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Activities of a Nitrofurazone-Containing Urinary Catheter and a Silver Hydrogel Catheter against Multidrug-Resistant Bacteria Characteristic of Catheter-Associated Urinary Tract Infection

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The in vitro inhibitory activity of a nitrofurazone-coated urinary catheter (NFC) against 86 recently obtained susceptible and multidrug-resistant (MDR) clinical isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Staphylococcus aureus*, coagulase-negative *staphylococci*, and *Enterococcus faecium*, which are species implicated in catheter-associated urinary tract infection and which traditionally have been susceptible to nitrofuran derivatives, was determined using an agar diffusion assay. In a subset of these strains, the activity of the NFC was compared with that of a silver hydrogel urinary catheter (SHC), and the durability of each catheter's inhibitory activity was assessed during serial daily transfers of catheter segments to fresh culture plates. Except for vancomycin-resistant *E. faecium*, the NFC was active against all isolates tested and showed comparable inhibition zones with susceptible and MDR strains of each species. In contrast, the SHC inhibited only certain staphylococci ($P < 0.01$ versus the NFC), and among these strains, the SHC produced smaller inhibition zones than did the NFC ($P < 0.01$). Inhibition was evident for up to 5 days with the NFC, but for only 1 day (if at all) with the SHC ($P < 0.01$). These data document that, for most genera which traditionally have been susceptible to nitrofuran derivatives, the NFC remains active against contemporary MDR isolates. They also demonstrate that the in vitro antibacterial activity of the NFC is markedly superior to that of the SHC in several respects. Thus, the NFC shows promise for clinical use in the current era of MDR bacteria.

Catheter-associated urinary tract infection (CUTI) is a major health care problem. It is the single most common type of nosocomial infection (13), and because of its high incidence, it is responsible for an enormous aggregate burden of morbidity, mortality, and increased health care costs (10, 12, 20, 36, 43). Although many interventions have been evaluated as possible ways to prevent CUTI, only reduced duration of indwelling catheter use, strict maintenance of a closed drainage system, and prophylactic systemic antimicrobial therapy have been consistently found to be effective (16, 29, 33, 35, 37, 43). Systemic antimicrobial prophylaxis is not recommended by authorities in the field because of the associated risk of selecting for resistant microorganisms (21, 40, 43).

In recent years, antimicrobial resistance has emerged explosively among diverse bacterial types, largely as a consequence of decades of unrestrained antimicrobial use in agriculture and in human and veterinary medicine (24, 42). Although specific data are lacking, it is likely that the increasing prevalence of multidrug-resistant (MDR) gram-negative bacilli, methicillin-resistant *Staphylococcus aureus* and *Staphylococcus epidermidis*, and vancomycin-resistant enterococci (VRE) has further increased the morbidity, mortality, and costs attributable to CUTI. Ironically, antimicrobial therapy given to patients who develop CUTI provides further selection pressure for the emergence of even more highly resistant organisms (9).

Antimicrobial urinary catheters, which are designed to prevent CUTI by blocking bacterial ascent into the bladder along the external or internal surfaces of the catheter, historically have had mixed clinical success (1, 3, 15, 19, 22, 25–27, 38, 39, 41, 43). Two antimicrobial catheters are currently marketed, a nitrofurazone-containing catheter (NFC) (17, 18) and a silver hydrogel catheter (SHC). The NFC was active in vitro against a broad range of gram-positive and gram-negative bacilli isolated in the 1980s from patients with indwelling urinary catheters (17). However, its activity against current MDR strains of these same species is unknown, and clinical efficacy data have not been reported. The SHC appeared partially protective in a recent randomized clinical trial, the results of which have been presented in abstract form (28). However, its activity against current MDR bacterial strains also is unknown.

We undertook the present study to assess the in vitro activity of the NFC against a diverse population of recently recovered MDR as compared with susceptible clinical isolates of bacterial species characteristic of CUTI and traditionally susceptible to nitrofuran derivatives. We also sought to directly compare the NFC and the SHC with respect to in vitro inhibitory activity against such isolates and to assess the in vitro durability over time of each catheter's activity against MDR bacteria.

MATERIALS AND METHODS

Bacterial strains. The six species selected for study, *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *S. aureus*, coagulase-negative *staphylococci*, and *Enterococcus faecium*, all are prominent as pathogens in CUTI (8, 10, 19, 40, 43), have traditionally been susceptible to nitrofuran derivatives (17), and have recently exhibited clinically significant increases in antimicrobial resistance (5, 9, 24, 42). Test strains were predominantly clinical isolates from the Minneapolis VA Medical Center clinical microbiology laboratory. From May through July 1998, laboratory personnel saved for the research laboratory four or more susceptible and MDR representatives (as defined below) of five of the six species of interest (isolates of all except *E. faecium*), with priority given to urine isolates. For *E. faecium*, susceptible urine isolates were selected from a prospectively assembled strain bank containing all enterococci isolated in the clinical microbiology laboratory from December 1997 through July 1998. A single isolate of vancomycin-resistant *E. faecium* was selected from each of 13 different clonal groups (as defined by restriction analysis of genomic DNA using *Pvu*II, performed by the hospital's molecular epidemiology unit) of all vancomycin-resistant *E. faecium* isolates encountered at the VA Medical Center since 1995 (VA VRE). To provide greater diversity of vancomycin-resistant *E. faecium*, the VA VRE were supplemented with additional isolates of vancomycin-resistant *E.*

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TABLE 1. Inhibitory activity of the NFC against susceptible (S) and MDR representatives of six bacterial types

Organism	Level of resistance (no. of isolates)	Inhibitory activity of catheters					
		Longitudinal sections			Cross sections		
		No. of isolates inhibited	Inhibition zone (mm)[a]		No. of isolates inhibited	Inhibition zone (mm)[a]	
			Median	Range		Median	Range
E. coli	S (5)	5	4.6	4.3–5.0	5	1.3	0.8–2.5
	MDR (9)	9	4.5	3.9–6.1	9	0.9	0.5–1.5
K. pneumoniae	S (5)	5	2.2	2.1–2.8	5	0.6	0.3–1.0
	MDR (7)	7	2.2	0.4–2.8	4	0.1	0–1.0
C. freundii	S (5)	5	4.5	4.2–8.1	5	1.1	0.3
	MDR (6)	6	3.5	3.0–7.8	6	0.7	0.3–2.8
S. aureus	S (5)	5	3.5	3.3–4.6	5	0.4	0.3–1.5
	MDR (7)	7	4.0	3.4–5.0	6	0.5	0–1.3
Coagulase-negative	S (5)	5	4.0	2.5–7.6	3	0.5	0–2.0
staphylococci	MDR (5)	5	5.8	4.4–8.0	5	2.3	0.5–2.5
E. faecium	S (5)	5	4.0	2.5–7.6	3	0.5	0–2.0
VA	MDR (12)	0	0	0	0	0	0
Other	MDR (10)	2[b]	0	0–7.5	0	0	0

[a] Zone sizes (median and range) are for all strains in the group, not just those inhibited by the catheter.
[b] These strains were not inhibited by either the NFC or the SHC in part two of the study.

faecium provided by other investigators (other VRE) (44). Isolates were stored at −70°C in nutrient broth containing 10% glycerol until ready for use.

Isolates were identified to the species level (or, for coagulase-negative *Staphylococcus*, to the subgenus level) using standard methods (23). Susceptibility testing for isolates from the VA clinical microbiology laboratory was by a standard broth microdilution MIC method (30, 31), and testing for other VRE was by broth microdilution (30, 31) or agar gradient diffusion (E test; AB Biodisk, Piscataway, N.J.). Isolates susceptible to all antimicrobial agents characteristically active against the most susceptible members of the species were defined as susceptible. Isolates exhibiting resistance to multiple antimicrobial agents, including one or more sentinel agents for that species, were defined as MDR. These key agents included, for gram-negative bacilli, extended spectrum cephalosporins, aminoglycosides, β-lactam–β-lactamase inhibitor combination drugs, and ciprofloxacin; for staphylococci, the key agent was methicillin (oxacillin), and for *E. faecium*, the key agent was vancomycin. Susceptibility and resistance were defined according to MIC breakpoints approved by the National Committee for Clinical Laboratory Standards (32). Susceptibility to nitrofuran derivatives or silver ion was not measured, and isolates were selected for inclusion in the study based solely on their identification and patterns of susceptibility to other antimicrobial agents.

Catheters. Catheters in sterile packaging were provided by the study sponsor and included the NFC (Release-NF; Rochester Medical Corp, Stewartville, Minn.), a comparable silicone elastomer control catheter (Rochester Medical Corp.), the SHC (Bardex IC Lubricath; C. R. Bard, Covington, Ga.), and a comparable hydrogel-coated latex control catheter (Bardex Lubricath; C. R. Bard). The antimicrobial catheters were used prior to the outdates indicated by the manufacturers. Catheters were sectioned with a scalpel as previously described (17) to yield both longitudinal strips (approximately 1.5 cm long and one-quarter of the catheter circumference wide) and transverse rings (cross sections approximately 3 mm thick). (Both types of catheter sections were used because longitudinal strips provide a greater area of contact between the coated portion of the catheter and the agar plate and thereby provide greater sensitivity for detection of weak antimicrobial activity, whereas transverse rings may more closely simulate the in vivo geometry of radial diffusion of antimicrobial activity away from the catheter surface into the urethral space.) Sectioning was either followed by autoclaving of catheter segments (part one of the study) or carried out using sterile technique without subsequent autoclaving, to exclude any artifactual decrement in antimicrobial activity due to autoclaving (parts two and three of the study). Sterile sections from the different catheter types were stored separately in sealed containers.

Catheter inhibition assays. Catheter segments were tested for their ability to inhibit bacterial growth by using an established agar diffusion assay, as previously described (17). Mueller-Hinton agar plates were streaked for confluence in duplicate using bacterial suspensions prepared at a standardized turbidity from fresh overnight agar plate cultures of the test strains. Sterile catheter segments (longitudinal strips plus cross sections) of each type of catheter being tested were placed on the inoculated agar surface using sterile forceps, and plates were incubated overnight at 37°C. Inhibition zones around catheter segments were measured at their widest diameter, and zone sizes were calculated by the formula (maximal zone width − catheter segment width)/2. Mean zone sizes from duplicate assay plates were analyzed.

Study design. In part one of the study, the NFC was tested against all of the clinical isolates, and results from sensitive and MDR isolates were compared. In part two of the study, the NFC and the SHC were tested in parallel against a subset of the total strain collection which included the first four susceptible and MDR isolates of each species from the VA clinical microbiology laboratory, plus the first four other VRE. Results from the NFC and the SHC were compared. In parts one and two of the study, control catheter segments were tested in parallel with antimicrobial catheter segments and gave no inhibition zones with any of the isolates. Neither the NFC nor the SHC inhibited a *Pseudomonas aeruginosa* isolate which was used as a negative control strain.

In part three of the study, the durability of each catheter's inhibitory activity was tested during serial daily transfer of longitudinal catheter segments to new agar plates using two of the representatives of each species from part two of the study. Isolates were selected with preference given to those (if any) inhibited by both catheters, to those that yielded (respectively) the largest and the smallest inhibition zones with the test catheters (with the SHC favored over the NFC when possible), and to MDR strains. After each overnight incubation, catheter segments were transferred from the old plates to new duplicate agar plates that had been seeded with freshly prepared suspensions of the test organisms. Serial daily transfer of catheter segments to fresh agar plates was continued until no inhibition zone was observed with either catheter type after overnight incubation.

Statistical analyses. Strains were considered as inhibited by a catheter segment if there was any measurable inhibition zone around the catheter and were considered as not inhibited if no inhibition zone was visible. Comparisons of proportions were tested using Fisher's exact test (for unpaired observations) or McNemar's test (for paired observations) (6). Relative sizes of inhibition zones were compared by using a paired two-tailed *t* test. Statistical significance was defined as $P < 0.05$.

RESULTS

We first assessed the inhibitory activity of the NFC against 30 susceptible isolates as compared with 56 MDR isolates of *E. coli*, *K. pneumoniae*, *C. freundii*, *S. aureus*, coagulase-negative *staphylococci*, and *E. faecium* (Table 1). The NFC inhibited all susceptible isolates of all species tested. With the exception of vancomycin-resistant *E. faecium*, it also inhibited all MDR isolates, yielding inhibition zones of approximately the same size for MDR and susceptible isolates of the same species (Table 1). Only 2 (9%) of 22 vancomycin-resistant *E. faecium* isolates were inhibited by the NFC (versus sensitive *E. faecium*; $P < 0.01$). Thus, except for vancomycin-resistant *E. faecium*, the NFC was similarly active against susceptible and MDR strains of the species tested.

We next directly compared the inhibitory activity of the NFC with that of the SHC against a systematically selected subset of the above strains (Table 2 and Fig. 1). The NFC inhibited a significantly greater proportion of isolates overall than did the SHC (for longitudinal sections, 44 of 52 [85% NFC] versus 12 of 52 [23% SHC], respectively, $P < 0.01$; for cross sections, 42

TABLE 2. Comparative inhibitory activity of the NFC and the SHC against susceptible (S) and MDR representatives of six bacterial types

Organism	Level of resistance (n = 4 for each group)	Inhibitory activity of catheters											
		Longitudinal sections						Cross sections					
		NFC			SHC			NFC			SHC		
		No. of isolates inhibited	Inhibition zone (mm)[a]		No. of isolates inhibited	Inhibition zone (mm)[a]		No. of isolates inhibited	Inhibition zone (mm)[a]		No. of isolates inhibited	Inhibition zone (mm)[a]	
			Median	Range		Median	Range		Median	Range		Median	Range
E. coli	S	4	4.6	4.3–5.5	0	0	0	4	1.1	0.8–1.5	0	0	0
	MDR	4	4.8	4.0–6.0	0	0	0	4	1.0	1.0	0	0	0
K. pneumoniae	S	4	2.3	2.0–2.5	0	0	0	4	0.5	0.3–0.5	0	0	0
	MDR	4	2.4	1.5–2.5	0	0	0	4	0.4	0.3–0.8	0	0	0
C. freundii	S	4	4.5	1.0–4.5	0	0	0	4	1.3	0.5–1.5	0	0	0
	MDR	4	3.5	3.3–4.0	0	0	0	4	0.5	0.3–1.5	0	0	0
S. aureus	S	4	3.8	3.5–4.5	4	1.5	1.0–2.0	4	0.6	0.5–1.0	3	0.3	0–0.5
	MDR	4	3.9	3.5–4.3	4	2.0	1.8–2.0	4	1.3	0.3–1.5	3	0.3	0–0.5
Coagulose-negative *staphylococci*	S	4	3.8	2.5–7.0	1	0	0–3.0	3	0.5	0–3.0	1	0	0–0.3
	MDR	4	6.3	4.3–8.3	3	0.4	0–3.0	4	1.9	0.5–2.5	0	0	0
E. faecium	S	4	3.0	1.0–3.5	0	0	0	3	0.1	0–0.1	0	0	0
VA	MDR	0	0	0	0	0	0	0	0	0	0	0	0
Other	MDR	0	0	0	0	0	0	0	0	0	0	0	0

[a] Zone sizes (median and range) are for all strains in the group, not just those inhibited by the catheter.

of 52 [81% NFC] versus 7 of 52 [13% SHC], respectively, $P < 0.01$). Among the gram-negative bacilli, the SHC failed to inhibit any isolates, whereas the NFC inhibited all isolates ($P < 0.01$ for both longitudinal and cross sections, NFC versus SHC). This difference between the proportion of isolates inhibited by the NFC versus the SHC was highly significant for each of the three gram-negative species (*E. coli*, *K. pneumoniae*, and *C. freundii*) ($P < 0.01$ for each species).

The NFC was active against all gram-positive organisms tested except the VRE (Table 2). In contrast, although the SHC was active against all *S. aureus* isolates, it was inactive against half of the coagulase-negative *Staphylococcus* isolates

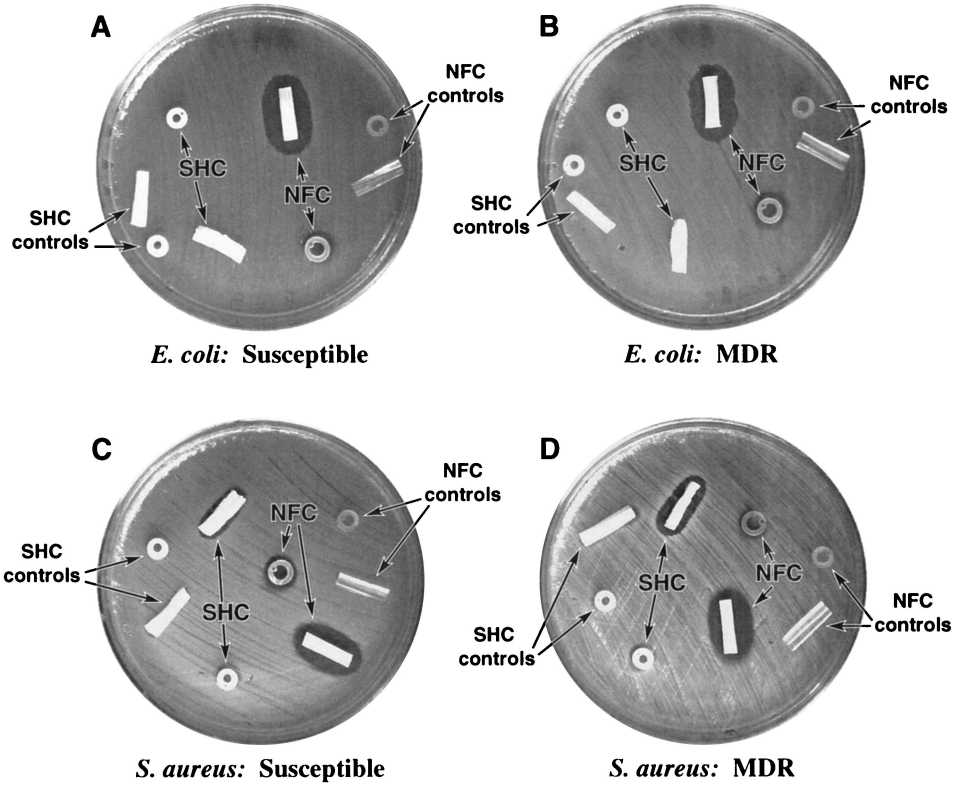

FIG. 1. Agar diffusion inhibition assay plates for four representative bacterial isolates. A, susceptible *E. coli*; B, MDR *E. coli*; C, susceptible *S. aureus*; D, MDR *S. aureus*. Each plate contains longitudinal and transverse sections of the SHC and the NFC, plus the corresponding control catheters.

TABLE 3. Durability of inhibitory activity of longitudinal segments of the NFC and SHC during serial daily transfer to fresh culture plates

Organism	Isolate	Level of resistance	Daily level of inhibition and total duration of inhibition by:							
			NFC						SHC	
			Inhibition zone size (mm) on:					Duration of inhibition (days)	Inhibition zone size (mm) on day 1[c]	Duration of inhibition (days)
			Day 1	Day 2	Day 3	Day 4	Day 5[b]			
E. coli	11	MDR	4.0	3.3	0.3	0	0	3	0	0
	12	MDR	5.5	2.5	1.5	0.8	0.5	5	0	0
K. pneumoniae	23	MDR	4.0	0	0	0	0	1	0	0
	26	MDR	4.5	1.4	0	0	0	2	0	0
C. freundii	2	MDR	5.5	3.5	2.5	0	0	3	0	0
	4	MDR	6.0	0.6	0	0	0	2	0	0
S. aureus	43	MDR	4.0	3.3	0.8	0.4	0	4	1.3	1
	45	MDR	6.0	3.3	0.9	0.6	0	4	1.5	1
Coagulase-negative *staphylococci*	57	MDR	4.3	2.3	0.8	0	0	3	0.5	1
	58	MDR	4.3	3.0	0.3	0	0	3	2.8	1
E. faecium	1,051	S[a]	0.9	0.3	0	0	0	2	0	0
	1,095	S	3.0	1.5	0	0	0	2	0	0

[a] S, susceptible.
[b] No inhibition observed beyond day 5.
[c] No inhibition observed beyond day 1.

(whether susceptible or MDR) and was inactive against all of the *E. faecium* isolates, whether susceptible or VRE (Table 2 and Fig. 1). Thus, the NFC inhibited a significantly greater proportion of the gram-positive organisms overall than did the SHC (for longitudinal sections, 20 of 32 [63% NFC] versus 12 of 32 [38% SHC], respectively, $P < 0.01$; for cross sections, 18 of 32 [56% NFC] versus 7 of 32 [22% SHC], respectively, $P < 0.01$). Furthermore, even among those gram-positive organisms that were inhibited by the SHC, inhibition zones in every instance were larger with the NFC than with the SHC (for longitudinal sections [$n = 12$], mean zone size difference was 3.1 mm, $P < 0.001$; for cross sections [$n = 7$], mean zone size difference was 0.8 mm, $P = 0.07$) (Table 2 and Fig. 1).

Finally, we assessed the durability of each catheter's in vitro inhibitory activity during serial daily transfer of catheter segments to fresh agar plates containing the test organisms. The NFC inhibited all isolates on day 1 and gave measurable inhibition zones for as long as 5 days for some isolates (median, 3 days). In contrast, as in part two of the study, the SHC inhibited only the *S. aureus* and coagulase-negative *Staphylococcus* isolates and yielded small zones on day 1 only (Table 3) (for NFC versus SHC, proportion of isolates inhibited for >1 day [11 of 12 versus 0 of 12], $P < 0.01$; proportion inhibited for ≥3 days [7 of 12 versus 0 of 12], $P < 0.02$).

DISCUSSION

In this study, we evaluated the in vitro inhibitory activity of the NFC, a marketed antimicrobial urinary catheter, against a broad range of susceptible and MDR gram-negative and gram-positive clinical isolates representing species traditionally susceptible to nitrofuran derivatives. We also compared the activity of the NFC with that of another marketed antimicrobial urinary catheter, the SHC, and assessed the durability of each catheter's antimicrobial activity during serial daily transfer to fresh agar plates. We found that, in contrast to the SHC, which was active only against a subset of the staphylococci, the NFC was active against representatives of all species tested and, with the exception of vancomycin-resistant *E. faecium*, was similarly active against susceptible and MDR strains of each species. Moreover, whereas the scant inhibitory activity of the SHC did not persist beyond 1 day, the NFC showed continued activity against representatives of all species tested for periods from 2 to 5 days, despite the artificial handicap of being transferred to a fresh plate each day.

These findings have several implications. First, they suggest that, to date, the emergence of multidrug resistance among diverse bacterial types (24, 42) does not pose a significant threat to the activity of the NFC against strains of genera which traditionally have been susceptible to nitrofuran derivatives (17). This probably is because nitrofuran derivatives, which are not widely used in clinical or veterinary medicine and have mechanisms of action distinct from those of other antimicrobial agents (4, 14, 34), have not exerted nearly the selective pressure for emergence of resistance on the global bacterial population as have other more widely used agents, nor do they encounter "innocent bystander" resistance induced by the use of other agents. (It should be noted that certain gram-negative genera, including *Pseudomonas*, *Serratia*, *Enterobacter*, and *Proteus*, as well as yeasts, are typically intrinsically resistant to nitrofuran derivatives [17]; hence they would not be expected to be inhibited by the NFC irrespective of their susceptibility profiles for other agents.)

Whether future widespread clinical use of the NFC might lead to emergence of nitrofurazone resistance among currently susceptible nosocomial bacteria, which in turn could undercut the clinical effectiveness of the NFC, is unknown. However, a urethral catheter's impact should be limited to the sparse and relatively immobile distal urethral flora, whereas oral and parenteral antimicrobial agents act on the much larger and more mobile bowel flora. The numbers of organisms subjected to selective pressure, hence the predicted statistical likelihood of the emergence of a spontaneously resistant mutant, is orders of magnitude lower with a urinary catheter than with bowel-active systemic agents. Additionally, the bacterial density to which a resistant clone could proliferate if one did emerge should be much lower in the urethral flora than the bowel flora, which would limit the risk of transfer to other hosts. Moreover, whereas stool commonly causes gross or microscopic contamination of hospital surfaces, thereby facilitating transfer of bowel organisms between patients via fomites and health care workers (11), nothing on a comparable scale occurs with the

urethral flora. Finally, the multiple mechanisms of action of nitrofuran derivatives (inactivation of ribosomal proteins and other macromolecules, with consequent inhibition of protein, DNA, RNA, and cell wall synthesis, and inactivation of aerobic energy metabolism) (4) may provide an intrinsic barrier to the development of resistance to these agents. Thus, although it would be naive to consider as impossible the emergence of strains resistant to the NFC, if this problem should occur, it likely would be a slower and more limited process than has occurred with resistance to conventional systemic antimicrobial agents (24, 42).

A second major finding of the study was the comparatively poor antimicrobial activity of the SHC. This catheter failed to inhibit most of the isolates studied, whether susceptible or MDR, and was altogether inactive against gram-negative bacilli, which are the pathogens of greatest concern in CUTI. SHC also exhibited rapidly waning activity against the few organisms that it was able to inhibit. It would appear that the NFC is substantially more effective than the SHC in providing antimicrobial activity in the vicinity of the catheter, both initially and over time. As such, the NFC would be predicted to be more effective than the SHC in blocking the migration of bacteria up the urethra of catheterized patients along the external catheter surface, which is the major route for acquisition of CUTI when closed collecting systems are used (2, 8). The results of the present study do not exclude the possibility that the SHC may inhibit microbial growth immediately at the catheter surface, despite the absence of any evident diffusible antimicrobial activity. However, the results of unpublished experiments involving the incubation of SHC and control catheter segments in bacterial suspensions suggest that this probably is not the case, at least for *E. coli* (7).

Our finding that the in vitro inhibitory activity of the SHC was limited to *S. aureus* and coagulase-negative *staphylococci* is consistent with the results of a recent clinical trial in which the SHC was associated with a significant reduction in the incidence of CUTI due to gram-positive bacteria but had no effect on CUTI due to gram-negative bacilli (28). This correspondence of in vitro and in vivo results suggests that the agar diffusion assay used in the present study (17) may predict the clinical efficacy of antimicrobial catheters, which would increase the clinical relevance of our positive in vitro findings with the NFC.

That no VRE isolates were consistently inhibited by the NFC was unexpected, since nitrofurantoin is one of the few traditional antimicrobial agents to which VRE typically remain susceptible (5). We enlarged our sample of VA VRE and also included strains from other institutions (for an example, see reference 44) specifically to increase the diversity of VRE strains tested, in order to avoid drawing false conclusions from what otherwise might have been a genetically restricted panel of VRE. Whether the absence of inhibition by the NFC of most vancomycin-resistant *E. faecium* isolates was due to these strains' resistance to nitrofuran derivatives in general, to nitrofurazone in particular, or to other factors remains to be determined.

A limitation of the present study is that the test organisms were predominantly from a single locale and a circumscribed patient population. Confirmation in different populations would increase confidence in the present study's findings. Additionally, that we did not include representatives of gram-negative genera against which the NFC is predictably inactive (17) might have biased the study in favor of the NFC. However, the complete inactivity of the SHC against the three gram-negative genera that were studied and against the *P. aeruginosa* control strain suggests that inclusion of isolates from the genus *Pseudomonas*, *Proteus*, *Enterobacter*, or *Serratia* probably would not have substantially altered the study's findings with respect to the comparative activities of the NFC and the SHC.

In summary, we found that the NFC was broadly active in vitro against both susceptible and MDR strains of diverse bacterial species characteristic of CUTI, and it exhibited persistent inhibitory activity against some isolates for up to 5 days. In contrast, the SHC was largely inactive, and when active, it was both less potent and had more rapidly waning activity than the NFC. The NFC shows promise as a possible means to prevent CUTI and to reduce antimicrobial use in the current era of emerging multidrug antimicrobial resistance. Clinical correlation of these in vitro findings is needed.

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