Influence of Triple-Lumen Central Venous Catheters Coated With Chlorhexidine and Silver Sulfadiazine on the Incidence of Catheter-Related Bacteremia

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Objective: To evaluate the efficacy of triple-lumen central venous catheters coated with a combination product of chlorhexidine and silver sulfadiazine (CSS) in reducing the incidence of local catheter infection and catheter-related bacteremia.

Design: Randomized, controlled trial.

Setting: The surgical intensive care units in a university hospital.

Patients: All patients who needed central venous catheterization were randomized to receive either an uncoated triple-lumen catheter (n=157) or a catheter coated with CSS (n=151).

Main Outcome Measure: Catheters were removed when no longer needed or suspected as a cause of infection. The tip and a 5-cm segment of the intradermal portion of the catheter were cultured semiquantitatively. Blood cultures were obtained when clinically indicated. The remaining segment of catheters coated with CSS were cut and incubated on an agar plate with strains of Staphylococcus aureus and Enterococcus. Zone of inhibition was determined 24 hours later. Data were analyzed by survival and logistic multivariate regression methods.

Results: Catheters coated with CSS were effective in reducing the rate of significant bacterial growth on either the tip or intradermal segment (40%) compared with control catheters (52%; P=.04). However, there was no difference in the incidence of catheter-related bacteremia (3.8% [uncoated] vs 3.3% [coated]; P=.81). In vitro activity of catheters with CSS against S aureus was evident up to 25 days but activity against Enterococcus dissipated more quickly over time and was absent by day 4. The most common colonizing organisms were coagulase-negative staphylococcus and enterococcus. Variables that were associated with a significant amount of growth on the tip or intradermal segment were a duration of catheterization of longer than 7 days, jugular insertion site, and the absence of a CSS coating. The use of a guidewire when the catheter was removed was associated with a lower risk of significant bacterial growth.

Conclusions: The use of CSS reduces the incidence of significant bacterial growth on either the tip or intradermal segments of coated triple-lumen catheters but has no effect on the incidence of catheter-related bacteremia. In this patient population, catheters coated with CSS provide no additional benefit over uncoated catheters.

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Despite improvement in central venous catheter (CVC) design and insertion techniques, catheter-related infections continue to be a significant problem in the intensive care unit. One popular strategy to reduce these infections is scheduled CVC change over a guidewire; however, several studies have indicated that this approach does not reduce the risk of infection. A collagen cuff impregnated with silver that fits around the CVC and resides in a subcutaneous pocket was shown to reduce the density of growth of bacteria on the catheter in some but not all studies. None of these studies individually demonstrated a statistically significant reduction in the incidence of catheter-related bacteremia (CRB); however, pooled data from 2 studies suggest that the use of the cuff resulted in a significant decrease in the rate of CRB. This product has not gained widespread popularity possibly because the use of the cuff can be cumbersome and a substantial portion of these cuffs extrude from their pockets over time. Antibiotic-bonded CVCs have been used in several animal and clinical studies, but concerns about the emergence of resistant organisms and the time needed to bond the catheter with antibiotics at the bedside has limited the use of this approach. The CVC coated with the antiseptic combination product of chlorhexidine and silver sulfadiazine (CSS)
MATERIALS AND METHODS

This study was reviewed and approved by the University of Massachusetts Medical Center Committee for the Protection of Human Subjects in Research in Worcester. Since both products (Arrow-Howes multilumen catheter and Arrowgard multilumen catheter, Arrow International Inc, Reading, Pa) are commercially available and no deviation from routine clinical protocols was made, informed consent was waived. All patients who were admitted to the surgical intensive care units at the University of Massachusetts Medical Center from March 1994 through June 1995 and who needed a CVC were eligible for the study. Randomization was based on the last digit of the medical record number; patients with an odd number received a standard uncoated CVC.

A total of 380 patients were planned to be enrolled into the study. A power analysis indicated that to observe a reduction in significant catheter colonization from 30% (our endemic rate) to 15% would require approximately 140 patients in each group. An additional 30 patients per group were added to allow for those who discontinued the study. Such a sample size, however, would be unlikely to detect changes in CRB rates (power approximately 10%).

CATHETER CARE

Catheters were inserted in external or internal jugular, subclavian, or femoral veins. Use of guidewires was allowed. House staff inserted all the catheters; use of masks, caps, gowns, gloves, and drapes was required.19,20 Prior to insertion, the skin was cleansed with a 10% povidone-iodine solution. A transparent dressing (Polyskin 2, Kendall Corporation, Mansfield, Mass) was used to cover the catheter at the insertion site; no antibiotic ointment was used. Dressings were changed every 48 hours or sooner at the discretion of the nurse caring for the patient and the site was cleaned with a solution of alcohol and acetone.

CULTURES

When the catheters were changed or removed, portions of the tip and intradermal segment were sent for semiquantitative culture by a technician in the hospital microbiology laboratory. In the laboratory, the segments were cut to approximately 5 cm and rolled 4 times on a 5% sheep blood agar plate. The plates were incubated in 5% carbon dioxide at 35°C to 37°C. Colony-forming units (CFUs) were counted at 48 hours.21 If there was a suspicion of bacteremia, peripheral venous blood cultures were obtained and sent to the hospital microbiology laboratory. For the coated CVC, the remaining portions were sent to a research microbiology laboratory, where they were flushed with nonbacteriostatic saline solution, cut, measured, weighed, and placed on Mueller-Hinton agar plates inoculated with a suspension (0.3 McFarland standard or approximately 1.5×10^8 CFUs/mL) of Staphylococcus aureus, which has been used in an animal model of catheter infection11,13 and of Enterococcus (a blood isolate from a patient). The plates were incubated for 24 hours at 35°C in ambient air. Zone of inhibition of S aureus and Enterococcus growth was measured. Significant growth was defined as the tip or intradural segment growing more than 14 CFUs.21 Catheter-related bacteremia was defined as the isolation of the same bacteria from either the tip or intradural segment (in significant quantities [≥4 CFUs]) and the blood. The antibiogram was used to determine if bacteria were the same isolates.

DATA ANALYSIS

Other data that were collected included duration of catheterization, use of guidewires, site of catheterization, use of other catheters, use of total parenteral nutrition, and use of antibiotics. Data were analyzed using life-table analysis, χ^2 test, Student t test, and multivariate logistic regression analysis (Statistica, Statsoft, Tulsa, Okla) where appropriate. Differences in the life-table analyses were considered significant if P<.05. Curve fitting was accomplished using a graphics software program (Fig P, Biosoft, Ferguson, Mo). In the multivariate logistic regression analysis, univariate analyses were performed first with variables that could have an impact on catheter colonization or infection. To avoid rejecting variables that could be important in catheter infection, the P value was set at .25.22 Variables that were found to be significant in the univariate analyses were included in the multivariate analysis where the P value for each variable was set at .05.

RESULTS

Three hundred sixty-five catheters were inserted in 251 patients. The characteristics of the patient population and catheters are presented in Table 1. There are no significant differences between the 2 groups. Fifty-seven catheters were removed or exchanged with other catheters and not cultured because the patient was transferred to a rehabilitation facility with the catheter in place or the patient had been transferred to a different area of the hospital (eg, operating room or ward) and the intensive care unit team was not notified that the catheter was being removed. The mean (±SEM) duration of catheterization was 9.0±0.6 days (range, 1-44 days) for the uncoated catheters vs 8.5±0.6 days (range, 1-65 days) for the coated group (P=.55). There was no significant difference in the sites of insertion between the 2 groups (54% subclavian sites for uncoated catheters vs 51% for coated catheters) (P>.05).

Fifty-two percent of either the tips or intradural segments cultured from uncoated CVCs exhibited growth of more than 14 CFUs compared with 40% of either the tips or intradural segments from CVCs with CSS, re-
spectively (P < .05). However, life-table analysis (Figure 1) did not demonstrate a significant difference in the development of significant growth on either the tip or intradermal segment between the groups (P = .13). The CRB rates for the 2 groups were not significantly different: 3.8% (n=6) for the patients with uncoated catheters and 3.3% (n=5) for those with coated catheters (Figure 2; P = .81). Coagulase-negative staphylococci, diphtheroids, and enterococci were the organisms cultured most often from the catheter segments; coagulase-negative staphylococcus and Enterococcus were the most frequent cause of CRB (Table 2 and Table 3).

Univariate and multivariate regression analyses were performed to determine which variables were associated with a growth of more than 14 CFUs on the tip or intradermal segment and CRB. A jugular site of catheterization and the absence of a CSS coating were the variables associated with a greater risk of significant growth of bacteria on either the tip or intradermal segment, whereas the use of a guidewire during catheter removal was associated with a lower risk (Table 4). In addition, there was a trend for a duration of catheterization of longer than 7 days associated with significant bacterial growth. With regard to CRB, there was only a trend for a greater incidence of CRB if duration of catheterization was longer than 7 days.

In vitro testing of coated CVC segments on the inhibition of the growth of S. aureus demonstrated that 50% of antibacterial activity was depleted by day 5 through 7 (Figure 3, top). However, some catheters exhibited activity against the staphylococci for up to 25 days of catheterization. Testing of uncoated CVCs failed to show any effect on bacterial growth (data not shown). The effect of a CSS coating on the inhibition of bacterial growth appears to be inconsistent since the ability to inhibit enterococcal growth declined rapidly, with few catheters demonstrating activity against Enterococcus beyond 4 to 5 days of catheterization (Figure 3, bottom). In one case of a documented Enterococcus CRB, the coated catheter segment retrieved from the patient inhibited growth of S. aureus but had no effect on the growth of the enterococci isolated from the same patient. The mean (±SEM) zone of inhibition of unused coated catheters against S. aureus was significantly greater than against Enterococcus (9.8±0.3 mm vs 8.2±0.5 mm, respectively; P = .03).

One of the major findings of this study is that CVCs coated with CSS are effective in reducing the risk of developing significant bacterial growth on the catheter. However, this efficacy does not become apparent until the catheter has been in the patient for approximately 7 days or longer (Figure 1) and does not translate into a reduced incidence of catheter-related bloodstream infection. Since antimicrobial activity drops off significantly within the first 5 to 7 days (Figure 3, top), it is not immediately clear why

**COMMENT**

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a benefit should only be seen for catheters that are left in place for longer periods. However, a study comparing CSS-coated triple-lumen catheters with uncoated catheters in pigs demonstrated that CSS catheters reduced the development of biofilm formation and subsequent adherence of bacteria. This ability of CSS to prevent the formation of biofilm may not result in a clinically beneficial effect for the first week of catheterization since the risk of colonization and infection of uncoated catheters is also low during this period. Only when the expected duration of catheterization is beyond 7 to 10 days will the patient realize a benefit from a CSS catheter.

The method used in this study was to culture catheter samples only from the external surface of the catheter. Luminal colonization assumes much greater importance in the pathogenesis of catheter-related infection the longer a catheter remains in place. Since the average duration of catheterization in this study was approximately 9 days, it is possible that a method that samples both the internal and external surfaces of the catheter would have found an even larger difference in the incidence of significant bacterial growth between the 2 catheter types. However, CSS catheters have the CSS coating only on the external surface of the catheter (D. A. Bishop, Arrow International Inc, oral communication); thus, the rate of luminal colonization between coated and uncoated catheters should be the same. As a result, it is unlikely that the use of quantitative culturing methods that detect both external and luminal bacterial growth would have greatly altered our findings.

Our findings support some of the results of previous studies published in abstract form and one small, recently published study. Van Heerden et al showed that triple-lumen catheters coated with CSS reduced the incidence of significant bacterial growth on the tip by 63%. Maki et al demonstrated that catheters coated with CSS were effective in reducing significant bacterial growth on the catheter and the incidence of CRB compared with uncoated catheters. Similar data have been presented by other groups. Irrespective of the type of catheter, the incidence of significant bacterial growth is higher in this study compared with others. The reason for this higher rate is not clear but may be explained in part by the fact that we combined the colonization rates for both the tips and intradermal segments and the duration of catheterization was longer in this study.

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However, the use of guidewire exchange when removing the catheter was associated with a lower risk of significant colonization. This finding is due to several reasons. The duration of catheterization when a guidewire was used to remove a catheter was shorter than when a guidewire was not used (mean ± SEM, 6.49 ± 0.74 days vs 9.20 ± 0.48 days; \( P = .01 \)). One would expect a lower incidence of significant catheter colonization if the duration of catheterization was shorter. However, this cannot be the only explanation since duration of catheterization and the use of a guidewire on catheter removal were important variables in the multivariate analysis. An examination of the multivariate analysis indicated that the use of the guidewire on catheter removal had only a moderate effect on duration of catheterization as a confounding variable. Another explanation for the lower risk is related to the method of catheter removal over a guidewire. In this situation, the insertion site and the catheter that was to be removed were prepared with copious amounts of 10% povidone-iodine solution. Any excess povidone-iodine solution could coat the catheter as it was removed, thereby reducing bacterial burden.

Several other variables were associated with the development of significant bacterial growth on the catheter tip or intradermal segment, including a jugular site of catheterization and absence of a CSS catheter. In addition, there was a trend suggesting that duration of catheterization of longer than 7 days was associated with a higher risk of significant growth. Other investigations have corroborated these observations. At least 2 studies have shown that jugular venous catheterization is associated with a higher risk of significant colonization. The reason for the higher rate of colonization for jugular venous catheterization remains obscure but may be related to difficulties in dressing the catheter, proximity of the insertion site to the mouth, and differences in the density of local skin flora. The lower risk of infection in the subclavian site must be tempered with the small but increased risk of a pneumothorax when that approach is used. A number of studies have demonstrated the increasing risk of infection the longer a catheter is left in place. Routine catheter changes do not appear to be efficacious in reducing the risk of catheter infection and recent guidelines from the Centers for Disease Control and Prevention, Atlanta, Ga, recommend against such a practice. Contrary to catheter colonization, no variable was significantly associated with the presence of a CRB, including the presence of a CSS catheter.

### Table 4. Univariate and Multivariate Analyses of Catheter Tip and Intradermal Segment Cultures and CRB*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bacterial Growth &gt;14 CFUs</th>
<th>CRB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio 95% CI P</td>
<td>Odds Ratio 95% CI P</td>
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<tr>
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<td></td>
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<tr>
<td>Univariate Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular site of insertion</td>
<td>3.46 (2.16-5.53) &lt;.01</td>
<td>...</td>
</tr>
<tr>
<td>Absence of a CSS coating</td>
<td>1.57 (1.0-2.45) .05</td>
<td>...</td>
</tr>
<tr>
<td>Catheterization &gt;7 d</td>
<td>1.43 (0.92-2.27) .12</td>
<td>3.45 (0.93-12.5) .07</td>
</tr>
<tr>
<td>Use of guidewire on removal of catheter</td>
<td>0.33 (0.17-0.63) &lt;.01</td>
<td>...</td>
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<tr>
<td>Multivariate Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jugular site of insertion</td>
<td>3.63 (2.23-5.93) &lt;.01</td>
<td>...</td>
</tr>
<tr>
<td>Absence of a CSS coating</td>
<td>1.69 (1.03-2.78) .04</td>
<td>...</td>
</tr>
<tr>
<td>Catheterization &gt;7 d</td>
<td>1.54 (0.93-2.5) .10</td>
<td>3.45 (0.93-12.5) .07</td>
</tr>
<tr>
<td>Use of guidewire for catheter removal</td>
<td>0.36 (0.18-0.73) &lt;.01</td>
<td>...</td>
</tr>
</tbody>
</table>

*CRB indicates catheter-related bacteremia; CFU, colony-forming unit; CSS, combination of chlorhexidine and silver sulfadiazine; and ellipses, not applicable.

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**Figure 3.** Zone of inhibition of catheters coated with a combination product of chlorhexidine and silver sulfadiazine on Staphylococcus aureus (top) and Enterococcus (bottom) as a function of duration of catheterization. The diameter of the catheter is 2.5 mm; therefore, a zone of inhibition of 2.5 mm (dashed line) represents no inhibition of growth. Each dot represents 1 catheter segment (only 1 segment from each patient was used).
Although the incidence of significant bacterial growth on either the catheter tips or intradermal segments was high, the incidence of CRB was less than 5% in both groups and is comparable with previously published reports.6,8,9 More than 300 catheters were cultured, yet we were unable to detect any difference in the rate of CRB between the 2 groups. It is likely that the power of this study was insufficient to determine a difference between coated and uncoated catheters in the prevention of CRB. Assuming an \( \alpha \) error of .05 and \( \beta \) error of .20, for a 50% reduction in the rate of CRB (+5-5%), more than 1300 patients would be needed in each group.39 Such a study, if not impossible, would require substantial resources.

The CSS coating was generally effective in vitro against the test strain of _S. aureus_. However, the antimicrobial activity against _Enterococcus_ was much less robust and dissipated more quickly as a function of duration of catheterization. This result probably explains why there was no difference in the number of _Enterococcus_ isolates for the CSS catheter compared with control catheters. The organism responsible for the largest number of catheters with significant colonization was coagulase-negative staphylococcus, a finding observed in other studies.29,40 Recently published data29 show that unused CSS catheters will inhibit the growth of _Staphylococcus epidermidis_ in vitro. Although we did not test in vitro activity of CSS against these species as a function of duration of catheterization, the absolute number of isolates of coagulase-negative staphylococcus isolated from CSS catheters was reduced by approximately 30% compared with the uncoated catheters. The majority of CRB that occurred in patients irrespective of the type of catheter that was used was due to either coagulase-negative staphylococcus or _Enterococcus_, an indication that these bacteria will continue to be an important cause of nosocomial bacteremias even if CSS catheters are used.

The method used to identify CRB in this study may have overestimated the rate of bacteremia. Recent data31 show that molecular typing of bacteria will result in a more accurate determination of CRB. In this study, the use of molecular typing could have resulted in lower rates of bacteremia, but it is unlikely that the difference between CRB rates would change. All 3 cases of coagulase-negative staphylococcus CRB were diagnosed on the basis of only 1 positive blood culture. Traditionally, 2 positive blood cultures are required before a CRB with the uncoated catheters. The organism responsible for the largest number of catheters with significant colonization was coagulase-negative staphylococcus or _Enterococcus_, an indication that these bacteria will continue to be an important cause of nosocomial bacteremias even if CSS catheters are used.

In summary, we demonstrated that central venous catheterization with triple-lumen catheters coated with CSS were effective in reducing significant bacterial growth compared with uncoated catheters. There was no apparent effect on the incidence of CRB. Activity of the coating on these catheters against enterococci appears limited. In our patient population, the use of the CSS catheter does not appear to provide any clinically significant benefit over uncoated catheters.

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REFERENCES