

Infection Risk with Nitrofurazone-Impregnated Urinary Catheters in Trauma Patients

A Randomized Trial

Jakob Stensballe, PhD; Michael Tvede, MD; Dagnia Looms, PhD; Freddy Knudsen Lippert, MD; Benny Dahl, DMSc; Else Tønnesen, DMSc; and Lars Simon Rasmussen, PhD

Background: Urinary tract infection is one of the most common nosocomial infections in hospitalized patients. It is predominantly associated with indwelling urinary catheters.

Objective: To determine whether nitrofurazone-impregnated urinary catheters reduce the incidence of catheter-associated bacteriuria and funguria (CABF).

Design: Randomized, double-blind, controlled trial.

Setting: Copenhagen Trauma Center, Copenhagen, Denmark.

Patients: 212 consecutive adult trauma patients admitted between July 2003 and August 2005. Eligible patients needed a urinary catheter on arrival and were excluded if they were HIV positive, were pregnant, had a primary burn injury, or were receiving steroid treatment or if informed consent was unattainable.

Interventions: Nitrofurazone-impregnated or standard silicone catheter throughout the duration of catheterization.

Measurements: Catheter-associated bacteriuria and funguria, defined as at least 10^3 colony-forming units/mL, was assessed daily until removal of the catheter, with a prespecified minimum of 24-hour follow-up for the primary analysis. The microbiologist was blinded to study group assignment.

Results: 1190 urine cultures were obtained over 1001 catheter-days. Catheter-associated bacteriuria and funguria occurred less frequently in the nitrofurazone catheter group than in the silicone catheter group (7 of 77 [9.1%] vs. 19 of 77 [24.7%]; incidence per 1000 catheter-days, 13.8 vs. 38.6; adjusted risk, 0.31 [95% CI, 0.14 to 0.70]; $P = 0.005$). Onset of CABF was delayed in the nitrofurazone group ($P = 0.01$), and nitrofurazone catheters led to fewer instances of new or changed antimicrobial therapy (adjusted risk, 0.27 [CI, 0.10 to 0.69]; $P = 0.006$).

Limitations: The clinical significance of asymptomatic bacteriuria and funguria is unclear. Data were missing in 27% of patients, and the magnitude of effect of the nitrofurazone catheters varied by assumptions about outcomes in patients who did not complete 24-hour follow-up.

Conclusions: Nitrofurazone-impregnated urinary catheters reduced the incidence of CABF in adult trauma patients, reducing the need to change or prescribe new antimicrobial therapy.

Ann Intern Med. 2007;147:285-293.

For author affiliations, see end of text.

ClinicalTrials.gov registration number: NCT00192985.

www.annals.org

Urinary tract infection (UTI) is one of the most common nosocomial infections in hospitalized patients and is most often associated with an indwelling catheter (1). The leading risk factor for bacteriuria is the duration of catheterization: With each day of catheterization, the prevalence of bacteriuria increases 3% to 10% (2).

Trauma patients are prone to infectious complications (3, 4), in part as a result of invasive devices in supportive therapy. Urinary catheters are often needed in the trauma care setting, and UTI accounts for 24% of nosocomial infections (5). Urinary tract infection is the focus for sepsis in 6% to 8% of injured patients (6), and sepsis is associated with increased mortality (7). The best preventive measure for catheter-associated UTI is to minimize the use of indwelling catheters and to remove catheters as soon as possible. However, other approaches to reduce catheter-associated UTI are required. One possibility is to incorporate antibacterial agents, such as nitrofurazone, in the catheter material. Doing so may prevent migration of bacteria, colonization of the catheter, and formation of biofilm. Like nitrofurantoin, nitrofurazone is a nitrofurantoin and has been used for more than 50 years without any sign of microbial resistance (8, 9). In vitro studies have shown that nitrofurazone-impregnated catheters inhibited the growth of 75%

of common urinary bacterial isolates (10) and of several multidrug-resistant isolates (11).

We designed a randomized, double-blind, controlled clinical trial to test the hypothesis that nitrofurazone-impregnated urinary catheters could reduce the incidence of catheter-associated UTI in adult trauma patients compared with standard silicone catheters.

METHODS

Design

We conducted a randomized, double-blind, controlled trial comparing a nitrofurazone-impregnated urinary catheter (Releen NF, Coloplast A/S, Humlebaek, Denmark)

See also:

Print

Editors' Notes 286

Web-Only

Conversion of graphics into slides

Audio summary

Context

Indwelling urinary catheters increase risk for bacteriuria and clinically significant urinary tract infection.

Contribution

In this randomized trial, trauma patients who received a catheter impregnated with nitrofurazone were less likely to have bacteriuria and funguria than were those who received a standard silicone catheter. They were also less likely to need a change in antibiotic or addition of new antibiotics.

Caution

Data on outcomes were missing for many patients.

Implication

By reducing the incidence of bacteriuria and funguria, nitrofurazone-impregnated urinary catheters appear to reduce the need to change or prescribe new antimicrobial therapy in patients who require indwelling catheters.

—The Editors

with a standard silicone urinary catheter (Simpla All Silicone, Coloplast A/S) in trauma patients.

Setting and Participants

During a 24-month period (July 2003 to August 2005), we included all consecutive adult (age ≥ 18 years) trauma patients who needed a urinary catheter and were admitted directly from the accident scene to the Trauma Center in Copenhagen, Denmark. Exclusion criteria were HIV infection; preinjury treatment with corticosteroids; pregnancy; primary burn injury; and unattainable signed informed consent.

The Trauma Center in Copenhagen is a level 1 trauma center at a tertiary university hospital. After the trauma resuscitation phase, patients were transferred to an intensive care unit or a surgical ward. On arrival, prophylactic antibiotics were given according to the site and type of injury. Antibiotics were not given for minor injuries. For closed injuries, intravenous cefuroxime, 1.5 g 3 times daily, was given for up to 3 days; for open injuries, intravenous ceftriaxone, 2 g twice a day for up to 3 days, combined with metronidazole, 500 mg 3 times daily, was given. This regimen was continued regardless of which ward or intensive care unit the patient was admitted to.

The local ethics committee and the Danish Data Protection Agency approved the study, and written informed consent was obtained from the patients or next of kin. The study was performed in accordance with the 1975 Declaration of Helsinki, as revised in 1983.

Randomization and Interventions

The randomization list was computer-generated, with a block size of 8 (Medstat, version 2.1; ASTRA Group A/S, Albertslund, Denmark), by a biostatistician who was inde-

pendent of the investigators. The trauma team leader enrolled patients; at enrollment, allocation to treatment groups was concealed. Two nurses from a team of nurses specially trained in the allocation and catheterization procedure performed the allocation by sequentially opening consecutively numbered, sealed randomization envelopes that contained the name of the assigned catheter. Catheterizing nurses were not formally blinded to catheter type, but both study catheters were new in the hospital. Thus, nurses caring for the patients did not know which of the new catheters was the nitrofurazone catheter. Patients were effectively blinded to their catheter assignment because 1) the catheter package was opened outside the patients' field of vision; 2) the patients could not see the catheter at the time of insertion because their necks were immobilized (12); and 3) although the catheters differed only in color, patients were not informed of the name or type of the catheter used.

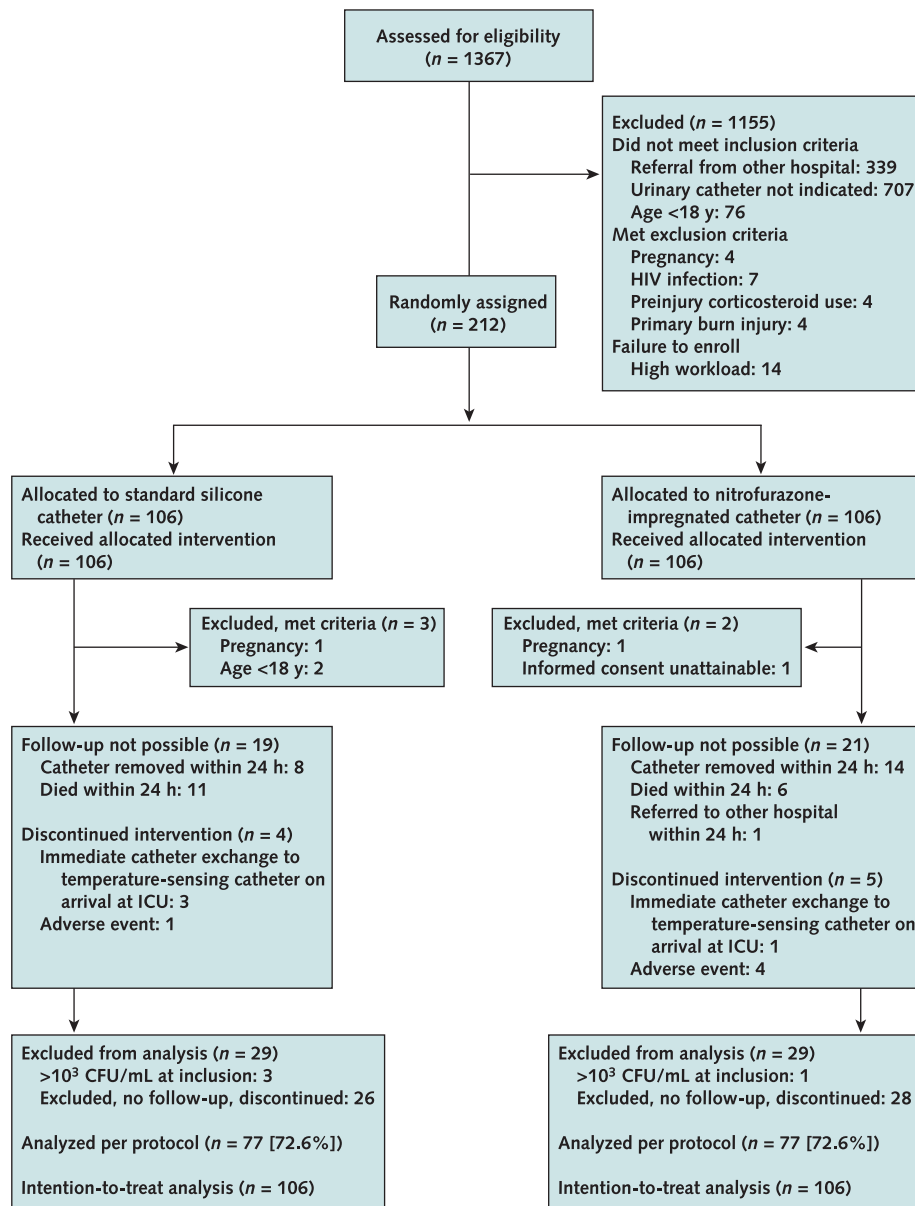
All catheterizations were performed according to standard hospital guidelines. The patient's genitals were washed with water and soap (Cutan Skin Care System, DEB, Belper, United Kingdom), sterile gloves and aseptic insertion technique were used, sterile antiseptic gel (Instil-lagel [lidocaine 2%, chlorhexidine 0.25%], Farco-Pharma, Köln, Germany) was inserted into the urethra, and isotonic sodium chloride was used to fill the balloon. Finally, the catheter was connected to a urine bag with an antireflux valve (UnoMeter, Unomedical A/S, Birkerød, Denmark) forming the closed drainage system. Adhesive tape was used to assess whether the system had remained unbroken. The size of the catheter used was determined by clinical evaluation; catheters were available in sizes 12 to 16 French. Catheters were removed at the treating physician's discretion as soon as permitted by the patient's condition.

Outcomes and Follow-up

The primary outcome variable was the incidence of catheter-associated bacteriuria and funguria (CABF), defined a priori as bacteriuria or funguria with at least 10^3 colony-forming units (CFU)/mL for at least 1 isolate, regardless of whether the patients experienced symptoms. The primary outcome variable was chosen as a surrogate end point for catheter-associated UTI. In addition, a post hoc analysis was done with CABF defined as at least 10^5 CFU/mL.

A urine sample for culture was taken immediately after catheter insertion and then daily until the catheter was removed. Aseptic 5-mL urine samples were taken by syringe aspiration from the sampling port without violating the closed drainage system. Samples were immediately refrigerated at 4 °C and were subsequently transferred to the laboratory as quickly as possible. On arrival in the laboratory, 1 μ L and 10 μ L of urine were cultivated on 5% horse blood agar plates and on McCoy agar plates (Statens Serum Institut, Copenhagen, Denmark) for the culture quantitative analysis. The procedure is standard at the lab-

Figure 1. Study flow diagram.



CFU = colony-forming unit; ICU = intensive care unit.

oratory, and the technicians were blinded to the type of catheter used. After incubation at 37 °C, the plates were inspected for growth and the number of CFU was calculated. Bacteria and fungi were identified by the automatic ATB Expression using the API identification system (bioMérieux, Marcy l'Étoile, France). Antibiotic sensitivity testing was performed by using Neo-sensitab (Rosco A/S, Taastrup, Denmark). The microbiologist evaluating the urine cultures was blinded to the type of catheter used. Blinded data were entered into the electronic database at the Department of Clinical Microbiology, and the treating physician was informed of the culture results. Decisions

regarding antimicrobial therapy were at the treating physician's discretion.

All patients were assessed daily by the investigators to ensure correct catheter assignment in enrolled patients, to ascertain whether enrolled patients still had the study catheter in place, and to determine whether the closed system had remained unbroken. If the closed system had been violated or the study catheter had been removed, results from subsequent urine samples were not included in the final analysis.

In addition, demographic characteristics, clinical variables, Injury Severity Score (ISS), and 30-day survival were

Table 1. Characteristics of Catheterized Trauma Patients

Characteristic	Silicone Catheter Group (n = 103)	Nitrofurazone Catheter Group (n = 104)
Median age (interquartile range), y	43.0 (30.0–56.0)	41.0 (28.0–54.5)
Women, n (%)	21 (20.4)	27 (26.0)
Median Injury Severity Score (interquartile range)	17.0 (9.0–29.0)	15.5 (9.0–26.5)
Preinjury comorbid conditions, n (%)		
Diabetes	1 (0.98)	1 (0.96)
Cardiac disease	2 (1.9)	1 (0.96)
Urologic disease	0	0
Urine cultures, n	577	613
Catheter-days		
Total	492	509
Median (interquartile range)	2.0 (0.0–7.0)	3.0 (0–8.0)
Duration of catheterization, n (%)		
0–1 d	26 (25.2)	27 (26.0)
1–6 d	49 (47.6)	49 (47.1)
7–14 d	20 (19.4)	21 (20.2)
>14 d	8 (7.8)	7 (6.7)
Systemic antimicrobial agents used in the first 3 days, n (%)		
None	11 (10.7)	17 (16.4)
Cefuroxime, 1.5 g 3 times daily, intravenously	11 (10.7)	13 (12.5)
Ceftriaxone, 2 g twice daily, and metronidazole, 500 mg 3 times daily, intravenously	81 (78.6)	74 (71.1)

recorded. The ISS is based on anatomical evaluation of the injury severity and was calculated according to the method of Baker and colleagues, with use of the 1998 update (13). The scores range from 0 (no injury) to 75 (unsurvivable injury), and a value greater than 15 indicates severe injury. It correlates linearly with mortality, morbidity, and length of hospital stay (13, 14).

Statistical Analysis

We expected 20% of catheterized trauma patients to develop CABF. On the basis of 80% power to detect a 65% reduction in the incidence of CABF in the nitrofurazone group, with a significance level of *P* less than 0.05 (2-sided), the required sample size was 200 patients. We therefore planned to enroll 212 patients to compensate for dropouts.

Data are presented as proportions or medians with interquartile ranges. We compared results by using regression models (log-binomial, log-binomial [negative], log-Poisson approximation to log-binomial), Fisher exact tests, or Mann–Whitney U tests, as appropriate.

For the prespecified primary analysis (per protocol), patients were excluded if 1 of the following criteria was fulfilled: removal of catheter within 24 hours after insertion, failure to obtain a follow-up urine sample after 24 hours, and bacteriuria or funguria (colonization $\geq 10^3$ CFU/mL) at admission.

To examine the effects of loss to follow-up, we performed an intention-to-treat analysis with a multiple imputation approach under the missing-at-random assumption. We used logistic regression imputation (implemented in PROC MI and MIANALYZE [SAS software, SAS Institute, Cary, North Carolina]), with catheter type as an explanatory factor variable and adjusted for sex, age, and an

offset term for catheter-days in a log-Poisson approximation to log-binomial regression model.

Furthermore, sensitivity analyses that included all randomly assigned patients were carried out with the assumption of no CABF for missing values, as well as assumptions for “best case” (no patients in the nitrofurazone group with missing data had CABF; all patients in the silicone group with missing data had CABF) and “worst case” (all patients in the nitrofurazone group with missing data had CABF; no patients in the silicone group with missing data had CABF).

We assessed the effect of catheter type on the onset time of CABF by Kaplan–Meier analysis that used the log-rank test and a Cox proportional hazards model that included sex and age as explanatory variables. For the Cox proportional hazards model and the logistic regression model, deviance residuals were plotted against each of the 3 covariates. From the plots, it appears that the data were fitted adequately by the models.

All statistical analyses were performed by using SAS software, version 9.1. A *P* value less than 0.05 (two-sided) represented a statistically significant difference.

Role of the Funding Source

No funding agency had any role in the design or conduct of the study or in the collection, management, or statistical analysis of the data. All authors handled and interpreted the data. The nitrofurazone-impregnated catheter was manufactured by Rochester Medical Corporation (Stewartville, Minnesota). At the time of the study and preparation of this manuscript, Coloplast A/S had distribution rights for the catheter worldwide, with the exception of the United States, Canada, Korea, and Turkey. Coloplast A/S donated all the catheters used in this study.

Table 2. Clinical Variables in Patients 2 Days before and on the Day of Confirmed Catheter-Associated Bacteriuria and Funguria*

Variable	Silicone Catheter Group (n = 19)		Nitrofurazone Catheter Group (n = 7)		P Value for Difference in Change between Groups†
	2 d before Day of First Positive Urine Culture	Day of First Positive Urine Culture	2 d before Day of First Positive Urine Culture	Day of First Positive Urine Culture	
Temperature, °C	37.6 (37.0–38.0)	38.0 (37.7–38.2)	37.0 (36.7–37.3)	37.5 (37.0–38.0)	0.42
Heart rate, beats/min	80.5 (79.0–90.0)	90.5 (85.0–97.0)	99.0 (89.0–100.0)	99.0 (89.0–101.0)	0.07
Leukocyte count, × 10 ⁹ cells/L	10.0 (9.2–14.0)	12.0 (10.0–15.0)	12.5 (10.3–14.5)	11.0 (10.0–11.0)	–‡

* Continuous variables are presented as median (interquartile range). Overall, 10.1% of data were missing.

† Calculated as the differences between values on the first day of positive urine culture minus the values 2 days before the day of first positive urine culture. P values were calculated by using the Mann–Whitney U test.

‡ Comparison not informative because leukocyte values were missing for all but 4 patients.

The submitted manuscript went through standard prepublication review at Coloplast A/S, and no changes were suggested.

RESULTS

Study Sample

A total of 212 patients were randomly assigned and allocated to either the standard silicone catheter group or the nitrofurazone catheter group (Figure 1). Five patients were enrolled despite not meeting eligibility criteria because they were misjudged at the assessment for eligibility (2 patients did not know they were pregnant, 2 patients were below the age limit, and 1 patient did not sign the informed consent form). These patients were excluded from the study as soon as the error was identified. Informed consent was obtained from next of kin for 45 of 212 patients. Trauma was caused by blunt injury in 89% of the cases and penetration injury in 11%, primarily resulting from traffic accidents (104 [49%]) and falls from a height (67 [32%]). Demographic and other characteristics were similar between the 2 groups (Table 1). The duration of catheterization did not exceed 35 days in either group.

Outcome Associated with Intervention

A total of 1190 urine cultures were obtained, covering 1001 catheter-days (Table 1). Table 2 lists clinical variables for patients who met the CABF end point at 2 days before the first positive culture and on the day of meeting the criterion for CABF. This analysis was done to evaluate whether CABF was affecting the clinical condition of the patients. Leukocytosis and increased heart rate and temperature were found at both time points, but the change in clinical variables did not significantly differ between groups. No urinary catheter-related bacteremia was seen during the study.

In the per-protocol analysis, the occurrence of CABF was significantly reduced in the nitrofurazone group compared with the silicone group (7 of 77 cases of CABF [9.1%] vs. 19 of 77 [24.7%]; adjusted relative risk, 0.31 [95% CI, 0.14 to 0.70]; P = 0.005), with no effect of age, sex, or catheter-days (Table 3). The incidence of CABF per 1000 catheter-days was 13.8 in the nitrofurazone group and 38.6 in the silicone group. In the post hoc analysis in which CABF was defined as at least 10⁵ CFU/mL, the occurrence of CABF was still significantly reduced in the

Table 3. Occurrence of Catheter-Associated Bacteriuria and Funguria in Trauma Patients*

Type of Analysis	Silicone Catheter Group, n/n (%)	Nitrofurazone Catheter Group, n/n (%)	Unadjusted Risk (95% CI)	Adjusted Risk (95% CI)	Adjusted P Value
Per-protocol, complete case analysis	19/77 (24.7)	7/77 (9.1)	0.37 (0.16–0.83)†	0.31 (0.14–0.70)‡	0.005
Post hoc per-protocol, CABF definition set at >10 ⁵ CFU/mL	15/77 (19.5)	5/77 (6.5)	0.33 (0.13–0.87)†	0.29 (0.11–0.78)‡	0.014
Intention-to-treat, multiple imputations	20–40/106§	7–19/106§	0.55 (0.35–0.88)§	0.30 (0.12–0.73)	0.008
Sensitivity analyses					
Assuming no CABF	19/106 (17.9)	7/106 (6.6)	0.37 (0.16–0.84)†	0.32 (0.14–0.71)‡	0.005
Assuming best case	48/106 (45.3)	7/106 (6.6)	0.15 (0.07–0.31)†	0.13 (0.06–0.28)‡	<0.001
Assuming worst case	19/106 (17.9)	36/106 (34.0)	1.89 (1.17–3.08)†	1.85 (1.06–3.24)‡	0.03

* Occurrence of CABF was calculated according to the prespecified analysis (per protocol, with exclusion of patients who had removal of catheter within 24 h after insertion, failure to obtain a follow-up urine sample after 24 h, or bacteriuria or funguria [$>10^3$ CFU/mL] at admission) or sensitivity analyses with missing values for all randomly assigned patients handled in 3 different ways. CABF = catheter-associated bacteriuria and funguria; CFU = colony-forming unit.

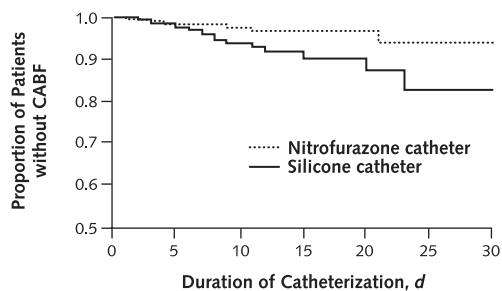
† Log-binomial regression model.

‡ Log-Poisson approximation to log-binomial regression model with sex, age, and an offset term for catheter-days (number of catheter-days for each individual) as explanatory variables.

§ Multiple imputation approach under the missing-at-random assumption.

|| Multiple imputation, log-Poisson approximation to log-binomial regression model with sex, age, and an offset term for catheter-days (number of catheter-days for each individual) as explanatory variables.

Figure 2. Onset of catheter-associated bacteriuria and funguria (CABF) in trauma patients, by type of urinary catheter.



Patients at risk, n	0	5	10	15	20	25	30
Nitrofurazone group	77	45	18	7	6	3	1
Silicone group	77	42	16	7	5	2	1

$P = 0.01$, log-rank test.

nitrofurazone group compared with the silicone group (Table 3).

Figure 2 shows the onset time of CABF by type of indwelling urinary catheter during 30 days of catheterization. The onset of CABF was significantly delayed in the nitrofurazone group ($P = 0.01$, log-rank test). Along with the simple log-rank test, we applied a Cox proportional hazards model that included the baseline variables of sex and age as explanatory variables. We found a hazard ratio of 3.17 ($P = 0.01$) for test of treatment effect, with no effect of age or sex.

A statistically significant correlation was found between ISS and the duration of catheterization ($r = 0.44$; $P < 0.001$, Spearman rank-correlation). Patients with severe injury (ISS > 15) were catheterized significantly longer than patients with mild injury (6.5 days [interquartile range, 3.0 to 9.5 days] vs. 3.0 days [interquartile range, 1.0 to 5.0 days]; $P < 0.001$, Mann-Whitney U test).

Intention-to-Treat Analysis

We investigated the potential effect of loss to follow-up by using an intention-to-treat analysis with a multiple imputation approach under the missing-at-random assumption. The estimated adjusted risk was 0.30 (CI, 0.12 to 0.73; $P = 0.008$). The sensitivity analyses included all 212 randomly assigned patients, although follow-up urine cultures were unavailable for 29 patients in each group (Table 3).

Microbiological Characteristics

Table 4 shows the distribution of urine isolates from patients with CABF. Apart from the reduction in the number of isolates, the distribution was similar in the 2 groups, including the proportion of cultures positive for multiple or single organisms.

Nitrofurantoin resistance was found in 3 isolates in the nitrofurazone group (1 with *Pseudomonas aeruginosa* and 2

with *Candida* species) compared with 7 in the silicone group (1 with *Enterobacter* species, 5 with *Candida* species, and 1 with *Enterobacter* species and *Candida* species).

Among the positive isolates, all urine cultures were processed within 24 hours of sampling (61% within 2 hours, 36% within 12 hours, and 3% within 12 to 24 hours).

Secondary Outcomes

Table 5 shows the secondary outcomes. Length of stay in the intensive care unit or hospital did not significantly differ between the 2 groups, nor did 30-day mortality. All patients except 1 had the study catheter removed as a consequence of CABF. Furthermore, CABF led to new or changed antimicrobial therapy in 5 of 7 patients (71.4%) in the nitrofurazone group and in 18 of 19 patients (94.7%) in the silicone group. No other patients were treated for presumed UTI during the study; thus, the proportion of patients treated for UTI was 5 of 104 (4.8%) in the nitrofurazone group and 18 of 103 (17.5%) in the silicone group.

Table 4. Organisms Isolated from Urine in Trauma Patients with Catheter-Associated Bacteriuria and Funguria*

Organism	Silicone Catheter Group (n = 77)	Nitrofurazone Catheter Group (n = 77)
Single organism		
<i>Enterococcus</i> species		
≥10 ³ CFU/mL	2	0
≥10 ⁴ CFU/mL	0	1
≥10 ⁵ CFU/mL	6	2
<i>Escherichia coli</i>		
≥10 ⁵ CFU/mL	2	0
<i>Candida</i> species		
≥10 ⁵ CFU/mL	3	2
Coagulase-negative staphylococci		
≥10 ⁴ CFU/mL	1	0
≥10 ⁵ CFU/mL	1	0
<i>Corynebacterium</i> species		
≥10 ⁴ CFU/mL	0	1
<i>Pseudomonas aeruginosa</i>		
≥10 ⁵ CFU/mL	0	1
Single organism total	15	7
Polymicrobial		
<i>Enterobacter</i> species ≥10 ³ CFU/mL	1	0
<i>Candida</i> species ≥10 ⁵ CFU/mL	0	0
<i>Enterococcus</i> species ≥10 ⁴ CFU/mL	1	0
<i>Candida</i> species ≥10 ⁵ CFU/mL	0	0
<i>Corynebacterium</i> species ≥10 ⁴ CFU/mL	1	0
<i>Candida</i> species ≥10 ⁴ CFU/mL	0	0
<i>Enterobacter</i> species ≥10 ⁵ CFU/mL	1	0
<i>Escherichia coli</i> ≥10 ⁵ CFU/mL	0	0
Polymicrobial total	4	0
Single organism and polymicrobial total	19	7

* Data are the number of patients. The presented organism concentration is from the first urine sample for a given patient that meets the prespecified catheter-associated bacteriuria and funguria criterion of ≥10³ CFU/mL. Four patients had asymptomatic bacteriuria at placement of the catheter (*Escherichia coli* concentration >10⁵ CFU/mL) and were excluded from the per-protocol analysis. CFU = colony-forming unit.

Table 5. Secondary Outcomes

Outcome	Silicone Catheter Group (n = 103)	Nitrofurazone Catheter Group (n = 104)	Unadjusted Risk (95% CI)	Adjusted Risk (95% CI)	Adjusted P Value
Median length of stay in intensive care unit (interquartile range), d	1.0 (0–3.0)	1.0 (0–4.0)	0.95 (0.54–1.65)*	1.12 (0.56–2.23)†	0.74
Median hospital length of stay (interquartile range), d	8.5 (2.0–14.0)	7.0 (3.0–13.0)	1.09 (0.68–1.75)*	1.07 (0.63–1.81)†	0.81
30-day mortality, n (%)	18 (17.5)	16 (15.4)	0.89 (0.48–1.65)‡	1.14 (0.64–2.04)§	0.65
New or changed antimicrobial therapy, n (%)	18 (17.5)	5 (4.8)	0.28 (0.11–0.72)‡	0.27 (0.10–0.69)§	0.006

* Log-binomial (negative) regression model.

† Log-binomial (negative) regression model with sex, age, and an offset term for catheter-days (number of catheter-days for each individual) as explanatory variables.

‡ Log-binomial regression model.

§ Log-binomial regression model with sex and age as explanatory variables.

Adverse Events

None of the 34 deaths were related to the use of indwelling catheters. Seven adverse events (6 in the nitrofurazone group and 1 in the silicone group; $P = 0.1$, Fisher exact test) were categorized as being related to the use of an indwelling catheter but not to the type of catheter or material. In 5 cases (4 in the nitrofurazone group and 1 in the silicone group), the balloon was inflated with a misplaced catheter, which led to bleeding and a need to insert a new catheter. There was 1 case of a false passage (nitrofurazone group), with subsequent insertion of a suprapubic catheter, and 1 case of difficult catheter removal due to ridging of the balloon (nitrofurazone group). None of these patients had additional morbidity or increased duration of hospitalization.

DISCUSSION

This double-blind, randomized, controlled clinical trial demonstrated a significant reduction of CABF in patients who had nitrofurazone catheters compared with those who had standard silicone catheters. The reduction was apparent after only a few days and lasted throughout the first 30 days of catheterization.

Two published studies investigated the effect of nitrofurazone catheters. One compared the nitrofurazone catheter with a latex catheter in various postoperative patients, with 50 patients in each group (15), and indicated a protective effect of the nitrofurazone catheter. The other compared the nitrofurazone catheter with a silicone catheter in a mixed group of 177 medical and surgical patients. A protective effect of the nitrofurazone catheter was apparent only in a subgroup analysis (16). In the latter study, the sex distribution and duration of catheterization were skewed. Both studies leave uncertainty about key methodologic issues, such as randomization, blinding, control, and post hoc analysis. A randomized, double-blind study reported only in abstract form included 344 patients and compared the nitrofurazone catheter with a silicone catheter. The nitrofurazone catheter significantly reduced the incidence of bacterial catheter-associated UTI but not the incidence of catheter-associated UTI overall. The authors concluded

that the nitrofurazone catheter can provide substantial protection against catheter-associated UTI, at least for the short term (17). It is difficult to compare these results with ours without details of patient eligibility and evaluability or antimicrobial therapy. In a recent systematic review of the efficacy of antimicrobial urinary catheters, Johnson and colleagues (18) identified the need for well-designed and adequately powered randomized trials reporting intention-to-treat analyses. They underlined the importance of well-characterized study samples and settings as well as transparent reporting of patient flow.

To our knowledge, our study is the first to incorporate these requirements into the design. The sample consisted of otherwise-healthy, consecutively catheterized trauma patients who received standardized catheter care and protocol-based antibiotic therapy. We studied 2 comparable silicone catheters that differed only by nitrofurazone impregnation. Furthermore, microbial surveillance was based on systematically collected urine samples, and the outcome was assessed according to predefined criteria. Although 58 of 212 enrolled patients were not included in the per-protocol analysis, the number of missing values was similar in the 2 groups, and all exclusions were prespecified in the study protocol. For 39 of 58 exclusions, urine samples were unavailable 24 hours after catheter insertion, either because the patients died or a catheter was no longer needed. The preventive effect of the nitrofurazone catheter was confirmed by the intention-to-treat analysis as well as by sensitivity analyses for missing values. In the worst-case analysis, the nitrofurazone catheters increased the risk for CABF, showing that the magnitude of the preventive effect of nitrofurazone catheters varies by the assumptions made about the outcome in patients who did not complete 24-hour follow-up. However, neither the best-case nor the worst-case analysis is likely. Patients who died within 24 hours were unlikely to all have been CABF positive had they lived until the 24-hour sample was taken, and the patients who did not need catheterization beyond 24 hours had sustained only minor injury. We therefore suggest that the effect of the nitrofurazone catheter lies somewhere between the 2 extremes, most likely closer to the per-protocol

and intention-to-treat analyses. Slightly more women were in the nitrofurazone catheter group. However, this did not bias the result because neither the log-binomial nor the Cox proportional hazards model showed any effect of sex. Furthermore, female sex is generally considered to be a risk factor for UTI.

A possible limitation of our study lies in the chosen primary outcome measure. We used the new appearance of bacteriuria or funguria with a concentration of at least 10^3 CFU/mL, with no requirement for reported symptoms as a surrogate end point for catheter-associated UTI, because trauma patients often have altered mental status; thus, patient-reported symptoms are not always available or reliable. Asymptomatic bacteriuria or funguria is a reasonable surrogate end point since it is part of the main causal pathway between catheter use and infection. It has previously been used (19–28) and is an objective measure independent of the trauma patient's ability to report symptoms.

We also evaluated whether length of stay, mortality, or a change in clinical variables could suggest a clinical impact of CABF. We found no statistically significant differences in length of stay or in mortality between groups. Clinical variables showed signs of a systemic inflammatory response both before and at the time of CABF. In a comparison of the changes in clinical variables before and after positivity for CABF, temperature, heart rate, and leukocyte count increased only moderately. These changes tended to be more pronounced in the silicone group for the latter 2 variables, but the clinical importance is probably limited.

In our study, CABF led to removal of the study catheter and new or changed antimicrobial therapy in most patients. In our hospital, trauma patients are under microbial surveillance, with urine cultures routinely performed twice a week and when clinically indicated. The primary outcome of CABF was therefore clinically relevant because it is normal hospital practice in cases of confirmed bacteriuria ($\geq 10^3$ CFU/mL) to remove the catheter and consider giving antibiotics.

The level of bacteriuria that should be used as the threshold definition for catheter-associated UTI has been debated in the literature; however, studies show that once bacteria have been isolated from urine at a concentration of at least 10^3 CFU/mL, the concentration increases to at least 10^5 CFU/mL within 24 to 48 hours (19, 22, 24, 29). The effect of the nitrofurazone catheter in a post hoc analysis that set the threshold for CABF at 10^5 CFU/mL was the same as the result obtained in the analysis that used the prespecified CABF definition. A 2006 systematic review found no studies comparing different antimicrobial catheters (18), so possible differences in efficacy between nitrofurazone-impregnated and other catheters, such as silver alloy-coated catheters, are unknown. The cost of nitrofurazone-impregnated and silver alloy-coated catheters is similar and 2 to 4 times that of a standard silicone indwelling catheter.

One concern about using antibacterials in catheter ma-

terials is related to antibiotic-resistant bacteria, which are the obvious disadvantage of systemic antibiotic prophylaxis (30, 31). In this study, the pattern of bacterial pathogens associated with CABF did not differ between the groups, although this could be anticipated from in vitro evidence (10). The occurrence of *Candida* or *Pseudomonas* species, which are intrinsically resistant to nitrofurazone, did not significantly increase (9, 11). The observed incidence and pattern of pathogens associated with CABF were similar to those in comparable groups—the same high proportion received antibiotic therapy (28, 32–34). In addition, nitrofurazone is not absorbed to the surrounding tissue or systemically (35). Thus, the risk for bacterial resistance with use of nitrofurazone catheters seems minimal.

In conclusion, we found that the incidence of CABF was lower in adult trauma patients when nitrofurazone-impregnated urinary catheters were used and that this reduced incidence was associated with a decreased need to change or prescribe new antimicrobial therapy. Use of nitrofurazone-impregnated catheters should therefore be considered in trauma patients. Whether a beneficial effect is also present in other patients needing indwelling urinary catheters is not known. This should be assessed in a randomized clinical trial.

From Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; Coloplast A/S, Humlebaek, Denmark; and Aarhus University Hospital, Aarhus, Denmark.

Acknowledgments: The authors thank the laboratory personnel at the Department of Clinical Microbiology, Rigshospitalet, and the trauma teams, for making this study possible. They also thank Søren Nyman Lophaven, PhD, for expert statistical assistance. They are indebted to the participants and their relatives.

Grant Support: By an unrestricted research grant to Jakob Stensballe from Coloplast A/S and grants from the Foundation in Commemoration of Holger and Ruth Hesse (Copenhagen); the Danish Hospital Foundation for medical research, region of Copenhagen, The Faroe Islands and Greenland; and H:S Research Committee, Copenhagen.

Potential Financial Conflicts of Interest: *Employment:* D. Looms (Coloplast A/S). *Grants received:* J. Stensballe (Coloplast A/S).

Requests for Single Reprints: Jakob Stensballe, PhD, Department of Anesthesia, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark; e-mail, jakob.stensballe@rh.regionh.dk.

Current author addresses and author contributions are available at www.annals.org.

References

- Burke JP. Infection control—a problem for patient safety. *N Engl J Med*. 2003;348:651–6. [PMID: 12584377]
- Warren JW, Platt R, Thomas RJ, Rosner B, Kass EH. Antibiotic irrigation and catheter-associated urinary-tract infections. *N Engl J Med*. 1978;299:570–3. [PMID: 210379]
- Claridge JA, Crabtree TD, Pelletier SJ, Butler K, Sawyer RG, Young JS.

- Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma*. 2000;48:8-14; discussion 14-5. [PMID: 10647559]
4. Stillwell M, Caplan ES. The septic multiple-trauma patient. *Infect Dis Clin North Am*. 1989;3:155-83. [PMID: 2647831]
 5. Papia G, McLellan BA, El-Helou P, Louie M, Rachlis A, Szalai JP, et al. Infection in hospitalized trauma patients: incidence, risk factors, and complications. *J Trauma*. 1999;47:923-7. [PMID: 10568723]
 6. Velmahos GC, Toutouzas KG, Sarkisyan G, Chan LS, Jindal A, Karaiskakis M, et al. Severe trauma is not an excuse for prolonged antibiotic prophylaxis. *Arch Surg*. 2002;137:537-41; discussion 541-2. [PMID: 11982465]
 7. Osborn TM, Tracy JK, Dunne JR, Pasquale M, Napolitano LM. Epidemiology of sepsis in patients with traumatic injury. *Crit Care Med*. 2004;32:2234-40. [PMID: 15640635]
 8. McOsker CC, Fitzpatrick PM. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. *J Antimicrob Chemother*. 1994;33 Suppl A:23-30. [PMID: 7928834]
 9. Guay DR. An update on the role of nitrofurans in the management of urinary tract infections. *Drugs*. 2001;61:353-64. [PMID: 11293646]
 10. Johnson JR, Berggren T, Conway AJ. Activity of a nitrofurazone matrix urinary catheter against catheter-associated uropathogens. *Antimicrob Agents Chemother*. 1993;37:2033-6. [PMID: 8239629]
 11. Johnson JR, Delavari P, Azar M. Activities of a nitrofurazone-containing urinary catheter and a silver hydrogel catheter against multidrug-resistant bacteria characteristic of catheter-associated urinary tract infection. *Antimicrob Agents Chemother*. 1999;43:2990-5. [PMID: 10582894]
 12. Advanced Trauma Life Support for Doctors. Student Course Manual. American College of Surgeons Committee on Trauma. Chicago: American Coll of Surgeons; 2005.
 13. Baker SP, O'Neill B, Haddon W Jr, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14:187-96. [PMID: 4814394]
 14. Lecky F, Woodford M, Yates DW. Trends in trauma care in England and Wales 1989-97. UK Trauma Audit and Research Network. *Lancet*. 2000;355:1771-5. [PMID: 10832827]
 15. Al-Habdan I, Sadat-Ali M, Corea JR, Al-Othman A, Kamal BA, Shriyan DS. Assessment of nosocomial urinary tract infections in orthopaedic patients: a prospective and comparative study using two different catheters. *Int Surg*. 2003;88:152-4. [PMID: 14584770]
 16. Lee SJ, Kim SW, Cho YH, Shin WS, Lee SE, Kim CS, et al. A comparative multicentre study on the incidence of catheter-associated urinary tract infection between nitrofurazone-coated and silicone catheters. *Int J Antimicrob Agents*. 2004;24 Suppl 1:S65-9. [PMID: 15364311]
 17. Maki DG, Knasinski V, Halvorson KT, Tambyah PA, Holcomb RG. A prospective, randomized, investigator-blinded trial of novel nitrofurazone-impregnated urinary catheter [Abstract]. *Infect Control Hosp Epidemiol*. 1997;18(Suppl):50.
 18. Johnson JR, Kuskowski MA, Wilt TJ. Systematic review: antimicrobial urinary catheters to prevent catheter-associated urinary tract infection in hospitalized patients. *Ann Intern Med*. 2006;144:116-26. [PMID: 16418411]
 19. Garibaldi RA, Mooney BR, Epstein BJ, Britt MR. An evaluation of daily bacteriologic monitoring to identify preventable episodes of catheter-associated urinary tract infection. *Infect Control*. 1982;3:466-70. [PMID: 6924646]
 20. Lipsky BA, Ireton RC, Fihn SD, Hackett R, Berger RE. Diagnosis of bacteriuria in men: specimen collection and culture interpretation. *J Infect Dis*. 1987;155:847-54. [PMID: 3559288]
 21. Stamm WE. Catheter-associated urinary tract infections: epidemiology, pathogenesis, and prevention. *Am J Med*. 1991;91:65S-71S. [PMID: 1928194]
 22. Stark RP, Maki DG. Bacteriuria in the catheterized patient. What quantitative level of bacteriuria is relevant? *N Engl J Med*. 1984;311:560-4. [PMID: 6749229]
 23. Tambyah PA, Halvorson KT, Maki DG. A prospective study of pathogenesis of catheter-associated urinary tract infections. *Mayo Clin Proc*. 1999;74:131-6. [PMID: 10069349]
 24. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. *Arch Intern Med*. 2000;160:678-82. [PMID: 10724054]
 25. Tambyah PA, Maki DG. The relationship between pyuria and infection in patients with indwelling urinary catheters: a prospective study of 761 patients. *Arch Intern Med*. 2000;160:673-7. [PMID: 10724053]
 26. Warren JW. Catheter-associated urinary tract infections. *Infect Dis Clin North Am*. 1997;11:609-22. [PMID: 9378926]
 27. Saint S, Lipsky BA. Preventing catheter-related bacteriuria: should we? Can we? How? *Arch Intern Med*. 1999;159:800-8. [PMID: 10219925]
 28. Riley DK, Classen DC, Stevens LE, Burke JP. A large randomized clinical trial of a silver-impregnated urinary catheter: lack of efficacy and staphylococcal superinfection. *Am J Med*. 1995;98:349-56. [PMID: 7709947]
 29. Tambyah PA, Knasinski V, Maki DG. The direct costs of nosocomial catheter-associated urinary tract infection in the era of managed care. *Infect Control Hosp Epidemiol*. 2002;23:27-31. [PMID: 11868889]
 30. Niël-Weise BS, van den Broek PJ. Urinary catheter policies for long-term bladder drainage. *Cochrane Database Syst Rev*. 2005;CD004201. [PMID: 15674931]
 31. Gupta K, Scholes D, Stamm WE. Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women. *JAMA*. 1999;281:736-8. [PMID: 10052444]
 32. Co-operative Group of the European Study Group on Nosocomial Infections. A European perspective on nosocomial urinary tract infections II. Report on incidence, clinical characteristics and outcome (ESGNI-004 study). European Study Group on Nosocomial Infection. *Clin Microbiol Infect*. 2001;7:532-42. [PMID: 11683793]
 33. Christensen M, Jepsen OB. Reduced rates of hospital-acquired UTI in medical patients. Prevalence surveys indicate effect of active infection control programmes. *J Hosp Infect*. 2001;47:36-40. [PMID: 11161896]
 34. Laupland KB, Zygun DA, Davies HD, Church DL, Louie TJ, Doig CJ. Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. *J Crit Care*. 2002;17:50-7. [PMID: 12040549]
 35. Marion-Landais G, Heotis JP, Mertz JL, Diaz JR, Van Hart DC, Newsom JH, et al. Non-absorption of nitrofurazone from the urethra in men. *Curr Ther Res Clin Exp*. 1976;19:550-3. [PMID: 820520]

Current Author Addresses: Dr. Stensballe: Department of Anesthesia, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.

Dr. Tvede: Department of Clinical Microbiology, Rigshospitalet, Copenhagen University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.

Dr. Looms: Coloplast A/S, 1 Holtedam, DK-3050 Humlebaek, Denmark.

Drs. Lippert and Rasmussen: Department of Anesthesia, Centre of Head and Orthopedics, Rigshospitalet, Copenhagen University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.

Dr. Dahl: Department of Orthopedic Surgery, Rigshospitalet, Copenhagen University Hospital, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.

Dr. Tønnesen: Department of Anesthesiology and Intensive Care, Aarhus University Hospital, 44 Nørrebrogade, DK-8000 Aarhus, Denmark.

Author Contributions: Conception and design: J. Stensballe, M. Tvede, F.K. Lippert, B. Dahl, E. Tønnesen, L.S. Rasmussen.

Analysis and interpretation of the data: J. Stensballe, M. Tvede, D. Looms, F.K. Lippert, B. Dahl, E. Tønnesen, L.S. Rasmussen.

Drafting of the article: J. Stensballe, M. Tvede, D. Looms.

Critical revision of the article for important intellectual content: J. Stensballe, M. Tvede, D. Looms, F.K. Lippert, B. Dahl, E. Tønnesen, L.S. Rasmussen.

Final approval of the article: J. Stensballe, M. Tvede, D. Looms, F.K. Lippert, B. Dahl, E. Tønnesen, L.S. Rasmussen.

Provision of study materials or patients: J. Stensballe.

Statistical expertise: J. Stensballe.

Obtaining of funding: J. Stensballe, F.K. Lippert.

Administrative, technical, or logistic support: J. Stensballe, B. Dahl, L.S. Rasmussen.

Collection and assembly of data: J. Stensballe, M. Tvede, F.K. Lippert.