**ABSTRACT**

**OBJECTIVE:** To test the evidence that the risk of infection related to central venous catheters (CVCs) is decreased by anti-infective coating or cuffing.

**DESIGN:** Systematic review of randomized, controlled trials comparing anti-infective with inactive (control) CVCs.

**INTERVENTIONS:** Average insertion times were taken as a measurement of the length of insertion. Dichotomous data were combined using a fixed effect model and expressed as odds ratio (OR) with 95% confidence interval (CI95).

**RESULTS:** Two trials on antibiotic coating (343 CVCs) had an average insertion time of 6 days; the risk of BSI decreased from 5.1% with control to 0% with anti-infective catheters. There were no trials with longer average insertion times. In three trials on silver collagen cuffs (422 CVCs), the average insertion time ranged from 5 to 8.2 days (median, 7 days); the risk of BSI was 5.6% with control and 3.2% with anti-infective catheters. In another trial on silver collagen cuffs (101 CVCs), the average insertion time was 38 days; the risk of BSI was 3.7% with control and 4.3% with anti-infective catheters. In five trials on chlorhexidine–silver sulfadiazine coating (1,269 CVCs), the average insertion time ranged from 5.2 to 7.5 days (median, 6 days); the risk of BSI decreased from 4.1% with control to 1.9% with anti-infective catheters. In five additional trials on chlorhexidine–silver sulfadiazine coating (1,544 CVCs), the average insertion time ranged from 7.8 to 20 days (median, 12 days); the risk of BSI was 4.5% with control and 4.2% with anti-infective catheters.

**CONCLUSIONS:** Antibiotic and chlorhexidine–silver sulfadiazine coatings are anti-infective for short (approximately 1 week) insertion times. For longer insertion times, there are no data on antibiotic coating, and there is evidence of lack of effect for chlorhexidine–silver sulfadiazine coating. For silver-impregnated collagen cuffs, there is evidence of lack of effect for both short- and long-term insertion (Infect Control Hosp Epidemiol 2002;23:748-756).

Central venous catheters (CVCs) are commonly used for hemodynamic monitoring, administration of medication, and parenteral nutrition. The most frequently reported problems are infection complications, occlusion of the catheter, vascular thrombosis, and catheter-related infections.1 Infection may be local or systemic, including thrombophlebitis, bloodstream infection (BSI), endocarditis, and metastatic distribution (eg, osteomyelitis, endophthalmitis, or arthritis).2,3 CVC-related bacteremia is a major cause of nosocomial BSI,4,5 with a reported incidence of approximately 5%.6 The consequences of these infections, in terms of morbidity, mortality, and additional healthcare costs, are of major importance.7

A novel technologic approach to reduce CVC-related infection is the impregnation of catheters with antiseptic or antimicrobial agents, but clinical trials to assess the efficacy of these agents have produced inconsistent results.8,9 Guidelines for the prevention of intravascular device-related infections published by the Centers for Disease Control and Prevention proposed the use of impregnated catheters for adults with an unacceptably high rate of infection,10 but no consensus has been reached about the definition of such a rate.

Recently, three studies reported important data on this subject. Two meta-analyses concluded that catheters impregnated with chlorhexidine–silver sulfadiazine decreased the incidence of catheter-related BSIs by 2.2% compared with inactive control catheters.11,12 However, a large, randomized, controlled trial showed that catheters treated with minocycline and rifampin were more efficacious in preventing BSI compared with those treated with chlorhexidine–silver sulfadiazine.13 In a few catheters with prolonged insertion times (> 1 week), an increased rate of BSI was observed for those treated with chlorhexidine–silver sulfadiazine compared with those treated with antibiotics. Although the numbers were small, it was suggested that these results should lead to a change in clinical practice for critical care patients.14

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The authors thank Daniel Haake from the Documentation Service of the Swiss Academy of Medical Sciences for his assistance in searching electronic databases and Rosemary Sudan for editorial assistance.
We undertook this study of randomized, controlled trials to quantify the relative efficacy of CVCs treated with different anti-infective agents and to identify factors that have an impact on the efficacy of these devices.

METHODS
Search Strategy
An extensive search of the relevant literature in all languages was performed using MEDLINE (Data Star, PubMed, and KnowledgeFinder 4.19 to January 20, 2000), EMBASE (to January 12, 2000), and Cochrane Library (2000, issue 1). Key words used alone or in combination included central venous catheter, infection, coated, impregnated, subcutaneous cuff, antibiotic bonding, antibiotic-coated, silver-sulfadiazine, chlorhexidine, and random. Reference lists of retrieved reports, review articles, and meta-analyses were checked. Data from abstracts, letters, review articles, and animal studies were not considered.

Inclusion Criteria, Endpoints, and Definitions
Included studies were full reports of randomized, controlled trials of adults that were published in peer-reviewed journals and that compared any antiseptic- or antimicrobial-coated or antiseptic- or antimicrobial-cuffed CVC (anti-infective) with a similar uncoated or uncuffed device (control). Relevant trials had to report on catheters that were inserted percutaneously; those in which catheters were exchanged over a guidewire were not considered.

One of two endpoints had to be reported in dichotomous form according to the definitions provided by the original authors: catheter colonization per 100 catheters inserted and BSI per 100 catheters inserted. Catheter colonization was considered as less important. It was defined as a documented growth from a proximal or distal catheter segment of either 15 or more colony-forming units (CFU) in a semiquantitative culture or more than 10^5 CFU in a quantitative culture. This definition was valid for the purpose of this study regardless of whether cultures were obtained from the external surface only or from both the internal and the external surfaces of the catheters. BSI was considered as the primary endpoint in this context. It was defined as the presence of the same organism isolated from a (semi)quantitative culture of a catheter segment and from the patient's blood in the absence of another source of infection. This subgroup included patients with or without accompanying clinical symptoms (ie, sepsis).

Scoring and Data Extraction
All authors independently read the included articles and assessed their methodologic quality using the validated Oxford scale. There was a pre hoc agreement to include trials with randomization according to the patients' date of birth, hospital chart number, or alternate allocation, but to exclude trials without randomization (eg, historical controls). Allocated scores were compared, and consensus was reached by discussion. Data abstraction was performed by one of the authors (BW) and independently cross-checked by the other two.

Qualitative, Quantitative, and Subgroup Analyses
For colonization, we calculated relative risk (RR) with 95% confidence interval (CI)_9_ and Peto odds ratio (OR); this is a more appropriate model when many trials show no events. We tested for statistical heterogeneity using a chi-square test. A fixed effect model was used throughout because we combined data only when they were clinically homogeneous.

There was a pre hoc agreement that an absolute risk reduction of 2% or more to prevent BSI (corresponding to a number-needed-to-treat of 50 or fewer) was a clinically relevant result and, therefore, would justify the use of anti-infective CVCs.

Sensitivity analyses were performed to test the impact of the duration of catheterization on the efficacy of these anti-infective devices to prevent BSI. For this purpose, we extracted information on the average catheter insertion times from the original articles.

RESULTS
Trial Characteristics
A total of 103 reports were screened. Twenty-seven were considered for inclusion and 4 were subsequently excluded due to the following: one had an inadequate control group; one used historical controls; one had inadequate endpoints; and one described the same cohort reported in a previous article. Finally, 23 trials published between 1988 and 1999 including data on 4,660 catheters (2,319 anti-infective and 2,341 control) were analyzed (Table 1). Eleven were conducted in an intensive care unit setting, four were conducted among oncologic patients, two were conducted among surgical patients, two were conducted among patients receiving total parenteral nutrition, and four were conducted among other patient populations. The average number of catheters per trial was 194 (range, 20 to 680). The dropout rate of catheters varied between 0% and 49%. Average observation periods ranged from 2 to 147 days. The median Oxford score was 2 (range, 1 to 5). In 18 trials, no attempt was made at blinding.

Anti-infective catheters were treated with chlorhexidine–silver sulfadiazine coating (12 trials, 1,456 catheters); silver-impregnated collagen cuffing (5 trials, 328 catheters); antibiotic coating with teicoplanin, minocycline plus rifampin, vancomycin, or cefazolin (5 trials, 329 catheters); and silver coating (2 trials, 206 catheters). One trial compared two devices with an inactive control group; all other trials compared one device with a control.

Qualitative and Quantitative Analyses
Catheter Colonization. Catheter colonization was reported in 22 trials (3,902 CVCs) (Table 1). There was a large variability in event rates with both anti-infective and control catheters: 1.7% to 62% (average, 22%) for anti-infective catheters; 1.7% to 62% (average, 22%) for anti-infective catheters; and 1.7% to 81% (average, 32%) for control catheters.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Setting</th>
<th>Anti-Infective Catheter and Control Catheter (No. of Catheters)</th>
<th>No. of Lumens</th>
<th>No. With Endpoint/Total No. Colonization</th>
<th>Bloodstream Infection</th>
<th>Insertion Time (d) Mean Range</th>
<th>Score (Random/Blinding/Dropouts)</th>
</tr>
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<tbody>
<tr>
<td>Bach et al.,28 1996</td>
<td>Major abdominal surgery</td>
<td>1. Catheter in teicoplanin bath for 15 min (10)</td>
<td>1</td>
<td>3/10</td>
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<td>Bach et al.,28 1996</td>
<td>Cardiac surgery</td>
<td>1. Silver sulfadiazine + chlorhexidine-impregnated catheter (116)</td>
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<td>18/116</td>
<td>0/116</td>
<td>7.5 to 8.1, 0.95 to 22.9</td>
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<tr>
<td>Boswald et al.,29 1999</td>
<td>Different populations</td>
<td>1. Silver-impregnated catheter (86)</td>
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<td>81/117</td>
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<td>8 to 9, 5 to 51</td>
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<td>Ciresi et al.,30 1996</td>
<td>Total parenteral nutrition</td>
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<td>10/124</td>
<td>8/124</td>
<td>11.5 to 12.9</td>
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<tr>
<td>Dahlberg et al.,31 1995</td>
<td>Dialysis</td>
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<td>7/47</td>
<td>2/47</td>
<td>34.8 to 41.5</td>
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<td>Flowers et al.,32 1989</td>
<td>Surgical ICU</td>
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<td>11/54</td>
<td>2/54</td>
<td>4.4 to 5.6, 2.0 to 16.9</td>
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<td>George et al.,33 1997</td>
<td>Immuno compromised transplant patients</td>
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<td>10/120</td>
<td>12.7 to 13.3, 3 to 61</td>
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<td>7.5 to 7.6, 1 to 32</td>
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<td>Heard et al.,37 1998</td>
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<td>8.5 to 9.0, 1 to 65</td>
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<td>Hematologic malignancies</td>
<td>1. Silver sulfadiazine + chlorhexidine-impregnated catheter (338)</td>
<td>2 or 3</td>
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### Analyzed Trials of Central Venous Catheters With Coating or Cuffing

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<th>Anti-Infective Catheter and Control Catheter (No. of Catheters)</th>
<th>No. of Lumens</th>
<th>Colonization</th>
<th>Bloodstream Infection</th>
<th>Insertion Time (d)</th>
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<td>6.6</td>
<td>0 to 18, 0/0/1*</td>
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<td></td>
<td>without granulocytopenia</td>
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<td>28/208</td>
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<td>1/36</td>
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<td>5/137</td>
<td>5.1 to 5.3</td>
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<td>1/0/0</td>
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<td>2. Normal catheter (85)</td>
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<td>van Heerden et al., 1996</td>
<td>ICU</td>
<td>1. Silver sulfadiazine + chlorhexidine-impregnated catheter (28)</td>
<td>2 or 3</td>
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<td>1/0/0</td>
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ICU = intensive care unit.

*Randomization according to patient's medical record number.

*Initially randomized, controlled trial, subsequently alternating allocation.

*Treatment allocation alternately (bimonthly).
Infection control and hospital epidemiology December 2002

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S 80%. 1 o 60%. 8 0 40%. 8 0 20%. 0%J

Incidence with anti-infective catheters

0% 20% 40% 60% 80% 100%

Incidence with anti-infective catheters

Incidence of (left) colonization and (right) bloodstream infection with anti-infective catheters (x axis) and control catheters (y axis). Each circle represents one trial. The sizes of the circles are proportional to the sizes of the trials. The dotted lines represent equality.

FIGURE 1. Incidence of colonization and bloodstream infection with anti-infective catheters (x axis) and control catheters (y axis). Each circle represents one trial. The sizes of the circles are proportional to the sizes of the trials. The dotted lines represent equality.

Antibiotic coating Insertion time (day) * „

Silver-Impregnated collagen cuffing ••

Chlorhexidine-silver sulfadiazine coating •—' Smith M

FIGURE 2. Impact of the average insertion times as reported in the original trials on the efficacy of anti-infective catheters to prevent bloodstream infection in the respective study. One study38 with no events has been excluded.

95% CI = 95% confidence interval.

Favors Favors Favors Favors Favors Favors Favors active control active control active control

Impact of Insertion Time on Anti-Infective Efficacy. Of all 18 trials that reported on BSI, one33 did not report on the average insertion time, one34 tested silver coating (ie, a technique that was not tested in any other trial reporting on BSI), and in one38 there was no BSI (ie, 0 events). Thus, sensitivity analyses to quantify the impact of insertion time on anti-infective efficacy could be performed with data from 15 trials (16 comparisons) that tested antibiotic coating, silver-impregnated collagen cuffing, and chlorhexidine-silver sulfadiazine coating (Fig. 2; Table 2).

In both relevant trials on antibiotic coating (343 CVCs), the average insertion time was 6 days.26,41 The combined risk of BSI decreased from 5.1% with control to 0% with anti-infective catheters (OR, 0.14; CI95, 0.04 to 0.51). There were no trials with longer average insertion times.

In three of four trials on silver-impregnated collagen cuffs (422 CVCs), the average insertion time ranged from 5 to 8.2 days (median, 7 days).32,40,43 The combined risk of BSI was 5.6% with control and 3.2% with anti-infective catheters (OR, 0.54; CI95, 0.21 to 1.36). In the fourth trial on silver-impregnated collagen cuffs (101 CVCs), the average insertion time was 38 days.31 The risk of BSI was 3.7% with control and 4.3% with anti-infective catheters (OR, 1.15; CI95, 0.16 to 8.49). One trial reported an average insertion time of 8.2 days.40 When data from this trial were pooled with the data from the trial with the longest average insertion time,31 long-term efficacy was still not statistically significant (incidence of BSI, 3.7% with control vs 2.1% with anti-infective catheters [OR, 0.56; CI95, 0.16 to 1.98]).

In five of 10 trials on chlorhexidine-silver sulfadiazine coating (1,269 CVCs), the average insertion time was homogeneous (P = .329). When data from all trials were combined, the difference in favor of anti-infective catheters was statistically significant (OR, 0.63; CI95, 0.45 to 0.87).

BSI. BSI was reported in 18 trials (4,045 CVCs) (Table 1). There was a large variability in event rates with both anti-infective and control catheters: 0% to 7.8% (average, 2.9%) for control catheters (Fig. 1, left). The scatter suggested improvement with anti-infective catheters. The data were heterogeneous (P < .001). When data from all trials were combined, the difference in favor of anti-infective catheters was statistically significant (RR, 0.61; CI95, 0.51 to 0.72).

Bacterial colonization and bloodstream infection (BSI) with anti-infective catheters and 9.4% to 80% (average, 35%) for control catheters (Fig. 1, left). The scatter suggested improvement with anti-infective catheters. The data were heterogeneous (P < .001). When data from all trials were combined, the difference in favor of anti-infective catheters was statistically significant (RR, 0.61; CI95, 0.51 to 0.72).

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ranged from 5.2 to 7.5 days (median, 6 days). The combined risk of BSI decreased from 4.1% with control to 1.9% with anti-infective catheters (OR, 0.48; CI95, 0.25 to 0.91). In the five other trials on chlorhexidine–silver sulfadiazine coating (1,544 CVCs), the average insertion time ranged from 7.8 to 20 days (median, 12 days). The combined risk of BSI was 4.5% with control and 4.2% with anti-infective catheters (OR, 0.94; CI95, 0.58 to 1.54).

**Adverse Events**

Twelve trials reported the presence or absence of adverse events. There was some evidence that cuffed catheters were more difficult to insert than control catheters, and that they extruded more often. No systemic allergic reaction or local hypersensitivity was reported in any trial.

**Conclusions of the Original Authors**

In 12 studies (52%), the original authors concluded from their data that anti-infective catheters were useful. In ten, they questioned the usefulness of such devices. The authors of one trial did not draw any conclusions.

**DISCUSSION**

One of the proposed strategies to prevent CVC-related infection is the antiseptic or antimicrobial coating or cuffing of catheters. BSI is the most relevant endpoint in this context. Two factors can be identified that have a major impact on the prevention of BSI with these catheters: insertion time and type of anti-infective method. In previous meta-analyses on the antimicrobial efficacy of catheters treated with chlorhexidine–silver sulfadiazine, and from data on short-term trials only (2 to 10 days), there was a statistically significant decrease in BSI compared with control catheters (OR, 0.56; CI95, 0.37 to 0.84). The authors concluded that these devices were effective in decreasing BSI. In our analysis, the result was similar for the subgroup of catheters treated with chlorhexidine–silver sulfadiazine and having short-term insertion (OR, 0.48; CI95, 0.25 to 0.91). However, one additional important conclusion from this systematic review is that first-generation chlorhexidine–silver sulfadiazine catheters are not efficacious when the average insertion time is longer than 8 days.

Microorganisms in contact with plastic surfaces produce a protective, multi-layer biofilm within which they can survive. It is tempting to speculate that such a biofilm could suppress the anti-infective action of the treated catheters. Indeed, with average insertion times of approximately 1 week, 1 in approximately 50 catheters treated with chlorhexidine–silver sulfadiazine will not lead to a BSI, which would have been the case with inactive devices (absolute risk reduction, 2.2%) (Table 2). When average insertion times were twice as long (approximately 12 days), this number was 1 in approximately 300 (absolute risk reduction, 0.3%). These results are in agreement with both in vitro and in vivo studies. In vitro, a steep exponential decrease in antimicrobial activity was shown during the
first week of insertion for devices treated with chlorhexidine–silver sulfadiazine. In vivo, the antimicrobial activity of CVCs treated with chlorhexidine–silver sulfadiazine was shown to be time dependent.

With antibiotic coating, there was not one single case of BSI. The absolute risk reduction compared with inactive control catheters was 5.1%, suggesting that approximately 20 patients need to receive an antibiotic-coated CVC for one patient not to develop a BSI who would have done so had they received inactive catheters. Thus, for short insertion times (ie, no longer than approximately 1 week), there was some evidence from indirect comparisons that antibiotic coating was more efficacious than chlorhexidine–silver sulfadiazine impregnation. These data are consistent with the results of a recently published large, randomized trial in which CVC-related BSI was less likely in catheters coated with minocycline–rifampin (incidence, 0.3%) compared with catheters treated with chlorhexidine–silver sulfadiazine (incidence, 3.4%) with a median insertion time of 6 to 7 days. For both devices, the degree of short-term antimicrobial efficacy falls into our pre hoc definition of worthwhile prevention (ie, absolute risk reduction of ≥ 2% corresponding to a number-needed-to-treat of ≤ 50). However, data from the randomized trial and from our meta-analysis suggest that twice as many catheters treated with chlorhexidine–silver sulfadiazine, compared with antibiotic-coated catheters, need to be inserted to prevent one BSI. We do not know whether the difference in efficacy between these catheter types is due to the anti-infective substances per se, different methods of coating, or both. Impregnation with chlorhexidine–silver sulfadiazine covers only the external surface of catheters. Some antibiotic coatings cover both the external and the internal surfaces of catheters. This may be associated with enhanced efficacy, as previously suggested, but needs to be formally tested.

No long-term data on antibiotic-treated CVCs were available. In one study, a complete loss of activity for teicoplanin-coated catheters within 36 hours was reported. Catheters treated with minocycline and rifampin may have antimicrobial activity extending up to 2 and possibly up to 4 to 6 weeks. This inconsistency may be interpreted as evidence of specific antibiotic activities. Further randomized trials are needed to establish the effect of different antibiotic coating methods on the long-term anti-infective efficacy of CVCs.

Silver-impregnated collagen capping did not prevent BSI, although one small trial with a short insertion time (average, 5 days) reported a borderline significant result in favor of the anti-infective catheters. In that trial, almost 14% of patients who received a control catheter had a BSI, a rate that was much higher than that in any other trial (Fig. 1, right). Because we have to assume that there is a relationship between the event rate in control catheters and the true underlying risk, it may be speculated that that trial studied patients at a particular high risk of infection. This was not the case (Table 1). However, small trials have been shown in other settings to overestimate the effect of an intervention. Because that trial was of limited size, it had no important weight in the combined analysis.

When inserted for no longer than 1 week, 1 in approximately 20 antibiotic-coated catheters and 1 in
approximately 50 catheters coated with chlorhexidine–silver sulfadiazine will not lead to a BSI, which would have occurred in critically ill patients. Anti-infective catheters are important in reducing the incidence of CVC-related infection, but further research is required to define the most efficacious method and the optimal time for device replacement and to identify subgroups of patients who might benefit most from this preventive measure. Cost-effectiveness analyses of such interventions are also required.

**References**


42. Pemberton LB, Ross V, Cudby P, Kremmer H, Fessler T, McCurk E. No difference in catheter sepsis between standard and antiseptic central