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Effect of a Second-Generation Venous Catheter Impregnated with Chlorhexidine and Silver Sulfadiazine on Central Catheter–Related Infections

A Randomized, Controlled Trial

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Background: **Central venous catheter–related infections are a significant medical problem. Improved preventive measures are needed.**

Objective: **To ascertain 1) effectiveness of a second-generation antiseptic-coated catheter in the prevention of microbial colonization and infection; 2) safety and tolerability of this device; 3) microbiology of infected catheters; and 4) propensity for the development of antiseptic resistance.**

Design: **Multicenter, randomized, double-blind, controlled trial.**

Setting: **9 university-affiliated medical centers.**

Patients: **780 patients in intensive care units who required central venous catheterization.**

Intervention: **Patients received either a standard catheter or a catheter coated with chlorhexidine and silver sulfadiazine.**

Measurements: **The authors assessed catheter colonization and catheter-related infection, characterized microbes by molecular typing, and determined their susceptibility to antiseptics. Patient tolerance of the catheter was monitored.**

Results: **Patients with the 2 types of catheters had similar demographic features, clinical interventions, laboratory values, and risk factors for infection. Antiseptic catheters were less likely to be colonized at the time of removal compared with control catheters (13.3 vs. 24.1 colonized catheters per 1000 catheter-days; $P < 0.01$). The center-stratified Cox regression hazard ratio for colonization controlling for sampling design and potentially confounding variables was 0.45 (95% CI, 0.25 to 0.78). The rate of definitive catheter-related bloodstream infection was 1.24 per 1000 catheter-days (CI, 0.26 to 3.62 per 1000 catheter-days) for the control group versus 0.42 per 1000 catheter-days (CI, 0.01 to 2.34 per 1000 catheter-days) for the antiseptic catheter group ($P = 0.6$). Coagulase-negative staphylococci and other gram-positive organisms were the most frequent microbes to colonize catheters. Noninfectious adverse events were similar in both groups. Antiseptic susceptibility was similar for microbes recovered from either group.**

Limitations: **The antiseptic catheter was not compared with an antibiotic-coated catheter, and no conclusion can be made regarding its effect on bloodstream infection.**

Conclusions: **The second-generation chlorhexidine–silver sulfadiazine catheter is well tolerated. Antiseptic coating appears to reduce microbial colonization of the catheter compared with an uncoated catheter.**

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Infections associated with central venous catheters are a substantial problem. Each year in the United States, at least 80 000 patients in intensive care units experience central venous catheter–associated bacteremia (1, 2). These infections are associated with an overall attributable mortality of approximately 3% (3), but estimates vary from 0% to greater than 30% depending on patient population, definitions, and pathogens (4). The attributable cost per infection ranges from $3240 to more than $50 000 (5–8).

Many strategies have been used to prevent catheter-associated infection. These measures can be divided into 2 groups: those that prevent microbes from gaining access to the catheters and those that discourage microbes from adhering and proliferating on the catheter, such as coating the catheters with various antimicrobial agents. The latter approach has shown promise and has included the use of chlorhexidine and silver sulfadiazine. In a randomized clinical trial, Maki and colleagues (9) observed a statistically significant decrease in colonization and bacteremia in patients who received a catheter coated with chlorhexidine and silver sulfadiazine compared with controls who received an uncoated catheter. In a randomized, comparative trial, Darouiche and colleagues (10) found that catheters impregnated with minocycline and rifampin were associated with fewer infectious complications than catheters coated with chlorhexidine and silver sulfadiazine. However, one of the main differences between the catheters was that the chlorhexidine–silver sulfadiazine coating involved only the external surface of the catheter, whereas the minocycline and rifampin catheter was coated on the internal

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and external surfaces. More recently, a second-generation antiseptic catheter was formulated that increased the chlorhexidine concentration on the external surface of the catheter 3-fold and incorporated chlorhexidine on the luminal surface of the catheter, extension lines, and hubs. This trial was conducted to assess the efficacy and safety of the second-generation antiseptic catheter compared with an uncoated control catheter.

Context

Bacterial colonization of central venous catheters is relatively common, and subsequent bacteremia is a serious iatrogenic complication of critical illness. Initial studies of antimicrobial-coated catheters have suggested that this approach might decrease catheter-associated infection.

Contribution

This randomized, double-blind, controlled study of a new antiseptic-coated catheter versus an uncoated catheter shows a substantial decrease in bacterial colonization in patients receiving the coated device.

Caution

The study was unable to show a substantial decrease in bloodstream infections, possibly because of the low infection rate as a result of meticulous aseptic techniques used during catheter insertion.

—The Editors

METHODS

Patients and Study Design

This study was a randomized, double-blind, controlled trial conducted between July 1998 and June 2001 at 9 university-affiliated hospitals. The objective was to determine whether the second-generation antiseptic central venous catheter was effective in preventing microbial colonization and bloodstream infection in comparison with an uncoated control catheter. The null hypothesis was that the incidence of bloodstream infection would be the same or worse for the patients who received the antiseptic catheter compared with the patients who received the control catheter. Secondary goals consisted of product safety evaluation, assessment of the microbiology of catheter-associated infection, and microbial susceptibility to chlorhexidine and silver sulfadiazine. The institutional review boards at each hospital approved the protocol. Adult patients who were cared for in critical care units and who required a triple-lumen central venous catheter were eligible for participation. Patients who were pregnant, were allergic to chlorhexidine or sulfa drugs, were hospitalized for burn injuries, had a chronic inflammatory skin disorder at the catheter insertion site, were suspected of having a catheter-associated infection, or were enrolled in another investigational trial were not eligible for participation. All patients or their authorized surrogates granted informed consent. The study sample size was calculated on the basis of an expected catheter-related bloodstream infection rate of approximately 4.5% in the control group and 1.5% in the antiseptic catheter group. Allowing for a 12% dropout rate, 793 patients were required to yield a study with an 80% power at the 0.05 level of statistical significance.

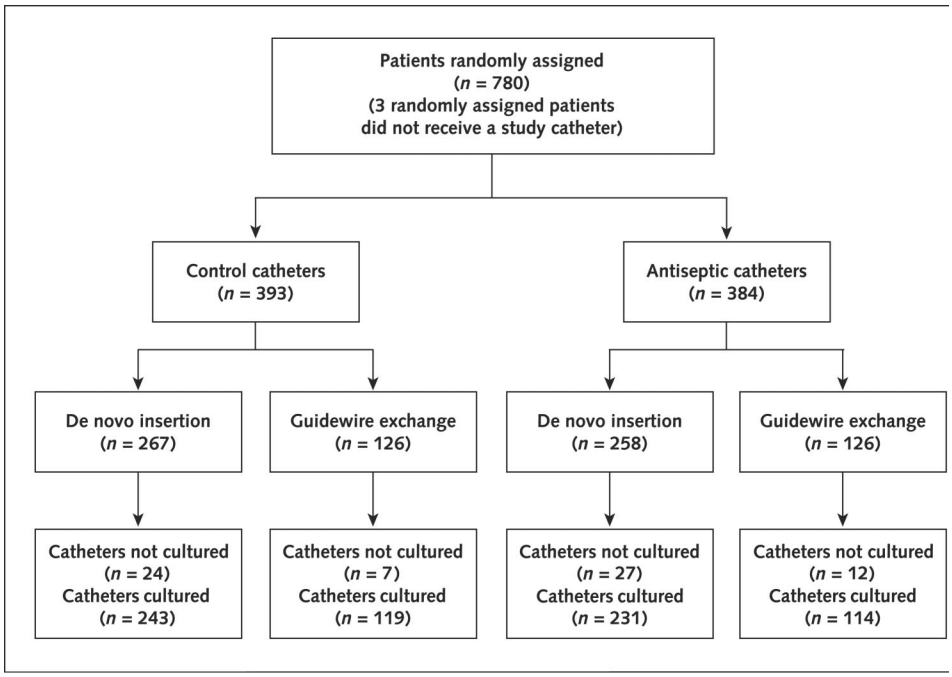
Catheters

All catheters were 7-French, 20-cm long polyurethane triple-lumen central venous catheters manufactured by Arrow International, Inc. (Reading, Pennsylvania). Control catheters were standard, uncoated triple-lumen catheters. Antiseptic catheters (ARROWgard II Blue Plus, Arrow International, Inc.) were coated with chlorhexidine acetate and silver sulfadiazine on the external surface and chlorhexidine and chlorhexidine acetate on the luminal surfaces. All catheters were indistinguishable in appearance and packaging.

Randomization, Catheter Insertion, and Care Procedures

Patients were randomly assigned to receive an individually numbered catheter and had an equal probability of assignment to either group. The randomization code was developed by using a computerized random-number generator to select permuted blocks. The block length was 4. Randomization stratification ensured that antiseptic and control catheters were evenly distributed in the de novo and guidewire exchange groups. Patients were randomly assigned in a 1:1 ratio within each of the study centers. Catheter allocation was concealed, and patients, study personnel, and all health care workers were unaware of whether the catheters were coated or uncoated. A subset of patients at each institution (approximately one third of patients) was allowed to receive an initial study catheter through guidewire exchange. Four institutions were also allotted a small number of exchange insertions in which a study catheter could be exchanged for a matched study catheter (randomization and blinding were protected). **Figure 1** shows the distribution of patients. Catheters were inserted by using full sterile barrier precautions, which included the operators wearing a sterile long-sleeve gown, sterile gloves, hat, and mask, and using a large sterile drape. Before insertion, the skin was cleansed with 10% povidone-iodine (chlorhexidine-based antiseptics were not approved by the U.S. Food and Drug Administration for insertion-site preparation). Before a study catheter was inserted over a guidewire into a preexisting site, the hub of the first catheter was cleansed with povidone-iodine. The tip of the preexisting catheter was submitted for microbiological testing. Insertion sites were dressed with a transparent polyurethane dressing (OpSite 3000, Smith & Nephew, Inc., Largo, Florida). No antimicrobial ointment was applied at the insertion site. Depending on institu-

Figure 1. **Distribution of initial study catheters by type and method of insertion.**



tional routine, dressings were changed every 72 to 96 hours using a standardized kit. At the time of dressing change, the insertion site was cleansed with povidone-iodine. The patient's attending physician made the decision to remove the catheter.

Measurements and Definitions

At the time of catheter insertion, the following data were recorded: patient demographic characteristics, indication for catheter insertion, underlying medical conditions, indication for admission to the intensive care unit, length of hospital stay and length of intensive care unit stay, and severity of illness score (Acute Physiology and Chronic Health Evaluation [APACHE] II score). Study catheters were inspected daily. Local and systemic signs and symptoms of infection were recorded. The presence of other intravascular and indwelling devices was noted, and the antibiotics that were administered were recorded. At the time of catheter removal, a 20-cm^2 circular template was placed at the catheter insertion site and a moistened swab (Culturette, Becton Dickinson and Co., Sparks, Massachusetts) was used to sample the pericatheter insertion site. The swab was sent to the institutional microbiology laboratory, where it was used to inoculate a blood agar plate. Catheters were removed by using an aseptic technique. The subcutaneous portion of the catheter was cut from the rest of the catheter, and the 2 portions were placed in separate sterile plastic bags for transport to the laboratory. The subcutaneous portion of the catheter was divided into four 2.5-cm segments. A neutralizing media (D/E Neutralizing Broth or Agar, Remel, Lenexa, Kansas) was used to minimize any potential antimicrobial carryover effect. Proximal and distal segments were cultured by using the roll-plate method (11), and similarly, proximal and distal segments were cultured by using a sonication technique (12). At 2 centers, the catheter hubs were cultured by using moistened swabs. Blood cultures were obtained from the catheter and from a peripheral vein on any patient with suspected catheter-associated infection. Signs and symptoms of a catheter-associated infection included fever (temperature $>$ 38 °C) without another obvious source and local signs of infection, such as erythema, cellulitis, purulent drainage, or excessive tenderness. All microbes recovered from cultures of the patient's blood, catheter, skin, or other sites were shipped to a central laboratory (University of Iowa, Iowa City, Iowa) for confirmatory identification and susceptibility testing.

Catheters were defined as colonized if cultures revealed at least 15 colony-forming units per segment by the roll-plate method or at least 100 colony-forming units per segment by the sonication method. Catheter-related bloodstream infection was defined as catheter colonization with positive blood cultures from the peripheral bloodstream for the same organism. Molecular typing by ribotype analysis was done on isolates of the same species when they were recovered from multiple sites on the same patient with a colonized catheter (13). If 2 or more isolates had identical ribotypes, further molecular differentiation by pulsed-field gel electrophoresis was done. Antimicrobial susceptibility testing for chlorhexidine and silver sulfadiazine was done by using a modified Kirby–Bauer technique on all strains of bacteria recovered from colonized catheters (14). Briefly, microbial isolates were inoculated onto Mueller–Hinton

agar plates (BBL Microbiology Systems, Cockeysville, Maryland) to achieve confluent growth. A 0.5-cm chlorhexidine–silver sulfadiazine catheter segment was inserted into the agar perpendicular to the surface. The plates were incubated at 37 °C for 24 hours, and the zone of inhibition around the catheter segment was measured.

Statistical Analysis

A modified intention-to-treat analysis was conducted on all patients who received a study catheter and had a catheter culture. Sensitivity analyses were done to assess the impact of assumptions regarding missing outcome data. Kaplan–Meier survival curves were constructed to compare groups regarding time to microbial colonization. Follow-up was censored on removal of the catheter. Statistical comparisons were done by using a log-rank statistic. A center-stratified Cox regression model was used to estimate hazard ratios with 95% CIs, which reflected the hazard rate ratio for microbial colonization between groups, controlling for clustering of patients within centers, and adjusting for potential confounding factors in the estimates of treatment effects. Only initial study catheters were considered in the primary test for efficacy. The Cox regression model included sampling design variables of catheter type, catheter insertion status, and potential confounding variables. Comparison of rates of colonization and bacteremia, expressed as number of events reported per 1000 catheter-days, were analyzed assuming a Poisson model, using an exact test for homogeneity. We used Stata, version 8 (Stata Corp., Bryan, Texas) for the Cox regression analysis and SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina) for all other analyses.

Adjudication

All cases of possible catheter colonization or bacteremia were considered by 2 infectious disease experts who were blinded to the study groups. Each of the physicians adjudicated the blinded data separately. Discrepant cases were reviewed again, and consensus was reached.

Role of the Funding Source

This study was funded by Arrow International, Inc., through individual research contracts with participating institutions. Several of the authors formulated the study design in conjunction with personnel from Arrow International. The investigators performed the study independently, but the sponsor collected and initially analyzed the data. All data in the study were source-documented. Preparation and approval of this manuscript were done independently by the authors. The authors had full independence in decisions regarding the reporting of results and the content of this paper.

RESULTS

Patient Characteristics

Seven hundred eighty persons were enrolled in the study (**Figure 1**). Three patients were randomly assigned but did not receive a study catheter and were excluded from additional analysis. Three hundred ninety-three patients and 384 patients received control and antiseptic catheters, respectively. **Table 1** lists the most frequently observed conditions precipitating admission to the intensive care unit, medical risk factors, therapeutic interventions, laboratory variables, severity of illness, and days in the intensive care unit. The 2 groups were similar with respect to all recorded factors.

Catheter Characteristics

Table 2 summarizes the catheter characteristics. The 2 groups were similar with respect to location of catheter insertion and difficulty of insertion. Catheters were graded as difficult to insert if more than 1 percutaneous puncture was required and the operator regarded the insertion procedure as difficult. The numbers of catheters inserted through guidewire exchange versus de novo insertion were similar (**Figure 1**). Twenty-two of the 252 (8.7%) catheters that were inserted through guidewire exchange exhibited colonization of the original (nonstudy) catheter. Twelve patients were in the antiseptic catheter group, and 10 patients were in the control catheter group. Fifteen of the study catheters (9 antiseptic catheters and 6 control catheters) were removed promptly when the data from the culture of the original catheter became available, and 7 of the study catheters remained in place. Forty-three patients (19 with antiseptic catheters and 24 with control catheters) received 58 subsequent catheters through guidewire exchange (randomization and blinding were protected). The initial study catheter was considered for evaluation of primary end points. All catheters were included in the safety analysis. Thirty patients (12 with antiseptic catheters and 18 with control catheters) received 1 subsequent catheter; 11 patients (6 with antiseptic catheters and 5 with control catheters) received 2 subsequent catheters; and 2 patients (1 with an antiseptic catheter and 1 with a control catheter) received 3 study catheters through guidewire exchange. There was no substantial difference in the duration of catheterization between the 2 groups and between the types of insertion (de novo insertion vs. guidewire exchange). The reasons for catheter removal and the appearance of the insertion site at the time of catheter removal were similar between groups (**Table 2**).

Microbial Colonization of Catheters and Bacteremia

Of the 780 patients enrolled in the trial, 3 were excluded from the analysis because they did not receive a study catheter. Seventy additional patients (9%) were excluded because cultures were not taken at the time of catheter removal and study end points could not be assessed. Uncultured catheters were proportionately distributed between the 2 groups (31 control catheters and 39 antiseptic catheters) (**Figure 1**). Fifty-nine (16.3%) of the control catheters and 32 (9.3%) of the antiseptic catheters were colonized as determined by either roll-plate or sonication techniques ($P < 0.01$). **Table 3** summarizes the rate of

Table 1. **Characteristics of Patients***

Characteristic	Control Catheter Group	Antiseptic Catheter Group
Patients, *n*	393	384
Mean age (SD), *y*	61 (15.5)	60 (16.4)
Men, %	60	61
Ethnic group, %		
White	86	87
African American	7	8
Hispanic	4	4
Asian	1	0.3
Native American	1	0.3
Other	1	1
Primary organ system dysfunction at time of admission to the ICU, *n* (%)		
Cardiovascular	70 (18)	58 (15)
Neurologic	28 (7)	16 (4)
Respiratory	151 (38)	132 (34)
Gastrointestinal	75 (19)	103 (27)
Renal	12 (3)	17 (4)
Metabolic	4 (1)	3 (1)
Hematologic	10 (3)	6 (2)
Other	12 (3)	10 (3)
Primary factor precipitating admission to the ICU, *n* (%)		
Neoplasm	78 (20)	68 (18)
Infection	50 (13)	42 (11)
Cardiac (MI, angina, VHD, arrhythmia, CHF, cardiac arrest)	49 (12)	37 (10)
Postoperative need for mechanical ventilation	30 (8)	17 (4)
Sepsis	28 (7)	27 (7)
Trauma	21 (5)	19 (5)
Bleeding or hypovolemia	14 (4)	17 (4)
Medical risk factors, *n* (%)		
CAD or CHF	196 (50)	159 (41)
Hemodialysis	42 (11)	41 (11)
Neoplasm	119 (30)	124 (32)
Type 1 diabetes	62 (16)	62 (16)
COPD	103 (26)	83 (22)
Gastrointestinal bleeding	47 (12)	61 (16)
Infection	248 (63)	222 (58)
Malnutrition	214 (55)	212 (56)
Therapeutic intervention, *n* (%)		
TPN	124 (32)	131 (34)
Mechanical ventilation	305 (78)	288 (75)
Blood products	144 (37)	153 (40)
Antibiotics	359 (91)	353 (92)
Steroids	116 (30)	118 (31)
Pressors	107 (27)	99 (26)
Chest tube	93 (24)	83 (22)
Nasogastric tube	294 (75)	279 (73)
Urinary catheter	379 (96)	368 (96)
Arterial catheter	279 (71)	255 (66)
Mean laboratory variables (SD)		
Hematocrit	0.31 (0.053)	0.31 (0.05)
Leukocyte count, $\times 10^9$ *cells/L*	13.8 (9.1)	13.6 (8.4)
Urea nitrogen level		
mmol/L	11.4 (8.9)	11.8 (9.3)
mg/dL	31.9 (24)	33.0 (26)
Glucose level		
mmol/L	9.6 (4.8)	9.2 (4.9)
mg/dL	173 (87)	167 (89)
Albumin level, μ*mol/L*	393 (212)	303 (136)
Mean APACHE II score (SD)	17 (7.3)	17 (7.5)
Mean time in ICU before CVC insertion, *d*		
De novo insertion	4.5	4.0
Guidewire exchange	4.8	6.5

* APACHE II = Acute Physiology and Chronic Health Evaluation II; CAD = coronary artery disease; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; ICU = intensive care unit; MI = myocardial infarction; TPN = total parenteral nutrition; VHD = valvular heart disease.

colonization and microbial cause, and **Figure 2** shows the risk for catheter colonization for the initial study catheters. The center-stratified Cox regression model yielded an adjusted hazard ratio for the coated catheter group compared with the control catheter group of 0.45 (95% CI, 0.28 to 0.75) ($P < 0.01$). No other variables besides the catheter type were significant predictors of colonization. The potential confounding factors included in the model were gastrointestinal dysfunction at the time of admission to the intensive care unit, underlying coronary artery disease, and days in the intensive care unit before catheter insertion. These factors were chosen from the list of potential variables (**Table 1**) because they were the only factors with relevant group differences. Because of missing values, albumin level was assessed separately and was not found to be an important confounder. Six hundred ninety-one patients were included in the stratified Cox regression analysis. The reasons for excluding patients were as follows: Three patients never received a study catheter, 70 patients had no outcome measure, and 16 patients were missing data on potential confounding variables. To assess the impact of assumptions regarding the 70 patients with missing outcome variables, the stratified Cox regression model was reestimated first by assuming that all 70 missing catheters were colonized and then by assuming that all catheters were sterile. The estimated hazard ratios in these 2 analyses were 0.70 (CI, 0.5 to 0.98) ($P = 0.04$) and 0.44 (CI, 0.28 to 0.71) ($P < 0.01$), respectively, providing assurance that primary results were robust regarding missing outcome variables. The potential for clustering of patients within centers was assessed in a model that included only center, catheter type, catheter exchange status, and center-by-treatment interaction. Although the hazard ratio for catheter colonization ranged from 0.45 to 0.96 in the 6 centers with at least 5 colonized catheters in each patient group, there was no statistically significant modification of the treatment effect by center ($P = 0.91$).

Of the 15 study catheters that were inserted through guidewire exchange and removed because of colonization of the original nonstudy catheter, 6 were colonized (4 antiseptic catheters and 2 control catheters). Of the 7 study catheters that remained in place despite colonization of the original nonstudy catheter, 2 were colonized at the time of catheter removal (1 antiseptic catheter and 1 control catheter). None of the patients who had guidewire insertion of a study catheter into a site with preexisting catheter colonization experienced catheter-associated bacteremia. Coagulase-negative staphylococci were the most frequently recovered microbes from control and antiseptic catheters (**Table 3**). The femoral insertion site was associated with the highest rate of microbial colonization of control catheters (30%), followed by the internal jugular (19%) and subclavian sites (5%). The rate of colonization of antiseptic catheters was 4.5% for the femoral site, 11% for the internal jugular site, and 4% for the subclavian site.

At the centers that were allotted exchange catheters, 43 patients received 58 subsequent catheters. Only the initial study catheters were included in the assessment of primary end points (colonization or bacteremia). Three of the subsequent control catheters (9.7%) and none of the antiseptic catheters (0%) were colonized. None of these patients experienced a catheter-related bloodstream infection.

Three cases of definite catheter-related bacteremia occurred in the control group (1.24 per 1000 catheter-days [CI, 0.26 to 3.62 per 1000 catheter-days]) compared with 1 case in the antiseptic catheter group (0.42

Table 2. **Characteristics of Study Catheters***

Characteristic	Control Catheter Group	Antiseptic Catheter Group
CVC location, *n (%)*		
Internal jugular	234 (60)	220 (57)
Subclavian	136 (35)	141 (37)
Femoral	23 (6)	22 (6)
Difficult insertion	46 (12)	42 (11)
Median duration of catheterization (range), *h*		
De novo insertion	142 (2–790)	123 (0.1–764)
Guidewire exchange	120 (0.1–719)	124 (0.1–1109)
Reason for CVC removal, *n (%)*		
CVC no longer needed	219 (55)	193 (51)
Death	28 (7)	35 (9)
Suspected infection with local signs	26 (7)	25 (7)
Suspected infection without local signs	57 (14)	44 (12)
CVC occlusion or thrombosis	9 (2)	10 (3)
CVC malfunction	3 (1)	6 (1.8)
Other	54 (14)	64 (17)
Appearance of insertion site at time of CVC removal, *n* (%)		
Erythema	54 (14)	61 (16)
Purulence	5 (1)	5 (1)
Tenderness	20 (5)	14 (4)
Edema or induration	12 (3)	14 (4)

* CVC = central venous catheter.

Table 3. **Catheter Colonization and Bloodstream Infection Associated with Initial Study Central Venous Catheter***

Variable	Control Catheter Group	Antiseptic Catheter Group
Definite and possible catheter colonization, *n (%)*†	59 (16.3)	32 (9.3)
Colonization/1000 catheter-days	24.1	13.3
De novo insertion, *n (%); rate/1000 d*	42 (17.3); 23.8	17 (7.4); 10.4
Guidewire exchange, *n (%); rate/1000 d*	17 (14.3); 24.9	15 (13); 19.1
Microbiological characteristics, *n*		
Coagulase-negative staphylococci	42	22
Staphylococcus aureus	10	4
Enterococcus sp.	6	6
Diptheroid	12	3
Gram-negative bacilli	9	1
Candida sp.	2	4
Other	1	2
Polymicrobic	19	9
Definite CVC-associated BSI, *n (%)*	3 (0.8)	1 (0.3)
BSI/1000 catheter-days	1.24	0.42
De novo insertion, *n (%); rate/1000 d*	3 (1.25); 1.7	1 (0.4); 0.6
Guidewire exchange, *n (%); rate/1000 d*	0	0
Microbiological characteristics, *n*		
S. aureus	2	0
Enterococcus sp.	0	1
Gram-negative bacilli	1	0
Candida sp.	0	1
Polymicrobic	0	1
Definite and possible CVC-associated BSI, *n (%)*‡	8 (2.2)	6 (1.7)
BSI/1000 catheter-days	3.27	2.48
De novo insertion, *n (%); rate/1000 d*	6 (2.5); 3.4	2 (0.9); 1.2
Guidewire exchange, *n (%); rate/1000 d*	2 (1.7); 2.9	4 (3.5); 5.1
Microbiological characteristics, *n*		
Coagulase-negative staphylococci	2	1
S. aureus	3	1
Enterococcus sp.	2	2
Gram-negative bacilli	1	0
Candida sp.	0	3
Other	1	0
Polymicrobic	1	2

* BSI = bloodstream infection; CVC = central venous catheter.
† 3 possible colonizations were adjudicated: 2 in control catheters and 1 in an antiseptic catheter.
‡ 10 possible bacteremias were adjudicated: 5 in control catheters and 5 in antiseptic catheters.

per 1000 catheter-days [CI, 0.01 to 2.34 per 1000 catheter-days]) ($P = 0.6$). The difference in bloodstream infection between the groups was 0.82 per 1000 catheter-days (CI, −1.71 to 3.34 per 1000 catheter-days). Ten cases of bacteremia were regarded as possibly catheter-related (5 cases in each group). Typically, these patients experienced bacteremia that was possibly secondary to sources other than the catheter, resulting in equivocal designations. Inclusion of the 10 possible cases resulted in bacteremia rates of 3.27 per 1000 catheter-days (CI, 1.41 to 6.44 per 1000 catheter-days) and 2.48 per 1000 catheter-days (CI, 0.91 to 5.4 per 1000 catheter-days) for the control and antiseptic catheter groups, respectively ($P = 0.79$). The difference in bloodstream infection between the groups was 0.79 per 1000 catheter-days (CI, −3.91 to 5.49 per 1000 catheter-days). There were no substantial differences when de novo insertions were compared with guidewire exchange insertions. The number of bloodstream infections precluded analysis for confounding. **Table 3** summarizes the rates of bacteremia and microbial cause.

Skin and Catheter Hub Colonization and Molecular Typing Studies

Three hundred thirty patients with control catheters and 349 patients with antiseptic catheters had skin cultures taken at the time of catheter removal. Sixty percent of patients with control catheters had positive skin cultures compared with 51% of patients with antiseptic catheters ($P = 0.01$). There was a close association between microbes recovered from the skin and those recovered from colonized catheters. Molecular typing by ribotype analysis demonstrated concordance between at least 1 strain recovered from the skin and 1 strain recovered from the catheter in 61 of 77 (79.2%) evaluable catheters. Concordance was observed in 43 of 53 (81%) evaluable control catheters and 18 of 24 (75%) evaluable antiseptic catheters. Microbial isolates were unavailable for ribotyping in 6 of the 59 (10%) control catheters that were colonized and 8 of the 32 (25%) antiseptic catheters that were colonized. Hub cultures were done in only a small number of patients (87 of 393 patients [22%] with control catheters and 81 of 384 patients [21%] with antiseptic catheters) and were positive

in 1 patient with a control catheter and in 1 patient with an antiseptic catheter.

In Vitro Susceptibility Tests

Microbial isolates recovered from colonized catheters or from the bloodstream of patients with catheter-associated bacteremia underwent susceptibility testing for chlorhexidine and silver sulfadiazine (**Table 4**). Overall, the zones of inhibition were similar for organisms recovered from antiseptic and control catheters.

Noninfectious Catheter-Related Adverse Events

All catheters (initial and subsequent) were included in the safety analysis. Comparable rates of adverse events were observed between the 2 groups. Forty-three patients (10.9%) with control catheters and 41 patients (10.7%) with antiseptic catheters died. The investigators attributed all deaths to underlying conditions. Nine (2.3%) catheter-associated adverse events (graded as definitely related or possibly related by the investigators), which consisted of pneumothorax, thrombosis, hematoma, hemothorax, allergic reaction, and pulmonary embolism, were described in patients with the control catheters. Similarly, 7 (1.8%) catheter-associated adverse events, which consisted of pneumothorax, thrombosis, air embolism, hematoma, and allergic reaction, were observed among patients with the antiseptic catheters. One patient in the control group and 2 patients in the antiseptic catheter group had a dermatologic allergic reaction (nonanaphylactic) thought by the investigators to be possibly attributable to the study catheters. Each of these patients were receiving several pharmacologic agents that may have been responsible for the observed dermatologic condition.

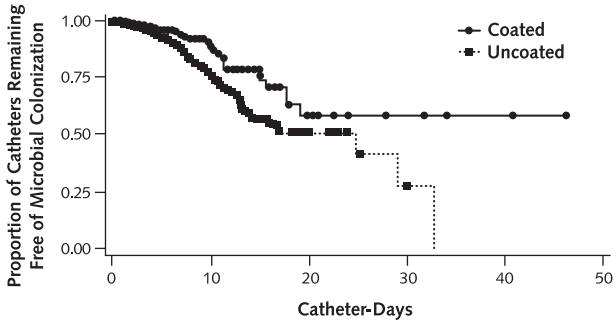
DISCUSSION

According to the Centers for Disease Control and Prevention (CDC), approximately 53% of adult patients in intensive care units have a central venous catheter on any given day (15). Central venous catheter–related infections are associated with significant mortality, morbidity, and excess cost, making them particularly worthy of preventive measures. The CDC has set a goal of decreasing catheter-associated adverse events by 50% as one of its top patient safety challenges (16). Previous studies indicate that approximately 50% of infections result from microbes gaining access to the catheters from the cutaneous surface, whereas the remaining 50% of infections result from contamination of the hub and infusate (9, 10). Our study supports the premise that colonization of short-term, nontunneled catheters largely results from the patient's skin flora and initially involves the external surface of the catheter. Once organisms (mainly coagulase-negative staphylococci) gain access to the device, infection is derived from their ability to adhere, proliferate, and elaborate biofilm (17, 18). Therefore, to prevent infection, catheters have been modified to reduce microbial adherence and proliferation.

This trial examined the efficacy of a second-generation antiseptic catheter, with a greater concentration of chlorhexidine on the external surface and chlorhexidine on the luminal surface, to prevent infection. The second-generation antiseptic catheter seemed to be more efficacious than the first-generation catheter in both in vitro and in vivo models (19). Production and marketing of the first-generation antiseptic catheter are being phased out by the manufacturer. Chlorhexidine is an effective antiseptic agent that is active against almost all nosocomial pathogens (20). Resistance is rarely observed. Silver sulfadiazine, long used topically and active against a broad spectrum of potential pathogens, is well tolerated; however, bacterial resistance has been described in various pathogens (21).

The antiseptic catheter demonstrated a protective effect in the prevention of bacterial colonization (9.3% [13.3 colonized catheters per 1000 catheter-days] vs. 16.3% [24.1 colonized catheters per 1000 catheter-days]; $P < 0.01$). There were fewer definite catheter-related bloodstream infections in the patients in the antiseptic catheter group (0.42 infection per 1000 catheter-days vs. 1.24 infections per 1000 catheter-days); however, this difference was not statistically significant and no conclusion can be reached regarding prevention of bloodstream infection. In retrospect, our study was underpowered in this regard because of an overestimation of the prevalence of catheter-related bloodstream infection. Nevertheless, the first step in

Figure 2. **Kaplan–Meier curve demonstrating initial study catheters free of microbial colonization versus time.**



Catheters remaining, *n*	Day 0	Day 10	Day 20	Day 30
Antiseptic CVC	345	68	13	3
Control CVC	362	68	16	1

Symbols indicate the point at which a catheter was censored. Chlorhexidine–silver sulfadiazine central venous catheters (*CVCs*) were substantially less likely to become colonized by microbes during their period of clinical use than the uncoated control catheters ($P \leq 0.01$, log-rank test). The percent of catheters free of colonization (and the standard error) at days 10, 20, and 30 for control and antiseptic-coated catheters, respectively, are as follows: day 10, 75.7% (3.6%) and 87.6% (3.0%); day 20, 51.5% (6.4%) and 58.8% (8.0%); and day 30, 27.5% (13.2%) and 58.8% (8.0%).

Table 4. **In Vitro Chlorhexidine and Silver Sulfadiazine Susceptibility of Organisms Colonizing and Infecting Antiseptic and Control Catheters Determined by Agar Diffusion Testing***

Catheter Category	Organism	Tested, *n*	Zone of Growth Inhibition, *mm*†		
			Range	50%	Mean
Antiseptic	*Candida* spp.	9	12–16	13	14
	Coagulase-negative staphylococci	35	14–25	19	19
	Enterococcus spp.	8	10–14	10	11
	BHS	3	16–18	17	17
	Corynebacterium spp.	2	18–24	18	21
	Micrococcus sp.	1	19	–	–
	Enterobacter sp.	1	14	–	–
	Serratia sp.	1	8	–	–
	Staphylococcus aureus	2	16–19	17	17
	All coated	62	8–25	17	17
Control	*Candida* spp.	2	14–18	14	16
	Coagulase-negative staphylococci	70	14–21	18	18
	Enterococcus spp.	12	10–15	13	13
	BHS	13	13–21	14	15
	Corynebacterium spp.	11	17–26	23	20
	Micrococcus sp.	1	18	–	–
	Aerococcus sp.	1	15	–	–
	Acinetobacter sp.	1	8	–	–
	Citrobacter sp.	1	10	–	–
	Escherichia coli	2	14	14	14
	Enterobacter sp.	2	9–10	9	10
	Neisseria sp.	1	17	–	–
	Proteus sp.	1	8	–	–
	Pseudomonas sp.	1	9	–	–
	Serratia sp.	1	8		–
	Staphylococcus aureus	13	16–19	14	15
	All uncoated	133	8–26	16	17

* BHS = β-hemolytic streptococci.
† Zone of inhibition surrounding a catheter coated with chlorhexidine and silver sulfadiazine in an agar diffusion test. 50% = the size of the zones (in millimeters) encompassing 50% of the isolates tested.

the pathogenesis of catheter-related infection is colonization of the device, which may serve as a surrogate marker for bloodstream infection (22). The low rate of bloodstream infection in the control group (1.24 per 1000 catheter-days) is noteworthy and may have been influenced by several factors. Careful attention to aseptic practices in the insertion and care of catheters was mandated. Full sterile barrier precautions were used during insertion of the catheters, and standardized kits and procedures were used to change the catheter dressings. These measures have been shown to substantially decrease the risk for catheter-associated infection (1, 23). Also, the use of precise definitions and molecular typing may have prevented overdiagnosis. A limitation of the study is that cultures were not taken at the time of catheter removal in 70 patients, making it impossible to assess the catheter colonization status in these cases. These patients were excluded from consideration in the modified intention-to-treat analysis. It is unlikely that this introduced substantial bias because the missing cultures were evenly distributed between groups and seemed to be random. Moreover, in the sensitivity analyses, in which missing catheters were assumed to be colonized or sterile, statistically significant group differences remained under either set of assumptions, providing additional assurance that primary results were robust.

Although our study was not a comparative trial with the minocycline–rifampin (antibiotic) catheter, the rates of colonization and infection observed in the patients in the antiseptic catheter group are similar to rates observed for patients with minocycline–rifampin catheters in 2 previously published studies (colonization was 8% and 7.9%, and rate of bloodstream infection was 0 and 0.3 per 1000 catheter-days, respectively) (10, 24). Although a randomized trial comparing these devices should be conducted, it would be logistically difficult to perform because a large sample size would be required to demonstrate a statistically significant difference between the 2 types of catheters.

This study supports the recommendation that a catheter should be promptly removed if it is inserted through guidewire exchange in the setting of a catheter-related infection or in emergent, nonaseptic conditions (2, 25). Six of 15 (40%) study catheters (6 control catheters and 9 antiseptic catheters) inserted through guidewire exchange and promptly removed because of colonization of the original catheter were found to be colonized (2 control catheters and 4 antiseptic catheters). Likewise, of the 7 catheters (4 control catheters and 3 antiseptic catheters) that remained in place despite colonization of the original catheter, 2 (29%) were colonized at the time of removal (1 control catheter and 1 antiseptic catheter). Although our

sample size was small, it seems that the risk for colonization of a catheter inserted into a contaminated site (36%) is greater than the overall colonization rate (12%) when insertional asepsis is maintained. The antimicrobial coating does not seem to offer a protective effect in the setting of insertion-site contamination (colonization rate, 5 of 12 [42%] for antiseptic catheters vs. 3 of 10 [30%] for control catheters).

One objective of this study was to assess device safety because of the increased concentration of chlorhexidine incorporated into the catheter. No cases of allergic reaction definitively related to the catheter were observed. At the time of removal, the antiseptic catheters did not have a greater degree of erythema or other signs of inflammation at the insertion site than the control catheters. It should be noted that some data link Japanese ancestry to chlorhexidine sensitivity (26) and that only 0.3% of the patients receiving the antiseptic catheter in our study were of Asian ancestry. It is doubtful that such a small sample size would discern any safety concerns in this population subgroup.

Theoretically, the prolonged use of antiseptic agents may lead to the emergence of microbial resistance. Small amounts of the antiseptic agents used to coat the chlorhexidine–silver sulfadiazine catheter diffuse from the catheter and may be detected in the bloodstream. Therefore, resident flora may be exposed to the antiseptic agents and the emergence of resistance is possible (27). It is reassuring that zones of inhibition to chlorhexidine and silver sulfadiazine were similar for microbes recovered from patients who received the control catheter or the antiseptic catheter. The mean duration of catheterization was 5.1 days for the patients with antiseptic catheters, and greater experience with longer durations of catheterization will be required to more fully assess the propensity for the emergence of resistance.

Catheter-related bloodstream infection in patients in intensive care units costs approximately $30 000 per episode (2, 5, 6, 28). A previous meta-analysis indicates that when baseline rates of catheter-associated infection are approximately 5%, use of the first-generation antiseptic catheter is cost-effective (29). The CDC recommends considering antiseptic- or antibiotic-coated catheters in populations where the rate of infection exceeds 3.3 per 1000 catheter-days despite adherence to other preventive strategies (2). In the current study, a baseline rate of bloodstream infection of 3.3 per 1000 catheter-days (both definitive and possible bacteremia) was achieved when full sterile barrier precautions and a standardized dressing change protocol were followed. The use of chlorhexidine for insertion-site preparation might further reduce catheter-associated infection (28, 30). However, in the current study, the low rate of infection does not seem to reflect standard experience in intensive care units in the United States. The CDC reported that rates of catheter-associated bloodstream infection range from 2.9 to 8.5 per 1000 catheter-days (mean rate, 4.9 per 1000 catheter-days) depending on the type of intensive care unit studied (31). Clearly, increased emphasis should be placed on appropriate catheter insertion and care. Adherence to guidelines that emphasize aseptic techniques seems to decrease the rate of catheter-related bloodstream infection to a level below the threshold of cost-effectiveness demonstrated in previous studies of the first-generation antiseptic catheter (2, 29). However, in situations in which the rate of catheter-related infection remains above this threshold, the chlorhexidine–silver sulfadiazine catheter may be a viable option to decrease infection rates.

In conclusion, this study demonstrates that the second-generation antiseptic catheter, coated with chlorhexidine and silver sulfadiazine on the internal and external surfaces, is effective in preventing microbial colonization and, in the group studied, is not associated with excess adverse events, hypersensitivity, or emergence of microbial antiseptic resistance. Decreased bacterial colonization, a critical step in the pathogenesis of catheter-associated infection, may correlate with prevention of catheter-related bacteremia. Clinicians should note that the low rate of bacteremia in the control group may have been attributable to careful attention to aseptic insertion and catheter care techniques. This study supports the recommendation that catheters inserted into colonized sites through guidewire exchange or under emergent, nonaseptic conditions should be removed. Additional study is warranted to demonstrate efficacy of the antiseptic catheter in comparison with antibiotic-coated catheters, to monitor emergence of antimicrobial resistance, and to assess cost-effectiveness.

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