRE on an uncoated catheter. VRE cells are present on the surface, with a biofilm matrix (arrows) seen at some spots covering the cells. (B) VRE on a silver hydrogel-coated catheter. Organisms are covered with an extensive biofilm, where the biofilm matrix looks like a granular structure with bacterial cells totally embedded within it. (C) VRE on a GND-UC. The GND-UC resulted in a reduction in biofilm, and no organisms as seen in panels A and B are visible in panel C. Magnification, ×5,000.

cant reductions in bacterial burden in urine and tissue cultures ($P > 0.25$) compared with that for rabbits with uncoated catheters. There were significantly more invasive bladder infections or occurrences of cystitis in rabbits with silver-coated or uncoated catheters than in rabbits with GND-UCs ($P = 0.001$) (Table 2).

A categorical analysis revealed that GND-UCs significantly reduced the bacteruria (urine culture of >100 CFU/ml) in

TABLE 2. Efficacy of antiseptic-coated catheters against multidrug-resistant *E. coli* in an in vivo rabbit model[a]

Sample parameter	No. (%) of rabbits with uncoated catheters	Silver hydrogel-coated catheters		GND-UCs	
		No. (%) of rabbits	*P* value[b]	No. (%) of rabbits	*P* value[b]
Bacterial burden in urine (72–96 h), CFU/ml					
≤100	6 (40)	2 (29)	>0.99	8 (100)	0.007
>100	9 (60)	5 (71)		0 (0)	
Bacterial burden in bladder wall, CFU/g					
≤100	8 (50)	4 (57)	>0.99	8 (100)	0.022
>100	8 (50)	3 (43)		0 (0)	
Invasive bladder infection[c]	9 (56)	3 (43)		0 (0)	0.001

[a] The numbers of rabbits tested are as follows: 16 with control, uncoated catheters; 7 with silver hydrogel-coated catheters; and 8 with GND-UCs.
[b] *P* values represent comparisons with values for uncoated catheters, obtained using chi-square or Fisher's exact tests.
[c] Invasive bladder infection is defined as ≥100 CFU/g of bladder wall tissue and histopathological evidence of cystitis.

urine cultures obtained at 72 to 96 h compared with the levels for uncoated and Bardex IC silver hydrogel-coated catheters. None of the 8 rabbits with GND-UCs had urine cultures of >100 CFU/ml; however, positive cultures were found in 9 of 15 rabbits with uncoated catheters (0% versus 60%; $P = 0.007$) and 5 of 7 rabbits with Bardex IC silver hydrogel-coated catheters (0% versus 71%; $P = 0.007$). GND-UCs also significantly reduced bacterial burdens in bladder wall tissue cultures compared with results for uncoated catheters (0% versus 50%; $P = 0.022$).

Histopathologic findings. We evaluated the histopathologic changes associated with *E. coli* infection of the rabbits' urinary tracts. Most rabbits had urethral and urinary bladder mucosal lesions, including erosion and subacute ulcerative urethritis, which are consistent with trauma induced by several days of catheter compression of the urinary bladder. Further, histopathologic analysis revealed no significant differences in toxicity or staining between GND-UCs and uncoated and silver hydrogel-coated catheters.

DISCUSSION

UTIs account for 30% to 40% of nosocomial infections and are associated with high morbidity and mortality rates, prolonged hospital stays, and increased medical costs, especially for critically ill patients (13). More than 90% of intensive care unit infections originate from urinary catheters (16), and more than 1 million episodes of nosocomial UTIs are estimated to occur annually in the United States (2). For these reasons, several different intervention methods, such as coating catheters with silver or antimicrobial agents, have been used. However, these approaches have resulted in limited benefits. Hence, novel and more effective technologies are needed.

In the past, one major advance in the prevention of catheter-related UTIs was the development of the closed drainage system in the late 1960s. This approach was used because the main sources of infection are the periurethral areas, junction, drainage tube, and collecting vessels of the catheter. Several studies have found that sterile closed drainage systems are effective at preventing UTIs (5–7, 14, 18, 21). However, catheter-related UTIs caused by multidrug-resistant organisms continue to occur commonly, even with closed drainage.

Another, more recent approach to preventing catheter-related UTIs is coating catheters with various antimicrobials. Silver has bactericidal activity, is nontoxic, and has been used topically to prevent infections in burn patients. Akiyama and Okamoto (1) were the first to use a modified Foley catheter coated with silver. They found that it reduced bacteruria to $<10^5$ CFU. Several other researchers have found that silver-coated catheters are effective, but others have not, even though two of these trials included large numbers of patients (8, 17).

In a prospective investigator-blinded trial, Maki et al. reported that the use of nitrofurazone-impregnated catheters reduced the rate of catheter-associated bacteruria by approximately 33% (D. G. Maki, V. Knasinski, and P. A. Tambyah, A prospective investigator-blinded trial of a novel nitrofurazone-impregnated indwelling urinary catheters, presented at the Seventh Annual Meeting of the Society for Healthcare Epidemiology of America, St. Louis, MO). In a prospective, randomized multicenter clinical trial, Darouiche et al. (4) demonstrated that the use of urinary Foley catheters impregnated with minocycline and rifampin significantly reduced the rate of catheter-associated gram-positive bacteruria without reducing gram-negative bacteruria or candiduria or the rate of symptomatic UTIs. However, these antimicrobial catheters resulted in no protection against gram-negative bacteria, the leading cause of catheter-associated UTI, or yeast.

Currently, the only widely used anti-infective urinary catheter in the United States is the silver alloy urinary catheter, which has been shown to reduce the relative risk of UTIs by only 32% (9, 19). Our results confirmed the limited activity of silver hydrogel-coated catheters: *E. coli* was reduced by only 30% in coated catheters compared with the level for uncoated catheters, both in our rabbit model and in vitro ($P > 0.2$) (Table 1). Furthermore, neither the silver hydrogel-coated nor the nitrofurazone- or minocycline/rifampin-coated catheters provide sufficient broad-spectrum protection against multidrug-resistant bacteria and *Candida*, which are most commonly associated with the use of Foley catheters.

Gendine has several unique features. First, our results demonstrate that Gendine has broad-spectrum antimicrobial activity against the resistant bacteria and yeast that cause most UTIs. Second, the components of the Gendine coating are Gentian violet and chlorhexidine, both of which are considered to be nontoxic at low levels and have been used in several medical applications. Gentian violet has been used topically to treat skin lesions and coat the oral cavities of neonates and as an oral rinse for patients with oropharyngeal candidiasis (3, 20, 23). In addition, chlorhexidine has been used successfully to impregnate vascular catheters, which have wide global distribution. Third, Gendine can coat devices made of various polymers, internally and externally, without affecting their biocompatibility. Finally, Gendine-coated catheters demonstrated prolonged antimicrobial durability, when soaked in body fluid and urine, that extends to several weeks (3). Through in vitro studies, we demonstrated that GND-UCs have broad-spectrum antiadherence and colonization activity against various multidrug-resistant bacteria (including *E. coli*, *P. aeruginosa*, ESBL *K. pneumoniae*, VRE, and methicillin [meticillin]-resistant *Staphylococcus aureus*) and *Candida* species (including *C. albicans*, *C. glabrata*, and *C. krusei*) tested, which is superior to the performance of uncoated and silver-coated Foley catheters. Therefore, our in vitro results demonstrate that GND-UCs are statistically significant and efficacious at reducing the adherence of various microbial biofilm-forming organisms (bacteria and fungi.) Furthermore, our rabbit model supported our in vitro findings showing that the antiseptic GND-UCs are more effective at preventing catheter-related UTIs than silver hydrogel-coated and uncoated Foley catheters. It is worthwhile to assess the effectiveness of Gendine-coated urinary catheters in patients to see if they can prevent nosocomial UTIs. GND-UCs significantly prevented and reduced the in vitro biofilm adherence of multidrug-resistant *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and VRE. They also had excellent activity against *C. albicans*, *C. glabrata*, and *C. krusei*.

We evaluated GND-UCs in vivo and found that they were safe and effective. GND-UCs significantly reduced *E. coli* bacteruria compared with uncoated or silver-coated catheters ($P < 0.007$). They also significantly reduced the bacterial bur-

den in the bladder wall and cystitis, as determined by tissue cultures, compared with uncoated catheters ($P = 0.022$).

A histopathologic analysis revealed that most rabbits had urethral and urinary bladder mucosal lesions, including erosion and subacute ulcerative urethritis, which are consistent with trauma induced by several days of catheter compression of the urinary bladder. Overall, however, no definitive toxicity-related histopathologic differences between GND-UCs and uncoated and Bardex IC silver hydrogel-coated catheters were found.

Although our findings are noteworthy, this study has several limitations. Only small numbers of rabbits were tested in each group. In addition, the duration of the infection model was short. Four days of observation may not be sufficient to establish severe infection. Finally, not all organisms that can cause UTIs were tested in vivo.

Conclusions. GND-UCs were more efficacious at, respectively, preventing catheter-associated biofilm colonization and UTIs than were silver hydrogel-coated Foley and uncoated Foley catheters in vitro and in a rabbit model. No Gendine-related toxicities or staining was observed by histopathologic analysis. Given their lack of toxicity and their broad-spectrum in vitro activity against gram-positive and -negative bacteria and *Candida*, as well as their superior efficacy in vivo, GND-UCs may be useful at clinically preventing catheter-associated UTIs in high-risk patients. Further prospective, randomized, multicenter clinical trials are needed to validate these findings.

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REFERENCES

1. **Akiyama, H., and S. Okamoto.** 1979. Prophylaxis of indwelling urethral catheter infection: clinical experience with a modified Foley catheter and drainage system. J. Urol. **121:**40–42.
2. **Centers for Disease Control.** 1992. Public health focus: surveillance, prevention, and control of nosocomial infections. MMWR Morb. Mortal. Wkly. Rep. **41:**783–787.
3. **Chaiban, G., H. Hanna, T. Dvorak, and I. Raad.** 2005. A rapid method of impregnating endotracheal tubes and urinary catheters with gendine: a novel antiseptic agent. J. Antimicrob. Chemother. **55:**51–56.
4. **Darouiche, R., J. A. Smith, H. Hanna, C. B. Dhabuwala, M. S. Steiner, R. J. Babaian, T. B. Boone, P. T. Scardino, J. I. Thornby, and I. I. Raad.** 1999. Efficacy of antimicrobial-impregnated bladder catheters in reducing catheter-associated bacteruria: a prospective, randomized multicenter clinical trial. Urology **54:**976–981.
5. **Desautels, R. E., C. W. Waler, R. C. Graves, and J. H. Harrison.** 1962. Technical advances in prevention of urinary tract infection. J. Urol. **87:**487–490.
6. **Gillespie, W. A., G. G. Lennon, K. B. Linton, and N. Slade.** 1964. Prevention of urinary infection in gynaecology. Br. Med. J. **2:**423–425.
7. **Gillespie, W. A., K. B. Linton, and A. Miller.** 1960. The diagnosis, epidemiology, and control of urinary tract infection in urology and gynecology. J. Clin. Pathol. **13:**187–194.
8. **Johnson, J. R., P. L. Roberts, R. J. Olsen, K. A. Moyer, and W. E. Stamm.** 1990. Prevention of catheter-associated urinary tract infection with a silver oxide-coated urinary catheter: clinical and microbiological correlates. J. Infect. Dis. **162:**1145–1150.
9. **Karchmer, T. B., E. T. Giannetta, C. A. Muto, B. A. Strain, and B. M. Farr.** 2000. A randomized crossover study of silver-coated urinary catheters in hospitalized patients. Arch. Intern. Med. **160:**3294–3298.
10. **Kuhn, D. M., T. George, J. Chandra, P. K. Mukherjee, and M. A. Ghannoum.** 2002. Antifungal susceptibility of *Candida* biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. Antimicrob. Agents Chemother. **46:**1773–1780.
11. **Kunin, C. M., and R. C. McCormak.** 1966. Prevention of catheter-induced urinary-tract infections by sterile closed drainage. N. Engl. J. Med. **274:**1155–1161.
12. **Lee, S. J., S. W. Kim, Y. H. Cho, W. S. Shin, S. E. Lee, C. S. Kim, S. J. Hong, B. H. Chung, J. J. Kim, and M. S. Yoon.** 2004. A comparative multicentre study on the incidence of catheter-associated urinary tract infection between nitrofurazone-coated and silicone catheters. Int. J. Antimicrob. Agents **24**(Suppl. 1)**:**S65–S69.
13. **Leone, M., F. Garnier, M. Avidan, and C. Martin.** 2004. Catheter-associated urinary tract infections in intensive care units. Microbes Infect. **6:**1026–1032.
14. **Miller, A., K. B. Linton, W. A. Gillespie, N. Slade, and J. P. Mitchell.** 1960. Catheter drainage and infection in acute retention of urine. Lancet **i:**310–312.
15. **Morck, D. W., M. E. Olson, R. R. Read, A. G. Buret, and H. Ceri.** 1999. The rabbit model of catheter-associated urinary tract infection, p. 453–462. *In* O. Zak and M. A. Sande (ed.), Handbook of animal models of infection. Academic Press, London, United Kingdom.
16. **Richards, M. J., J. R. Edwards, D. H. Culver, and R. P. Gaynes.** 1999. Nosocomial infections in medical intensive care units in the United States: National Nosocomial Infections Surveillance System. Crit. Care Med. **27:**887–892.
17. **Riley, D. K., D. C. Classen, L. E. Stevens, and J. P. Burke.** 1995. A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal super-infection. Am. J. Med. **98:**349–356.
18. **Roberts, J. B. M., K. B. Linton, B. R. Pollard, J. P. Mitchell, and W. A. Gillespie.** 1965. Long-term catheter drainage in male. Br. J. Urol. **37:**63–72.
19. **Saint, S., D. L. Veenstra, S. D. Sullivan, et al.** 2000. The potential clinical and economic benefits of silver allow urinary catheters in preventing urinary tract infection. Arch. Intern. Med. **160:**2670–2675.
20. **Saji, M., S. Taguchi, K. Uchiyama, E. Osono, N. Hayama, and H. Ohkuni.** 1995. Efficacy of gentian violet in the eradication of methicillin-resistant *Staphylococcus aureus* from skin lesions. J. Hosp. Infect. **31:**225–228.
21. **Sanford, J. P.** 1964. Hospital acquired urinary tract infections. Ann. Intern. Med. **60:**903–914.
22. **Thibon, P., X. LeCoutour, R. Leroyer, and J. Fabry.** 2000. Randomized multi-centre trial of effects of a coated catheter with hydrogel and silver salts on the incidence of hospital acquired urinary tract infections. J. Hosp. Infect. **45:**117–124.
23. **Vazquez, J. A.** 1999. Options for the management of mucosal candidiasis in patients with AIDS and HIV infection. Pharmacotherapy **19:**76–87.
24. **Warren, J. W.** 1987. Catheter associated urinary tract infection. Infect. Dis. Clin. N. Am. **1:**823–854.