

A Randomized Crossover Study of Silver-Coated Urinary Catheters in Hospitalized Patients

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Background: Urinary tract infections (UTIs) account for 30% to 40% of nosocomial infections resulting in morbidity, mortality, and increased length of hospital stay.

Objective: To assess the efficacy of a silver-alloy, hydrogel-coated latex urinary catheter for the prevention of nosocomial catheter-associated UTIs.

Methods: A 12-month randomized crossover trial compared rates of nosocomial catheter-associated UTI in patients with silver-coated and uncoated catheters. A cost analysis was conducted.

Results: There were 343 infections among 27878 patients (1.23 infections per 100 patients) during 114368 patient-days (3.00 infections per 1000 patient-days). The relative risk of infection per 1000 patient-days was 0.79 (95% confidence interval, 0.63-0.99; $P = .04$) for study wards randomized to silver-coated catheters compared with those randomized to uncoated catheters. Infec-

tions occurred in 291 of 11032 catheters used on study units (2.64 infections per 100 catheters). The relative risk of infection per 100 silver-coated catheters used on study wards compared with uncoated catheters was 0.68 (95% confidence interval, 0.54-0.86; $P = .001$). Fourteen catheter-associated UTIs (4.1%) were complicated by secondary bloodstream infection. One death appeared related to the secondary infection. Estimated hospital cost savings with the use of the silver-coated catheters ranged from \$14456 to \$573293.

Conclusions: The risk of infection declined by 21% among study wards randomized to silver-coated catheters and by 32% among patients in whom silver-coated catheters were used on the wards. Use of the more expensive silver-coated catheter appeared to offer cost savings by preventing excess hospital costs from nosocomial UTI associated with catheter use.

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AN ESTIMATED 2 million nosocomial infections occur in US hospitals each year, causing 19027 deaths, contributing to another 58092 deaths, and adding more than \$4.5 billion in excess hospital costs.¹ It was estimated that there were 900000 nosocomial urinary tract infections (UTIs) in 1992, prolonging the mean duration of hospital stay by 1.0¹ to 3.8 days² and increasing costs by more than \$500 million.

In another large national study,³ UTIs accounted for 40% of nosocomial infections. Mortality of patients with bacteriuria was found to be nearly 3 times higher than that for those without bacteriuria.⁴ Although the prevalence has decreased in recent decades from 23% in the 1960s⁵ to 10% in the 1990s,⁶ nosocomial UTIs continue to cause significant morbidity and mortality.

A randomized crossover trial was conducted to evaluate the effectiveness of sil-

ver-coated urinary catheters in decreasing these infections.

RESULTS

During the study period, 343 catheter-related UTIs occurred among 27878 patients (1.23 infections per 100 patients) during 114368 patient days (3.00 infections per 1000 patient days). Wards randomized to silver-coated catheters experienced 154 infections among 13945 patients (1.10 infections per 100 patients) compared with 189 infections among 13933 patients on wards randomized to uncoated catheters (1.36 infections per 100 patients) (relative risk [RR], 0.81; 95% confidence interval [CI], 0.65-1.01; $P = .07$). Infections on wards using silver-coated catheters occurred during 57945 patient-days (2.66 infections per 1000 patient-days) compared with the 189 infections per 56423 patient-days on wards randomized to uncoated catheters

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MATERIALS AND METHODS

The University of Virginia Hospital, Charlottesville, contains 600 beds and provides primary and tertiary care. A 12-month randomized crossover study compared the rates of catheter-associated UTI in hospitalized patients with silver-alloy, hydrogel-coated latex Foley catheters (Bardex IC; C. R. Bard, Inc, Covington, Ga) vs silicone-coated (uncoated) latex catheters manufactured by the same company. Randomization was performed by categorizing hospital wards into 3 strata according to baseline infection rates (high, medium, and low) between May 1, 1995, and April 30, 1996. Hospital wards were randomized into 2 groups (1 and 2) within each stratum. Intensive care units and their step-down units were linked to minimize the chance of duplicate data collection among patients transferring between wards. Pediatric wards were not included since children's catheters were not available. Obstetrics, gynecology, and psychiatry were excluded because of their low infection rates and infrequent catheter use in these specialties.

The study was conducted from November 1, 1996, to November 30, 1997. During the first 6 months, wards randomized to group 1 were stocked with silver-coated catheters, and wards randomized to group 2 used uncoated catheters. This was followed by a 1-month washout period during which all wards were stocked with uncoated catheters. In the second 6 months of the study, group 1 wards used uncoated catheters and group 2 wards had silver-coated catheters.

Hospital-wide surveillance for nosocomial infections was conducted as described by Wenzel et al.⁷ Nosocomial catheter-associated UTIs and secondary bloodstream infections were identified and ascribed to particular hospital wards by infection control practitioners using definitions from the Centers for Disease Control and Prevention⁸ (**Table 1**). Hospital records of patients with secondary bloodstream infections were reviewed to determine whether any deaths appeared to be related to these infections.

Data collection included type of catheter, infecting organisms, demographic information, hospital location to which the infection was ascribed, location at the time the catheter was placed, and duration of catheterization. The type of catheter was determined by visual examination of the urinary catheter and a review of the medical record. If a patient had one catheter removed and another inserted, the catheter in place for the 24 hours before the onset of infection was considered to be the catheter related to the infection. If the catheter related to the infection was not the type of catheter that had been assigned to the unit by randomization, this was considered a crossover catheter infection. The duration of catheterization and number of different catheters in place before the development of an infection were determined through a review of the medical record.

Rates were calculated for the number of infections per 100 patients, per 1000 patient-days, and per 100 catheters.

Within the intensive care units, rates were calculated per 100 patients, per 1000 patient-days, and per 1000 catheter days.

DATA ANALYSIS

One analysis was based on the study ward randomization and assumed that the type of catheter present when the infection developed was the same as the type of catheter randomly allocated to the ward on which the infection developed.

A second analysis of actual catheter use was conducted, based on the number of infections that were linked to the use of catheters (silver-coated or uncoated) inserted in patients on the study wards (ie, excluding infections that occurred with catheters inserted at outside hospitals or on nonstudy wards). Denominators for this analysis were the number of silver-coated and uncoated catheters purchased for study wards during the investigation.

STATISTICAL METHODS

Based on the rate of 1.54 catheter-associated UTIs per 100 patients from July 1994 through June 1995, it was estimated that a sample size of 29 184 hospital admissions would be needed to detect a 25% relative reduction in the rate of infection per 100 patients with the silver-coated catheter at the 5% significance level with 80% power.⁹ The frequency of qualitative variables was compared between groups using χ^2 or 2-tailed Fisher exact tests. An exact test was used for comparing incidence densities.⁹

COST ANALYSIS

The numbers of silver-coated and uncoated urinary catheters and components used per month were obtained from the hospital's computer records. The manufacturer provided the purchase costs of catheters and components in 1997 US dollars.

Estimates of the excess cost per UTI have ranged from \$680¹ to \$3803,² both of which were in 1992 US dollars. These estimates were adjusted for inflation from 1992 to 1997 US dollars using the *Consumer Price Index* for medical care (\$839.18 and \$4693.23, respectively).¹⁰

The total excess cost of infections for the study wards was calculated by multiplying the annualized number of infections for each group (silver-coated vs uncoated) by the published estimates of excess cost per infection. The total cost of catheters and components was based on the annualized number of urinary catheters and components used on the study wards, multiplied by the cost of each catheter or component in 1997 US dollars. The total catheter-related costs were calculated by summing the cost of infections and the cost of catheters and their components. Cost savings were estimated by subtracting the total catheter-related cost for silver-coated catheters from the total cost for uncoated catheters.

(3.35 infections per 1000 patient-days) (RR, 0.79; 95% CI, 0.63-0.99; $P=.04$) (**Table 2**).

Of the 343 infections, 89 (26.0%) involved crossover catheters. Sixty-three (70.8%) of the 89 occurred in patients on wards randomized to silver-coated catheters but who had uncoated catheters in place at the time of

infection, and 26 (29.2%) occurred in patients on wards randomized to uncoated catheters but who had silver-coated catheters in place.

Fifty-two of the 343 infections occurred in persons whose catheters had been placed at outside hospitals or on nonstudy wards (2 silver-coated and 50 uncoated).

Table 1. Definition of Nosocomial Catheter-Associated UTI

Urinary tract infection (UTI) includes symptomatic UTI and asymptomatic bacteriuria*

Symptomatic UTI must meet one of the following criteria†:

One of the following: fever ($>38^{\circ}\text{C}$), urgency, frequency, or dysuria or suprapubic tenderness; AND a urine culture of $\geq 10^5$ colonies per milliliter with no more than 2 species of organisms.

Two of the following: fever ($>38^{\circ}\text{C}$), urgency, frequency, or dysuria or suprapubic tenderness; AND any of the following:

Dipstick test positive for leukocyte esterase or nitrate or both

Pyuria (≥ 10 white blood cells/mL³ or ≥ 3 white blood cells/high-power field of unspun urine)

Organisms seen on Gram stain of unspun urine

Two urine cultures with repeated isolation of the same uropathogen with $\geq 10^2$ colonies per milliliter in nonvoided specimens

Urine cultures with $\leq 10^5$ colonies per milliliter of single uropathogens in patient being treated with appropriate antimicrobial therapy

Physician's diagnosis

Physician institutes appropriate antimicrobial therapy

Asymptomatic bacteriuria must meet the following criteria:

An indwelling urinary catheter is present within 7 days before urine is cultured AND patient has no fever ($>38^{\circ}\text{C}$), urgency, frequency, dysuria or suprapubic tenderness; AND has a urine culture of $\geq 10^5$ colonies per milliliter with no more than 2 species of organisms.

*The hospital location to which the urinary tract infection was assigned was defined as the location of the patient 48 hours before the diagnosis of the UTI. Taken from article by Garner et al.⁹

†To be considered a catheter-associated urinary tract infection, the patient had to have had an indwelling catheter within 7 days before the urine was cultured.

Table 2. Incidence of Nosocomial Catheter-Associated UTI: Analysis as Randomized*

	UTI per 100 Patients	UTI per 1000 Patient-Days
Silver-coated catheters	1.10	2.66
Uncoated catheters	1.36	3.35
Relative risk	0.81	0.79
95% Confidence interval	0.65-1.01	0.63-0.99
P	.07	.04

*UTI indicates urinary tract infection.

Table 3. Incidence of Nosocomial Catheter-Associated UTI: Analysis by Actual Catheter Use*

	UTI per 100 Catheters
Silver-coated catheters	2.13
Uncoated catheters	3.12
Relative risk	0.68
95% Confidence interval	0.54-0.86
P	.001

*Excludes infections that occurred with catheters inserted on nonstudy wards or at outside hospitals. UTI indicates urinary tract infection.

The remaining 291 infections were in patients whose catheters had been inserted on study units, 115 with silver-coated catheters and 176 with uncoated catheters. A total of 11 032 catheters were used on the wards during the study period, 5398 silver-coated and 5634 uncoated. The overall rate of infection in patients with catheters inserted on study wards was 2.64 infections per 100 catheters used. For silver-coated catheters, the rate was 2.13 infections per 100 catheters compared with 3.12 infections per 100 uncoated catheters, for an RR of 0.68 (95% CI, 0.54-0.86; $P = .001$) (**Table 3**).

One hundred eighteen infections occurred among 2674 intensive care unit patients during 10 797 patient days and 9221 catheter days. Overall rates of infection were 4.41 per 100 patients, 10.93 per 1000 patient-days, and 12.80 per 1000 catheter-days. Intensive care units were the site of 34.4% of all infections. When analyzed based on the study ward randomization, the RR of infection with silver-coated catheters compared with uncoated catheters in intensive care units was 0.94 per 100 patients (95% CI, 0.64-1.38; $P = .80$). Thirty-one (26.3%) of the 118 infections involved crossover catheters. Twenty-five (80.6%) of the 31 occurred in patients in intensive care units randomized to silver-coated catheters but who had an uncoated catheter in place at the time of infection. The other 6 (19.4%) were in persons in units randomized to uncoated catheters but who had silver-coated catheters inserted.

Fourteen (4.1%) of the 343 infections were complicated by secondary bloodstream infections. The rate of secondary infection was 0.04 per 100 patients on units randomized to silver-coated catheters and 0.07 per 100 on units assigned to uncoated catheters, for an RR of 0.56 (95% CI, 0.19-1.66; $P = .42$). Three of the 14 patients died during the hospitalization, for a case fatality rate of 21.4%. All 3 of these secondary bloodstream infections involved *Candida*. One death appeared temporally and clinically related to the secondary infection. This patient had a UTI associated with an uncoated catheter. In a second patient with an uncoated catheter, death was possibly related to the secondary bloodstream infection. In the third patient who died, death occurred 21 days after a silver-coated catheter-related UTI; this patient had negative blood cultures and was afebrile for 14 days before death.

There were no statistically significant differences in the proportion of infections attributed to different organisms following use of silver-coated and uncoated catheters. The 4 most common organisms causing infection in this study were *Escherichia coli* (18.4%), *Escherichia faecalis* (16.9%), *Candida albicans* (13.4%), and *Pseudomonas aeruginosa* (11.7%). Gram-negative bacilli accounted for 49.6% of all infections (48.7% of silver-coated vs 50.0% of uncoated catheter infections, $P = .91$). Yeast accounted for 26.2% of all infections (24.8% in silver-coated vs 27.0% in uncoated catheter infections, $P = .76$). Gram-positive cocci, including *Staphylococcus aureus*, coagulase-negative staphy-

lococci, and enterococci, were responsible for 28.0% of infections overall (26.5% silver-coated vs 30.8% uncoated catheter infections, $P=.48$).

Sixty percent of infections occurred in female patients in both study groups. The average duration of catheterization before development of infection was 9 days in both groups. The interval between initial catheterization and the onset of infection was the same in the 2 study groups despite whether a single catheter or multiple catheters had been present before the development of the infection.

By using silver-coated catheters, the total estimated catheter-related costs were reduced between \$14456 and \$573293, depending on which estimate of cost per nosocomial UTI was used (**Table 4**). These savings represented between 3.3% and 35.5% of the total catheter-related costs. Most of these costs appeared due to the excess cost of infections, 84.6% to 96.9 with uncoated and 58.4% to 89.1% with silver-coated catheters.

COMMENT

The last significant advance in the prevention of catheter-related UTI involved implementation of closed drainage systems in the 1960s.¹¹⁻¹⁴ Different types of catheter coatings have been studied in an attempt to decrease infections. One antibiotic coating that was investigated did not show benefit, and furthermore its use raised concerns about promoting the development of antibiotic resistance.¹⁵

Silver has bactericidal characteristics, is nontoxic, and has been used topically to prevent infections in other settings, such as burn wounds. Two types of silver-coated urinary catheters have been studied. One of these, the silver-oxide catheter, was assessed in 3 trials, with conflicting results, and is no longer marketed in the United States.^{6,16,17}

Two previous investigations of the second type of silver-coated catheter, which was evaluated in this study, showed significant decreases in bacteriuria among male surgical patients not receiving antibiotics.^{18,19} The present study is the first to use a silver-alloy coating in a controlled trial involving adult patients throughout a university hospital with a wide variety of types and severity of underlying illnesses. The significant reduction in infections that we observed supports the results of the 2 earlier studies. Another recent randomized trial at the University of Wisconsin Hospital, Madison, found significant infection prevention using the same catheter.²⁰ Taken together, these findings suggest that the results of our study may be generalizable to other hospitals. Effectiveness has not yet been assessed in pediatric or long-term catheterized patients.

A limitation of our study is that hospital wards rather than individual patients were used as the unit of catheter randomization. If catheterized patients crossed over from silver-coated to uncoated catheter wards or vice versa, this would have tended to bias the study toward the null, underestimating any true benefit of silver-coated catheters. As randomized, however, the rate of infection per 1000 patient-days was significantly reduced with the use of silver-coated catheters compared with uncoated catheters ($RR=0.79$; $P=.04$), while the rate of infection per 100 patients approached a statistically significant reduction

Table 4. Cost Analysis Based on Estimated Excess Cost of Nosocomial Urinary Tract Infections*

	Uncoated	Silver-Coated	Savings
Catheters and components	\$68 795	\$176 020	...
Using Lower Estimate¹ of \$839.18 (1997 US Dollars)¹⁰			
Total excess cost of infection	\$379 309	\$257 628	...
Total catheter-related cost	\$448 104	\$433 648	\$14 456
Using Higher Estimate² of \$4693.23 (1997 US Dollars)¹⁰			
Total excess cost of infection	\$2 121 340	\$1 440 822	...
Total catheter-related cost	\$2 190 135	\$1 616 842	\$573 293

*Estimates are annualized cost in US dollars.

($RR=0.81$; $P=.07$). Given our known crossover rate of catheters resulting in infection (26.0%), the finding of a significant decrease in infections as randomized offers strong evidence of the effectiveness of this catheter for preventing infection. The RR of infection with silver-coated catheters used on study wards compared with uncoated catheters ($RR=0.68$; $P=.001$) corroborated this finding.

An advantage of randomizing to wards rather than to individuals was that a larger number of subjects could be exposed to study and control catheters, thereby maximizing the power of the study while limiting the necessary resources and workforce. For example, the randomized crossover design made it possible to study 12-fold more catheters during 1 year than had been possible in another 1-year study of the same catheter in which the randomization was by individual patients in a hospital of comparable size.²⁰

Other potential sources of systematic error were detection and misclassification bias. Detection bias might have resulted if resident or attending physicians, identifying the silver-coated catheters by their labels, ordered more urine cultures for patients with uncoated catheters because of preexisting confidence in the antimicrobial properties of silver. The opposite could also have occurred among clinicians doubting the efficacy of silver. Nevertheless, because nurses inserted almost all the urinary catheters in our study, and because there was no posted information about which wards were randomized to which catheters during which months, it is doubtful that physicians focused on catheter type. Detection bias could also have resulted if hospital infection control practitioners were influenced by ward randomization. However, although they were aware that an evaluation was being conducted, they were not privy to details about the randomization and were asked to ignore catheter type when assessing nosocomial UTIs as part of their regular hospital-wide surveillance.

Misclassification bias might have occurred in the event of poor documentation of catheter insertions, but nursing notes were believed to be complete in 97% of cases that were being reviewed because of nosocomial infection. Since infections occurred a mean of 9 days after insertion in both study groups, and because catheters were usually changed monthly in this hospital unless they became obstructed or infected sooner, this documentation was considered adequate for the purposes of our study. Misclassification of silver-coated catheters as uncoated (or vice versa) would have tended to bias the study result toward the null.

Serious sequelae can result from nosocomial UTIs. Prospective studies from the late 1970s and 1980s found the rate of secondary bloodstream infection to range between 1% and 4%, with a case fatality rate between 13% and 30%.²¹⁻²⁴ The present study suggests that there has been little change in these rates in the last decade. We found the relative rate of secondary bloodstream infection to be 44% lower on units randomized to silver-coated catheters. Because only 14 secondary bloodstream infections occurred during the study, however, this relative reduction was not statistically significant ($P = .42$). Nevertheless, the observed concordance of significantly fewer UTIs and a trend toward fewer bloodstream infections on wards randomized to silver-alloy catheters may be clinically important, indicating the need for further study.

A previous study of a silver-oxide catheter showed in subset analysis a protective effect only in women who had not received antimicrobial therapy.⁶ By contrast, results from our study suggest that the silver-alloy catheter is equally effective in men and women.

The cost analysis conducted in this investigation is the first to report that most of the costs associated with the use of urinary catheters appear to stem from the excess cost of complicating infections. The lower estimate of cost per infection was based on an uncontrolled case series of 84 patients from 1975 in which researchers attempted to estimate the excess costs of nosocomial UTIs.²⁵ The estimate was then adjusted for inflation in 1981²⁵ and again in 1992.¹ This uncontrolled estimate of excess cost was significantly exceeded by the measured attributable cost from a 19-month case-control study at the University of Utah, Salt Lake City, with 675 cases and 5337 control subjects matched by age, sex, date of infection, primary diagnosis-related group, and average nursing acuity.² It was again greatly exceeded by the attributable cost in a more recently published case-control study in Spain, in which control patients were matched for surgical procedure, American Society of Anesthesiologists score, age, emergency surgery, preoperative stay, and presence of a urinary catheter.²⁶ Although in our study the purchase cost of silver-coated catheters and their components exceeded those of uncoated catheters by more than 2.5-fold, use of the silver-coated catheters was found to provide an estimated annual cost savings to the hospital of \$14456 to \$573293 that resulted from the prevention of excess costs due to infection.

In conclusion, we found that silver-alloy, hydrogel-coated catheters significantly decreased catheter-associated UTIs of all etiologic types in male and female patients in a university hospital population. These catheters appeared to offer significant cost savings when the excess cost of UTIs was considered.

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