

**A REPORT ON THE RANDOMIZED, CONTROLLED
CLINICAL TRIAL OF THE NITROFURAZONE-IMPREGNATED,
ANTIBACTERIAL, INDWELLING URINARY CATHETER**

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NOTICE

For patients with catheters inserted for 7 days or less (91.5% of the population, median=3 days), the group receiving the Release-NF Catheter had an approximate threefold reduction in the rate of bacterial CAUTI compared to the conventional silicone catheter group. (2.4% vs.6.9% incident). The difference in actuarial survival curves for the time until the occurrence of bacterial CAUTI, between the two groups was found to be statistically significant for the first five days of use.

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1.0 INTRODUCTION

This report summarizes the results of a large, randomized, controlled trial of a new antibacterial Foley catheter manufactured by Rochester Medical Corporation to control the occurrence of catheter-associated urinary tract infections (CAUTI) in patients requiring catheterization. The new catheter contains the broad-spectrum antibacterial compound, nitrofurazone, which is released gradually over a period of days into the boundary layer between the catheter body and urethral wall after insertion. The study enrolled a total of 344 evaluable patients at the University of Wisconsin-Madison in the period from October 17, 1995 to August 10, 1996. The patients, who required the use of an indwelling catheter because of trauma, surgical procedures or urinary incontinence, were randomly assigned to receive either the new antibacterial catheter or a standard silicone catheter. Although the overall incidence of catheter-associated urinary tract infections was lower than expected during the study compared to published and historical rates, which may be related to aggressive infection control measures in effect at the institution and the use of an all-silicone control catheter, the use of the antibacterial catheter still resulted in significantly fewer bacteria-related CAUTI events than were seen with the control catheter.

2.0 BACKGROUND

Nosocomial catheter-associated urinary tract infection (CAUTI) is the most common hospital-acquired infection in acute care hospitals, accounting for forty percent of all nosocomial infections [CDC (1986), Kunin and McCormack (1966), Stamm (1991), Warren (1991)]. It is estimated that up to one-half of patients receiving an indwelling urethral catheter for five days or longer may develop nosocomial bacteriuria [Kunin and McCormack (1966), Stark and Maki (1984), Garibaldi et al (1982)]. Catheter-associated urinary tract infection is a major cause of nosocomial blood stream infection [Maki (1981), Krieger et al (1983)]. Silent catheter-associated bacteriuria comprises an important reservoir of resistant organisms in the hospital, with spread to other patients on the same care units, particularly within Intensive Care Units. Studies by Platt and coworkers suggest that even though most cases of catheter-associated bacteriuria are asymptomatic, CAUTI appears to be associated with significantly increased mortality [Platt et al, 1982].

The major routes of CAUTI include organisms ascending in the mucous film between the external surface of the catheter and the urethra, thought to be most common in females, and contamination of urine in the collection bag, with retrograde ascent through the catheter lumen into the catheterized bladder [Stamm (1991), Warren (1991)]. It is known that the incidence of catheter-associated bacteriuria approaches 100 percent within several days in patients in which the drainage system is not maintained in a completely closed condition [Kunin et al, 1966].

A number of measures to prevent CAUTI have been examined in prospective trials, with the greatest success achieved by the use of sterile, closed urine drainage systems [Kunin et al (1966), Platt et al (1982), Stamm (1991), Warren (1991)]. Other measures, such as the daily application of antiseptic solutions or antiseptic ointments to the catheterized

meatus and perineum [Burke et al,1983], and the use of antiseptic solutions in the urine collection bag [Classen et al, 1991] have given disappointing results.

Considering that infected urethral catheters are covered by a dense biofilm containing large numbers of the infecting organisms embedded in a matrix of host proteins and microbial exudates [Nickel, Gristina et al, 1985] with the organisms in the biofilm exhibiting greatly increased resistance to antibiotics [Nickel, Ruseka et al, 1985], it has been hoped that the use of medicated catheters exhibiting antimicrobial activity at the catheter surface might reduce the risk of catheter-associated bacteriuria. Studies of silver-oxide coated catheters have yielded conflicting and generally disappointing results [Classen et al (1991), Schaeffer et al (1988), Johnson et al (1990), Liedburg and Lundeburg (1990), Liedburg, Lundeburg, and Ekman (1990)].

The subject of the current investigation was a newly developed antibacterial-coated catheter which incorporates the broad-spectrum antimicrobial agent nitrofurazone on the outer surface of a standard silicone urinary catheter. The catheter has shown *in vitro* inhibitory activity against most of the bacteria associated with CAUTI [Johnson et al, 1993]. Nitrofurazone is a nitrofuran derivative similar to the urinary antiseptic nitrofurantoin, both of which have been used worldwide for over 40 years. Its antimicrobial spectrum of activity includes most gram-positive and facultative gram-negative bacteria, with the exception of *Pseudomonas aeruginosa*. Nitrofurazone (Furan[®]) is formulated for topical use in burn wound therapy. There is no detectable systemic absorption of nitrofurazone for the urethra in men [Marion-Landais et al, 1976], nor the related Furan[®] from the vagina in women [Marion-Landais et al, 1975]. Adverse effects related to nitrofurazone use are uncommon (1.2%) and usually involve cutaneous reactions [Hooper and Covarrubias, 1983].

Organisms recovered for culturing during the study were identified and enumerated using standard techniques and criteria [Balows et al, 1992].

3.0 DESCRIPTION OF STUDY DEVICE

The Rochester Medical Corporation antibacterial catheter is an all silicone (Dow Corning Silastic[®] Medical Grade Elastomer) Foley catheter for continuous drainage of the bladder in incontinent subjects or patients with impaired voiding, and the monitoring of urine in hospitalized patients. It is available in sizes from 12 French (4 mm) to 20 French (7 mm). The attached retaining balloon (5 cc capacity), which is inflated with sterile water when positioned within the bladder, keeps the catheter in place until removed by the nurse or physician.

The outer wall and inner drainage lumen of the silicone catheter is impregnated with an antibacterial agent nitrofurazone (5-nitro-2-furaldehyde semicarbazone), which elutes from the catheter over a period of days when inserted within the urethra of a patient.

4.0 STUDY OBJECTIVES

The clinical study had the following specific objectives:

1. Comparison of the relative risk of catheter-associated urinary tract infections (CAUTI) between the antibacterial catheter group and a control group receiving a standard all-silicone Foley catheter
2. Comparison of the time to onset of CAUTI between the antibacterial and control catheter groups
3. Evaluation of the tolerance of the antibacterial and control catheters in study patients

5.0 STUDY DESIGN

The clinical study of the relative risks of developing a CAUTI event between the new antibacterial catheter and a standard silicone catheter was designed as a prospective, randomized, double-blind investigation, with enough patients enrolled to detect clinically significant differences in CAUTI outcomes between catheters.

5.1 Study Endpoints

The clinical investigation followed patients inserted with Foley-type catheters for the development of catheter-associated urinary tract infections (CAUTI). A CAUTI event in the study was defined as the presence of $\geq 10^3$ / ml colony forming units of infection organisms in patient urine (single type of organism or total for mixed population). The period of interest for comparison of the two catheters was the first 7 days post-insertion. This period represents the period of therapeutic release of the nitrofurazone into the urethral environment (estimated 80% reduction by day 5 in the daily amount of nitrofurazone released by the antibacterial catheter) and expected antimicrobial benefit. The period of 7 days is also expected to include the majority of patient catheterization times. In the present study 91.9% of evaluable patients had catheter insertion times of 7 days or less (median = 3 days).

Since the expected activity of the antibacterial catheter is against bacterial organisms which can cause urinary tract infections, the primary efficacy endpoint for the study was the occurrence, and associated onset time, for CAUTI events of bacterial origin.

A secondary efficacy endpoint for the study was the occurrence and onset times for CAUTI events which are of any origin, that is, catheter-associated urinary tract infections caused by bacterial, yeast or fungal agents. Although the antibacterial catheter was not expected to have any anti-yeast or anti-fungal activity, it was of interest to determine whether any reduction in the occurrence of bacterial infections comes at the cost of an increased risk of yeast/fungal infections.

The primary safety endpoint for the study was the occurrence of any complications or side-effects associated with the use of the antibacterial catheter, beyond either in type or frequency those which would be expected with ordinary Foley catheter use.

5.2 Control Population

The control population for the study will be those patients who are randomized to the group receiving a standard, silicone Foley catheter.

5.3 Study Hypotheses

The study objectives comparing the new antibacterial (New) and the control silicone (Control) Foley catheters can be formulated in the following testable hypotheses:

Endpoint 1: Risk of Bacterial CAUTI

H₀: The risk of developing a CAUTI of bacterial origin within 7 days of insertion is the same with the new antibacterial catheter as with the standard silicone catheter.

$$\text{Bacterial CAUTI Risk}_{\text{New}} = \text{Bacterial CAUTI Risk}_{\text{Control}}$$

H₁: The risk of developing a CAUTI of bacterial origin within 7 days is different for the antibacterial and standard silicone catheters.

$$\text{Bacterial CAUTI Risk}_{\text{New}} \neq \text{Bacterial CAUTI Risk}_{\text{Control}}$$

Endpoint 2: Risk of All CAUTI

H₀: The risk of developing a CAUTI from all infectious organisms (of bacterial, yeast or fungal origin) within 7 days of insertion is the same with the new antibacterial catheter as with the standard silicone catheter.

$$\text{All CAUTI Risk}_{\text{New}} = \text{All CAUTI Risk}_{\text{Control}}$$

H₁: The risk of developing a CAUTI from all infectious organisms within 7 days of insertion is different for the antibacterial and standard silicone catheters.

$$\text{All CAUTI Risk}_{\text{New}} \neq \text{All CAUTI Risk}_{\text{Control}}$$

The difference in risk of developing a CAUTI between the two catheter groups (Risk_{New} versus Risk_{Control}) for both Bacterial infections and All Infections will be evaluated using four statistical methods: Association (incidence), Kaplan-Meier survivorship (no adjustment for possible covariates), Logistic regression (adjustment for covariates but not survivorship), and Cox regression (survivorship with covariate adjustment).

Endpoint 3: Complications Associated with Use of the Catheters

H₀: The risk of having a complication is the same with the new antibacterial catheter as with the standard silicone catheter.

$$\text{Complication Rate}_{\text{New}} = \text{Complication Rate}_{\text{Control}}$$

H₁: The risk of having a complication is different for the antibacterial and standard silicone catheters.

$$\text{Complication Rate}_{\text{New}} \neq \text{Complication Rate}_{\text{Control}}$$

5.4 Randomization

Patients meeting the inclusion and exclusion criteria for enrollment and giving Informed Consent were randomized in a 1:1 assignment to either receive the new antibacterial or standard silicone Foley catheter.

5.5 Blinding

The clinical trial can be considered a double-blind design, in that neither the patient nor physician investigator evaluating CAUTI event outcomes were aware of the type of catheter used. Although patients were unaware of the catheter group assignment, it is not likely that patients in this study could have biased the diagnosis of urinary tract infections with that knowledge. While hospital staff personnel inserting the catheters were aware of the type of catheter being used, importantly, the investigator responsible for assessing CAUTI events was masked as to the treatment group assignment.

5.6 Sample Size

It was estimated based on published rates and historical data at the University of Wisconsin that approximately 25% of the control catheters would be associated with nosocomial CAUTI. Assuming a Type I error (α) of 0.05 (two-tailed) and a statistical power of 80%, it was estimated that a total of 350 evaluable patients would be required (175 per treatment group) to detect a 50% difference in rates between the two groups (i.e., 25% for control catheter versus 12.5% for antibacterial catheter) [see Lee ET (1980); Snedecor GW and Cochran WG (1978)].

To account for those patients who would be lost to evaluation (catheter withdrawn within first 2 days), it was estimated that a total of 500 patients would need to be enrolled to obtain an evaluable study population of 350.

5.7 Data Analysis Methods

Summary statistics were calculated for all study variables collected. These statistics included estimates of means, standard deviations, standard errors, and ranges for all continuous variable, and frequency distributions for categorical variables. In some cases, for purposes of analysis, new dichotomous variables were created from existing variables by defining two groups based on the median values of the observations.

The association of individual patient risk factors or prognostic variables to the CAUTI events were evaluated using Chi-square or Fisher's Exact tests in the case of categorical variables or Student's t-tests for continuous variables. Variables exhibiting p-values of 0.20 or less for association with the CAUTI outcomes in these univariate tests were selected as candidates for inclusion in further multivariate analyses.

Several different analysis approaches were utilized to identify important predictive variables for the development of CAUTI and to evaluate the role of the treatment groups in the presence of these factors:

1. A Kaplan-Meier actuarial analysis was performed first, to evaluate the difference in survival curves (freedom from CAUTI) between the two treatment groups. This difference was tested with the standard logrank test statistics. The Kaplan-Meier method explores the time-dependent nature of the occurrence of infections, but assumes a balance between the two groups in the effects of potentially important covariates, and does not explicitly control for them.
2. A stepwise, logistic regression was then performed to determine the role of the catheter type in the development of CAUTI, after adjusting for the effects of other covariates. This approach allows for the evaluation of the relative importance of the antibacterial and control catheters in CAUTI, while controlling for the impact of other factors. Although the logistic regression does not effectively incorporate the possible time-dependent nature of the CAUTI events, it was used to further evaluate the independent contribution of those covariates identified previously in the univariate tests.
3. In the last type of multivariate analysis, a Cox regression was performed which incorporated both the actuarial nature of the CAUTI events and the role of covariates in their development. This approach allowed both a test of the significance of the type of catheter used in the occurrence of CAUTI, and the relative risk reduction for the antibacterial catheter, if present.

The comparison of the frequency of complications between the two catheter groups, for the evaluation of the safety endpoint, was evaluated with the Fisher's Exact test.

6.0 STUDY PROTOCOL

The following elements were contained in the investigational plan for the study:

6.1 Investigational Site

The study was conducted at single site, the University of Wisconsin Medical Center in Madison, under the direction of Dennis G. Maki MD, Professor of Medicine, and Head of the Section of Infectious Diseases. The principal investigator Dr. Maki is a well-known and published researcher in the area of infectious disease control, and has participated in the development and conduct of previous investigations of nosocomial urinary tract infections. Use of this clinical center enabled the study to enroll a patient population from both urban and rural environments, and utilize a research and support staff familiar with the investigation of urinary tract infections and identification of related risk factors.

6.2 Patient Selection

The following inclusion and exclusion criteria were used to qualify candidate subjects for enrollment in the investigation:

Inclusion Criteria

1. Subject at least 18 years of age
2. Scheduled to receive 16 Fr or 18 Fr Foley catheter
3. Expected catheterization for 24 hours or longer

Exclusion Criteria

1. Unable to obtain Informed Consent, or prisoners
2. Pregnancy
3. Allergic to silicone, nitrofurazone or nitrofurantoin

6.3 Catheter Assignment

After an evaluation to determine that candidate patients met the enrollment criteria and Informed Consent was obtained, patients were randomized to either the antibacterial catheter group or control silicone catheter group, and the catheter was inserted.

6.4 Study Variables

Upon enrollment into the study baseline patient and medical history data bearing on the risk of development of CAUTI were collected. During the study, occurrence and onset time of CAUTI events, types and counts of organisms recovered, concurrent antibiotic therapy, patient symptoms, and evidence of urine drainage system integrity were also recorded for each patient. Specific variables included by category were:

Demographic

- Age
- Gender
- Height
- Weight

Medical History

- Urinary tract infection at enrollment
- Number of previous catheters inserted
- Hospital admission date
- Diabetes
- Insulin
- AIDS / HIV
- Structural abnormality of urinary tract
- Neoplastic disease
- Malnourishment
- Transplant recipient
- Pyelonephritis
- Urethritis
- Cystitis
- Apache Score (severity of illness index)

On entry into the study and daily thereafter, an aliquot of urine was aspirated from the newly-placed catheter for quantitative culture, using a recovery technique that can detect $< 10^2$ CFU per milliliter.

CAUTI Events

- Randomization assignment

- Time of catheter insertion \ removal
- CAUTI event occurrence (First 3 events)
- Organism types
- Onset times
- Bacterial counts (CFU's)

Hospital Care Unit

- Personnel inserting catheter
- Service care unit where catheter inserted
- Location of care unit where inserted
- Reasons for catheter insertion

Patient Symptoms / Treatment

- Mean and average body temperature for CAUTI patients
- Gauge of catheter used
- Stent in bladder
- Active infection at other site in body
- Antibiotics given
- Steroids
- Neutropenia
- Chemotherapy
- Diarrhea
- Surgery during catheterization
- Vulvitis
- Vaginitis
- Dysuria
- Urethral burning
- Voiding urgency
- Itching in area of catheter
- Urine white blood cell counts

As part of the study, a faint linear line was made across the catheter-collection tube junction at the outset and inspected each day. If there was a discontinuity of the line on follow-up, it was assumed that the collection system had been opened and that closed drainage had not been consistently maintained. The status of the closed drainage system will be used to quantify a risk of urinary tract infection from this external source of contamination.

Urine Drainage System

- Tamper evidence
- Irrigation
- Clamp integrity
- Catheter positioning
- Drainage tube position
- Urine bag position

- Drainage port exposure

7.0 DESCRIPTION OF STUDY POPULATION

The characterization of the patient population receiving one of the study catheters is described in the following sections.

7.1 Duration of Study

Patients were enrolled in the clinical evaluation over a 10 month period from October 17, 1995 to August 10, 1996.

7.2 Evaluable Patients

A total of 535 patients were screened for participation in the study. A total of 344 patients met the following criteria and were considered evaluable for analysis:

- CAUTI diagnosis made
- Catheter inserted for at least 24 hours
- No urinary tract infection at enrollment
- Catheter was first catheter inserted after admission
- Catheter was inserted during first 7 days of hospitalization

The reasons that patients were considered non-evaluable included the following:

- Informed Consent not obtained
- Catheter not inserted or inserted for less than 24 hours
- Urinary tract infection already present at enrollment
- Patient received non-study catheter
- Patient had prior catheterization, confounding risk of UTI development
- Patient hospitalized for longer than 7 days prior to catheter insertion, indicative of complicating patient injury \ illness status

7.3 Randomization

The numbers of evaluable patients assigned to the two catheter groups are given below in

Table 1. There was an approximately equal number of patients allocated to each study arm. The effectiveness of the randomization in balancing baseline factors is discussed in

Section 9.2 .

Table 1
Randomization Assignment

Catheter Group	Number (%)
<i>Antibacterial</i>	170 (49.4%)
<i>Standard Silicone</i>	174 (50.6%)
<i>Total</i>	344 (100.0%)

7.4 Demographics

The distribution of gender by catheter group is presented in Table 2.

Table 2
Gender by Catheter Group

Gender	Antibacterial Catheter (%)	Standard Catheter (%)
<i>Male</i>	123 (72.4%)	112 (64.4%)
<i>Female</i>	47 (27.6%)	62 (35.6%)
<i>Total</i>	170 (100.0%)	174 (100.0%)

There was a small but not statistically significant difference ($p = 0.132$, two-tailed, Fisher's Exact test) in the distribution of males and females in the two catheter groups. A somewhat higher proportion of females was enrolled in the standard catheter group. It is known that the risk of urinary tract infections differs for males and females, with females expected to experience higher incidence rates.

The age distribution of patients by catheter group is shown in Table 3.

Table 3
Age Distribution by Catheter Group

Age (years)	Antibacterial Catheter (%)	Standard Catheter (%)
<i>19-30</i>	18 (10.6%)	13 (7.5%)
<i>31-40</i>	22 (12.9%)	21 (12.1%)
<i>41-50</i>	23 (14.7%)	29 (16.7%)
<i>51-60</i>	23 (13.5%)	30 (17.2%)
<i>61-70</i>	44 (25.9%)	43 (24.7%)
<i>71-80</i>	31 (18.2%)	27 (15.5%)
<i>81-91</i>	7 (4.1%)	11 (6.3%)
<i>Total</i>	170 (100.0%)	174 (100.0%)

The mean age of patients was 55.25 years (SE 1.34) in the antibacterial catheter group and 56.62 years (SE 1.27) in the standard catheter group. The difference was not significant ($p = 0.458$, two-tailed, Student's t-test).

7.5 Patient Characteristics

Comparison of the numbers of patients with specific medical history conditions in the two catheter groups are displayed in Table 4 below. The difference in the percentages of patients between the groups was tested with Fisher's Exact test, and the resulting two-tailed p-values are given.

In examining the results in Tables 2 through 4 it can be seen that there were no statistically significant differences between the catheter groups in any of the baseline factors examined.

Table 4
Medical History by Catheter Group (% of Patients with Condition / Factor)

Condition / Factor	Antibacterial Catheter (%) (n = 170)	Standard Catheter (%) (n = 174)	P-value (2-tailed)
<i>Diabetes</i>	20.0%	27.7%	0.130
<i>Insulin</i>	12.9%	17.8%	0.234
<i>AIDS / HIV</i>	0 %	0.6%	1.000
<i>Structural abnormality</i>	0.6%	2.3%	0.372
<i>Neoplastic disease</i>	22.4%	22.4%	1.000
<i>Malnourishment</i>	23.5%	33.3%	0.056
<i>Transplant recipient</i>	18.8%	21.8%	0.506
<i>Pyelonephritis</i>	0%	2.3%	0.123
<i>Urethritis</i>	0.6%	0%	0.494
<i>Cystitis</i>	2.4%	3.4%	0.750

8.0 RESULTS THAT ADDRESS STUDY OBJECTIVES

The sections that follow present the observed results of CAUTI events in the two catheter groups, and the steps that were taken to evaluate the differences between the two groups in light of potentially important contributing risk factors.

8.1 Evaluation of Study Hypotheses

8.1.1 Frequency of CAUTI Endpoints

The incidence of CAUTI of bacterial origin is shown in Table 5.

Table 5

Bacterial CAUTI Within 7 Days by Catheter Group

Catheter Group	CAUTI	No CAUTI
<i>Antibacterial</i>	4 (2.4%)	166 (97.6%)
<i>Standard Silicone</i>	12 (6.9%)	162 (93.1%)
<i>Total</i>	16 (4.7%)	328 (95.3%)

There was an approximate three-fold risk ($6.9\%/2.4\% = 2.9$) of having a bacterial CAUTI in the standard silicone catheter group compared to the antibacterial catheter group, based on an examination of only the observed number of infections. This difference had an associated p-value of 0.070 (two-tailed, Fisher's Exact test).

The number of CAUTI events from any type of organisms by catheter group is presented in Table 6.

Table 6
All CAUTI Within 7 Days by Catheter Group

Catheter Group	CAUTI	No CAUTI
<i>Antibacterial</i>	8 (4.7%)	162 (95.3%)
<i>Standard Silicone</i>	14 (8.0%)	160 (92.0%)
<i>Total</i>	22 (6.7%)	322 (93.3%)

The rate of All CAUTI for the standard silicone catheter (8.0%) also exceeds that for the antibacterial catheter (4.7%). The p-value for this difference, however, did not reach statistical significance ($p = 0.271$, two-tailed, Fisher's Exact test).

8.1.2 Organisms Identified in CAUTI

The specific organisms recovered from the urine cultures for CAUTI infections within 7 days post-insertion are listed in Table 7. The organisms have been grouped to indicate those microorganisms for which nitrofurazone has shown antimicrobial activity based on *in vitro* testing [Johnson et al, 1993]. Because some patients had several organism types present, patient totals in Table 7 exceed those presented in Tables 5 and 6.

The frequencies of specific bacterial organisms in patients with CAUTI was greater in 6 of the 7 bacteria types in the group receiving the standard catheter than in the group receiving the antibacterial catheter. In the seventh, they were equal with one patient in each group having *Klebsiella pneumoniae*. For the yeast/fungal class of organisms, the overall frequencies were small and comparable between the two catheter groups (4 patients for the antibacterial catheter vs. 3 for the standard catheter; no patient with multiple yeast types).

Table 7
Number of Patients with CAUTI Organisms: Grouped by
Type for Which Nitrofurazone Has Shown Antimicrobial Activity

Organism	Antibacterial Catheter	Standard Catheter
1. Antimicrobial Activity		
<i>Corynebacterium species</i>	0	1
<i>Enterobacter cloacae</i>	1	3
<i>Escherichia coli</i>	0	2
<i>Enterococcus</i>	1	2
<i>Klebsiella pneumoniae</i>	1	1
<i>Staphylococcus negative</i>	1	4
2. No Antibacterial Activity		
Bacteria		
<i>Pseudomonas aeruginosa</i>	1	2
Yeast / Fungal		
<i>Candida albicans</i>	3	2
<i>Candida species</i>	1	1

8.1.3 Kaplan-Meier Survival Curves: Freedom from CAUTI

The Kaplan-Meier actuarial curves for bacterial infections and all infections within 7 days are displayed below in Figures 1 and 2. There was a statistically significant improvement in freedom from bacterial CAUTI for the 7 day period with use of the antibacterial catheter ($p = 0.007$, Breslow logrank statistic). Although comparable at the end of the 7 day period, there was a 97.55% estimated cumulative survival for the antibacterial catheter through day 5 post-insertion, compared to a 90.46% survival for the standard silicone catheter (Table 8 and 9). A total of 86.9% of patients had catheter insertion times of 5 days or less.

FIGURE 1

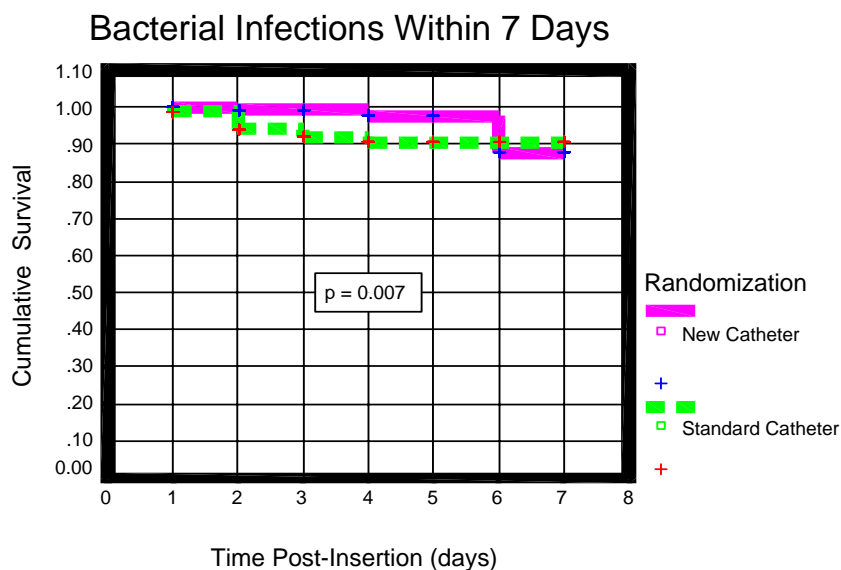


FIGURE 2

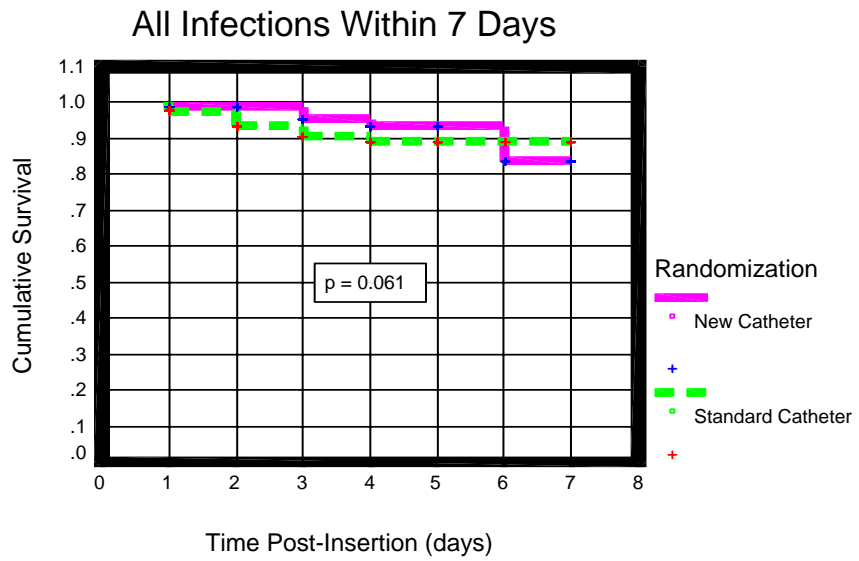


Table 8
Antibacterial Catheter: Freedom from Bacterial Infections

Day Post-Insertion	No. of Subjects	Cumulative Survival	SE
1	170	1.0000	0
2	141	0.9930	0.0070
3	84	0.9930	0.0070
4	56	0.9755	0.0186
5	26	0.9755	0.0186
6	19	0.8780	0.0675
7	13	0.8780	0.0675

Table 9
Standard Catheter: Freedom from Bacterial Infections

Day Post-Insertion	No. of Subjects	Cumulative Survival	SE
1	174	0.9885	0.0081
2	141	0.9398	0.0195
3	95	0.9202	0.0235
4	58	0.9046	0.0278
5	37	0.9046	0.0278
6	20	0.9046	0.0278
7	15	0.9046	0.0278

A similar result was obtained for the comparison of all CAUTI. The antibacterial catheter had an estimated cumulative survival curve that was better than the standard silicone catheter through day 5 post-insertion (Table 10 and 11, 95.37% versus 89.00%), although for the 7 day period the curves were borderline non-significant ($p = 0.061$, Breslow logrank statistic)

Table 10
Antibacterial Catheter: Freedom from All Infections

Day Post-Insertion	No. of Subjects	Cumulative Survival	SE
1	170	0.9882	0.0083
2	139	0.9882	0.0083
3	84	0.9534	0.0213
4	53	0.9357	0.0273
5	26	0.9537	0.0273
6	18	0.8372	0.0703
7	12	0.8372	0.0703

Table 11
Standard Catheter: Freedom from All Infections

Day Post-Insertion	No. of Subjects	Cumulative Survival	SE
1	174	0.9770	0.0114
2	139	0.9351	0.0199
3	94	0.9056	0.0256
4	57	0.8900	0.0295
5	35	0.8900	0.0295
6	19	0.8900	0.0295
7	14	0.8900	0.0295

8.1.4 Identification of Study Variables Correlated with CAUTI Events

An initial univariate examination of all study variables, baseline and treatment, which may have been risk factors for the development of CAUTI, was performed. This examination consisted of testing the association between the variable and the CAUTI result with either a Chi-square or Fisher's Exact test. Those variables which may have originally been continuous in nature (e.g., age) were dichotomized for this screening process.

A summary of the results of these examinations are presented in Table 12. Those variables which had an associated test statistic p -value of 0.05 or less for either bacterial infections or all infections are given. In addition to the statistical significance of the association, the prevalence of the risk factor in the study population and the relative risk ratio are also given. The relative risk ratio represents the percent of patients with the risk factor who have the CAUTI event, compared to the percent of patients without the risk factor who have the CAUTI event.

As can be seen in Table 12, there were a number of variables with a significant test of association with the CAUTI outcomes, many of which, undoubtedly, play a role in the development of CAUTI. These variables, together with other variables which had a test of association p-value of 0.20 or less were included in the multivariate analyses which follow. The multivariate procedures also provide a method of considering the correlation between risk factors, since it is known that the effect of some of the variables are reflecting the same underlying cause (e.g., the effect of gender and the presence of vulvitis or vaginitis).

Table 12
Study Variables Correlated with CAUTI Events

Variable	Prevalence (Risk Factor)	Bacterial Infection		All Infections	
		Risk Ratio	P-Value	Risk Ratio	P-Value
<i>Catheter</i>	50.6% (Std)	6.9 / 2.4	0.070	8.0 / 5.3	0.389
<i>Other Active Infect</i>	16.0% (Yes)	9.1 / 3.8	0.088	14.5 / 5.2	0.011
<i>Sex</i>	31.7% (F)	8.3 / 3.0	0.031	11.9 / 4.3	0.008
<i>Active Infection</i>	17.0% (Yes)	11.3 / 3.4	0.012	17.0 / 4.8	0.001
<i>Antibiotics Use</i>	6.7% (No)	21.7 / 3.4	0.000	21.7 / 5.6	0.028
<i>Surgery Patient</i>	17.7% (No)	21.3 / 1.1	0.000	24.6 / 2.8	0.000
<i>Vulvitis</i>	0.9% (Yes)	66.7 / 4.1	0.000	66.7 / 6.2	0.000
<i>Vaginitis</i>	0.6% (Yes)	50.0 / 4.4	0.002	50.0 / 6.4	0.014
<i>Duration of Use</i>	54.4% (2+days)	6.4 / 2.5	0.090	9.6 / 3.2	0.017
<i>Inserting Person</i>	70.1% (Nurse)	6.6 / 0	0.007	9.1 / 1.0	0.006
<i>Service of Inserter</i>	25.3% (NonSurg)	13.8 / 1.6	0.000	17.2 / 3.1	0.000
<i>Randomization Followed</i>	19.8% (No)	13.2 / 2.5	0.000	16.2 / 4.3	0.000
<i>Tamper Evidence Line</i>	34.5% (NotIntact)	7.6 / 3.1	0.006	11.0 / 4.4	0.021
<i>Tube Position</i>	63.0% (Improper)	6.5 / 1.6	0.037	9.7 / 1.6	0.004
<i>Bag Position</i>	1.5% (Improper)	20.0 / 4.4	0.214	40.0 / 6.2	0.003
<i>Catheter Care: Overall</i>	28.9% (Below Median)	9.1/2.9	0.021	12.1/4.1	0.013

8.1.5 Logistic Regression: Predictive Modeling of CAUTI

Stepwise, logistic regression analyses were performed using bacterial CAUTI and all CAUTI as the dependent variables, and the risk factors identified during the univariate examinations discussed above as potential predictor variables. Variables were entered one at a time into the logistic model, with the variable with the most predictive power entered at each step. Variables had to have a significance level of 0.05 to enter the model, and were dropped from the model if their significance level fell below 0.10, as a result of the information then contained in a combination of the other variables present in the model. The results of these logistic regression analyses are presented in Table 13.

Only four variables, meeting the entry criteria, qualified for inclusion in the logistic regression for bacterial CAUTI. These were the catheter type (antibacterial or standard silicone), whether the patient underwent surgery, the service of the inserter, and the presence of vaginitis. After correcting for the contribution of the other three predictor

variables the p-value associated with use of the antibacterial catheter was statistically significant at 0.0219.

The logistic analysis of all CAUTI (which included bacteria, yeast, and fungal infections) resulted in four variables qualifying for inclusion: whether the patient underwent surgery, duration of catheter use, inserting person, and vaginitis. In this analysis, the effect of the catheter was not significant ($p = 0.4039$) after including the four predictor variables in the regression.

Table 13
Results of Logistic Predictive Modeling

Group / Variable	Log Odds (SE)	Odds	Significance P-value
<i>Bacterial Infections (7 days)</i>			
<i>Catheter</i>	1.469 (0.698)	4.349	0.0219
<i>Surgery Patient</i>	-18.021 (52.721)	0.000	0.0000
<i>Service of Inserter</i>	-14.499 (52.711)	0.000	0.0056
<i>Vaginitis</i>	11.608 (37.418)	109986.2	0.0040
<i>All Infections (7 days)</i>			
<i>Surgery Patient</i>	-2.448(0.525)	0.087	0.0000
<i>Duration of Use</i>	1.365 (0.562)	3.914	0.0090
<i>Inserting Person</i>	-8.483 (24.941)	0.002	0.0008
<i>Vaginitis</i>	3.584 (1.562)	36.023	0.0415
<i>Catheter (not in model)</i>			0.4039

8.1.6 Cox Regression: Survivorship with Covariates

The ability to address both survivorship (actuarial freedom from CAUTI infections) and the effects of covariates on CAUTI occurrence are contained in the Cox regression procedure. Stepwise, Cox regression (proportional hazards) analyses were performed for both bacterial CAUTI and all infections CAUTI. The criteria for inclusion in the model were the same as used for the logistic regression: significant levels of 0.05 or less to enter, significance levels of 0.10 or less to remain in the model. The results of these analyses are presented in Table 14.

The results presented in Table 14 are consistent with those presented earlier in Table 13 for the logistic analyses. The antibacterial catheter was found to be a significant factor ($p = 0.0127$) in the reduction of bacterial CAUTI events, even in the presence of the other contributing variables. The catheter type, however, did not reach statistical significance ($p = 0.1618$) in the Cox modeling of all infections.

Table 14

Results of Cox Regression Modeling

Group / Variable	Hazard Ratio	Significance P-value
<i>Bacterial Infections</i>		
<i>Catheter</i>	4.3518	0.0127
<i>Surgery Patient</i>	0.0037	0.0000
<i>Service of Inserter</i>	0.0882	0.0412
<i>Vaginitis</i>	96.4574	0.0097
<i>All Infections</i>		
<i>Surgery Patient</i>	0.1009	0.0000
<i>Vaginitis</i>	39.5532	0.0223
<i>Bag Status</i>	0.2043	0.0845
<i>Catheter (not in model)</i>	---	0.1618

Insight into its estimated contribution to the cumulative freedom from CAUTI events can be seen in Figures 3 and 4 below.

In Figure 3, the estimated Cox survivorship function for bacterial CAUTI for the antibacterial (new) and standard silicone catheter are plotted at the mean values of the covariates identified as significant in the model. It can be seen that the cumulative survival for the antibacterial catheter remains near 1.00 out through 6 days post-insertion, and exceeds that of the standard catheter for all time periods.

FIGURE 3

Cox Regression: Bacterial Infections

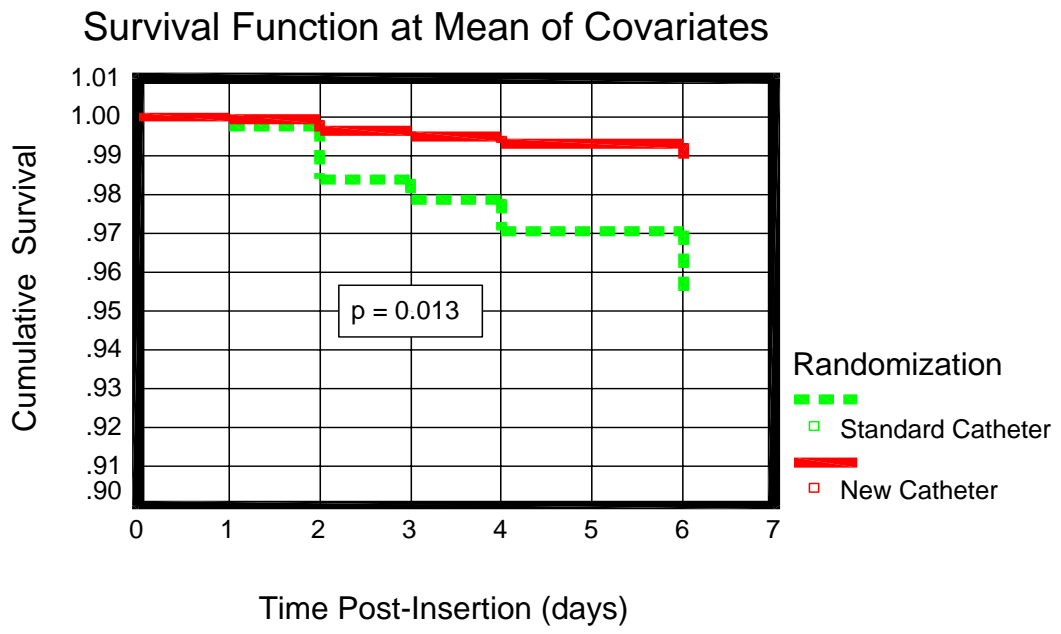
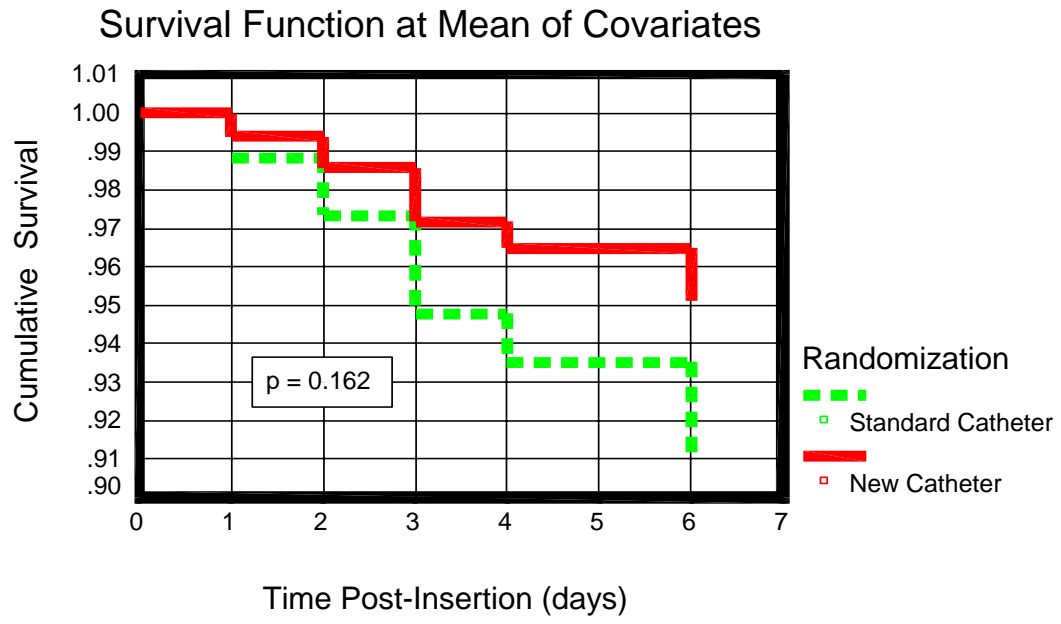


FIGURE 4

Cox Regression: All Infections



In Figure 4, the estimated Cox survivorship function for all CAUTI for the antibacterial (new) and standard silicone catheter are plotted at the mean values of the covariates for this regression. Although statistical significance ($p = 0.1618$) for the difference between the antibacterial catheter and standard silicone catheter was not reached, it can be seen that the estimated cumulative survival for the antibacterial catheter is higher for all time periods within the first 7 days.

8.1.7 Test of Efficacy Hypotheses

The foregoing statistical analyses provide a basis for testing the efficacy study hypotheses presented in *Section 5.3*.

Endpoint 1: Risk of Bacterial CAUTI

The null hypothesis is rejected. The antibacterial catheter resulted in significantly fewer bacterial CAUTI in the Kaplan-Meier analysis ($p = 0.007$), the logistic predictive modeling ($p = 0.0219$), and the Cox regression survivorship ($p = 0.0127$).

Endpoint 2: Risk of All Infection CAUTI

The null hypothesis is not rejected. Although the antibacterial catheter resulted in fewer all infections CAUTI, this difference did not reach statistical significance (Kaplan-Meier p -value = 0.061, logistic p -value = 0.4039, Cox regression p -value = 0.1618).

The difference between the number of patients with bacterial infections and the number with infections of any kind (i.e., all infections) represents those patients who had yeast or fungal infections only. The occurrence of yeast and fungal infections within the first 7 days after catheter insertion was also examined. There were three patients (1.7%) with yeast/fungal infections within the first 7 days in the standard catheter group and four patients (2.4%) in the antibacterial catheter group. This difference was not statistically significant ($p = 0.721$, Fisher's Exact test). When examined using the Cox regression method discussed above, two variables were identified as having predictive ability for development of yeast/fungal infections: the presence of Vulvitis ($p = 0.0424$, odds ratio = 22.2) and Urine Bag Status ($p = 0.0702$, odds ratio = 14.1). The contribution of catheter type was not significant ($p = 0.6374$).

8.2 Safety of Antibacterial Catheter

8.2.1 Complications

The antibacterial catheter was well tolerated in the study population. There were no reports of any complications associated with its use or use of the standard silicone catheter. This permits an evaluation of the safety hypothesis for the study.

Endpoint 3: Complications Associated with Use of the Catheters

The null hypothesis is not rejected. There was no evidence of a difference in the risk of complications associated with use of either catheter. In the case of no observations, the associated Fisher's Exact test p -value for the comparison would be 1.00.

8.2.2 Clinical Observations

As part of the study, patient symptoms associated with use of the catheter were collected. These findings are presented in Table 15.

There were no significant differences between catheters seen in the incidence of any of these patient symptoms measures..

Table 15
Patient Symptoms by Catheter Group (% of Patients with Symptoms)

Condition / Factor	Antibacterial Catheter (%) (n)	Standard Catheter (%) (n)	P-value (2-tailed)
<i>Neutropenia</i>	1.2% (170)	0.6% (174)	0.620
<i>Diarrhea</i>	4.7% (170)	8.0% (174)	0.271
<i>Vulvitis</i>	0.6 % (170)	1.1% (174)	1.000
<i>Vaginitis</i>	0% (170)	1.1% (174)	0.499
<i>Dysuria</i>	2.6% (153)	0% (153)	0.123
<i>Burning</i>	3.9% (153)	3.3% (153)	1.000
<i>Urgency</i>	5.2% (153)	1.3% (153)	0.104
<i>Itching</i>	0.7% (153)	0% (153)	1.000

9.0 SCIENTIFIC SOUNDNESS

This section addresses some of the issues involved in evaluating the scientific soundness of the study that was performed.

9.1 Adequacy of Sample Size

The original study design estimated that a total of 350 evaluable patients would be required to evaluate the comparative CAUTI risks associated with the new antibacterial catheter compared to the standard silicone catheter device. A total of 344 evaluable patients were enrolled in the investigation

Although the overall incidence of CAUTI infections was less than originally expected (observed 8.0% infection rate for control silicone device compared to an expected 25% rate), the study had sufficient statistical power to detect a significant difference in the rate of bacterial CAUTI, the type of infection source for which the device is designed to be effective.

A lower rate of all infections CAUTI was also observed for the antibacterial catheter, but the differences did not reach statistical significance. Given the observed overall rates of infections in the two catheter groups, a substantially larger study would be required to demonstrate statistical significance, if the estimated difference in rates were valid.

9.2 Effectiveness of Randomization

A total of 174 evaluable patients were randomized to the control standard catheter group, and a total of 170 were randomized to the new antibacterial catheter group. There was found to be no significant differences in any of the baseline variables recorded between the two catheter groups, indicating that the randomization was effective in balancing potential pre-existing risk factors. These factors were discussed in *Sections 7.4* and *7.5*.

9.3 Methods to Minimize Bias

Prospective steps were taken to prevent the introduction of bias into the investigation. The study was conducted as an investigator-blinded trial to minimize the potential effect of knowledge of the catheter assignment on the evaluation of patient outcomes measures. Quantitative definitions for the CAUTI outcomes were also included in the study protocol prior to initiation of patient enrollment.

9.4 Generalizing Results to Target Population

It is expected that the results of the study can be generalized to the eventual population of patients who will use the antibacterial catheter device. The study included a significant representation of both males and females, patients from 19 to 91 years of age, rural and urban residents, and a variety of indications for use of a Foley catheter including the monitoring of urine in trauma cases and surgical procedures, bladder dysfunction, and urinary incontinence.

9.5 Gender Analysis

The study had a significant enrollment of females (31.6%). The contributions of gender and gender-related variables to the development of the CAUTI outcome events were both directly evaluated and incorporated in the overall statistical analyses of study endpoints that were performed.

10.0 CONCLUSIONS

1. The antibacterial Foley catheter manufactured by Rochester Medical Corporation demonstrated that it could significantly reduce the incidence of CAUTI of bacterial origin, when compared to the use of a standard silicone catheter.
2. The antibacterial catheter was well-tolerated by patients receiving it and no complications or attributable side-effects were observed.

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