

# Efficacy of Antiseptic-Impregnated Central Venous Catheters in Preventing Catheter-Related Bloodstream Infection

## A Meta-analysis

David L. Veenstra, PharmD, PhD

Sanjay Saint, MD, MPH

Somnath Saha, MD, MPH

Thomas Lumley, PhD

Sean D. Sullivan, PhD

CENTRAL VENOUS CATHETERS ARE commonly used for parenteral nutrition and fluid or drug administration in a variety of hospital settings. While providing convenient and beneficial venous access, these catheters also increase the risk of nosocomial bloodstream infection, contributing to the more than 200 000 cases that occur annually in the United States.<sup>1</sup> Catheter-related bloodstream infection (CR-BSI) can be a serious complication, leading to increases in mortality, hospital stay, and medical costs.<sup>2</sup>

A variety of methods have been used to prevent catheter-related infections. Aseptic insertion techniques and proper catheter care have proved effective, while silver-coated catheter cuffs have produced mixed results.<sup>3</sup> Recently, the use of antibiotic-coated and antiseptic-impregnated catheters to reduce the incidence of CR-BSI has been evaluated. Examples of the antibiotics that have been used to coat catheters include cefazolin<sup>4</sup> and minocycline-rifampin.<sup>5,6</sup> Although antibiotic-coated catheters show promise clinically, the technical requirements for coating the catheter and concerns of antibiotic resistance may limit their widespread use.

Catheters impregnated with the combination antiseptic chlorhexidine–silver

**Context** Central venous catheters impregnated with chlorhexidine and silver sulfadiazine have recently been introduced for the prevention of catheter-related infections. However, there remains some uncertainty regarding the efficacy of these catheters because of conflicting reports in the literature.

**Objective** To evaluate the efficacy of chlorhexidine–silver sulfadiazine–impregnated central venous catheters in the prevention of catheter-related bloodstream infection.

**Data Sources** Studies identified from a computerized search of the MEDLINE database from January 1966 to January 1998, reference lists of identified articles, and queries of principal investigators and the catheter manufacturer.

**Study Selection** Randomized trials comparing chlorhexidine–silver sulfadiazine–impregnated central venous catheters with nonimpregnated catheters were included. The outcomes assessed were catheter colonization and catheter-related bloodstream infection confirmed by catheter culture.

**Data Extraction** Twelve studies met the inclusion criteria for catheter colonization and included a total of 2611 catheters. Eleven studies with a total of 2603 catheters met the inclusion criteria for catheter-related bloodstream infection. Most patients in these studies were from groups considered to be at high risk for catheter-related infections. Summary statistics were calculated using Mantel-Haenszel methods under a fixed-effects model.

**Data Synthesis** The summary odds ratio for catheter colonization was 0.44 (95% confidence interval [CI], 0.36-0.54;  $P < .001$ ), indicating a significant decrease in catheter colonization associated with impregnated catheters. The studies examining the outcome of primary interest, catheter-related bloodstream infection, had a summary odds ratio of 0.56 (95% CI, 0.37-0.84;  $P = .005$ ).

**Conclusions** Central venous catheters impregnated with a combination of chlorhexidine and silver sulfadiazine appear to be effective in reducing the incidence of both catheter colonization and catheter-related bloodstream infection in patients at high risk for catheter-related infections.

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sulfadiazine do not require coating before insertion and may be less susceptible to antibiotic resistance.<sup>7</sup> Several recent randomized trials<sup>8-22</sup> have assessed the efficacy of these catheters in reducing catheter colonization and CR-BSI. Although most of the studies have shown a significant reduction in catheter colonization, only 1 study<sup>9</sup> has shown a significant reduction in the clinically more important

**Author Affiliations:** Departments of Pharmacy (Drs Veenstra and Sullivan), Medicine (Drs Saint and Saha), Biostatistics (Dr Lumley), and Health Services (Dr Sullivan), University of Washington, Seattle. Dr Saint is now with the University of Michigan Medical Center, Ann Arbor.

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**Corresponding Author and Reprints:** David L. Veenstra, PharmD, PhD, University of Washington School of Pharmacy, PO Box 357630, Seattle, WA 98195-7630 (e-mail: veenstra@u.washington.edu).

outcome of CR-BSI, making it difficult to reliably discern the overall effectiveness of chlorhexidine–silver sulfadiazine–impregnated catheters.

We performed a meta-analysis of available studies to quantitatively assess the efficacy of chlorhexidine–silver sulfadiazine–impregnated central venous catheters for the prevention of nosocomial catheter colonization and CR-BSI. Meta-analytical techniques provide a framework for evaluating the merits of a novel technology in an unbiased manner and can clarify discrepancies of previous trials as well as provide sufficient power to detect differences in outcomes with low incidence.<sup>23,24</sup>

## METHODS

### Data Sources

A computerized search of the MEDLINE databases from January 1966 to January 1998 for publications in any language was conducted using the exploded key words *chlorhexidine*, *antiseptic*, and *catheter*. The reference lists of the retrieved articles were reviewed for additional studies, as were review articles on the subject. The manufacturer of chlorhexidine–silver sulfadiazine–impregnated catheters (Arrow International, Reading, Pa) and the corresponding author of each of the studies located by initial literature review were contacted for additional sources of information.

### Study Selection

Inclusion criteria for the meta-analysis were the following: randomized, controlled clinical trials using chlorhexidine–silver sulfadiazine–impregnated central venous catheters in the treatment group and nonimpregnated central venous catheters in the control group; reporting of the incidence of catheter colonization or CR-BSI as a study outcome; and sufficient data to calculate effect size. Studies with a quasi-randomized design (eg, randomization by patient record number) were included in the main analysis. Studies that did not initially provide sufficient information were also included if the required information was subsequently provided by an author.

### Outcome Definitions

Catheter colonization is typically defined as isolation of an organism from a subcutaneous or intravenous catheter segment on catheter removal.<sup>3,25,26</sup> In the analysis of catheter colonization, all studies that defined catheter colonization as growth from a catheter segment using semiquantitative<sup>27</sup> or quantitative<sup>28</sup> culture techniques were included. One study<sup>21</sup> that reported catheter colonization but did not define the method used was excluded from the main analysis but examined separately in a sensitivity analysis. Greater variability exists in the definition of CR-BSI. The Centers for Disease Control and Prevention defines CR-BSI as isolation of the same organism from a semiquantitative or quantitative culture of a catheter segment and from the blood of a patient with accompanying clinical symptoms of bloodstream infection and no other apparent source of infection.<sup>3</sup> The majority of studies had no explicit requirements for the presence of clinical symptoms of bloodstream infection or for the absence of other sources of infection. Thus, in the main analysis of CR-BSI, we included all studies that defined CR-BSI as isolation of the same organism from blood and catheter cultures using semiquantitative or quantitative culture techniques with or without clinical signs of systemic infection or lack of evidence of other sources of infection. Sensitivity analyses were conducted to explore the effect of using different definitions of CR-BSI. One study<sup>22</sup> that reported the incidence of CR-BSI based on paired blood cultures<sup>29</sup> was excluded from the main analysis of CR-BSI and examined separately in a sensitivity analysis.

### Data Extraction

Two authors (D.L.V. and S. Saha) independently abstracted information from each of the selected studies; 1 abstractor was blinded to author, journal, title, year, study site, and source of support of the publication. Each study was reviewed for sample size, patient population, type of catheters used, catheterization site, use of catheter exchange with

guide wire, concurrent interventions, catheter colonization and CR-BSI definitions, catheter colonization and CR-BSI incidence in treatment and control groups, duration of catheterization, and reports of adverse effects. We also evaluated the following methodological components of each study: appropriateness of randomization, extent of blinding, and description of eligible subjects.<sup>30</sup> Attempts were made to acquire additional information from authors of the studies as required. Any discrepancies between the abstractors were resolved by a third author (S. Saint).

### Statistical Methods and Sensitivity Analysis

The incidences of catheter colonization and CR-BSI were analyzed separately. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each study, and the summary ORs were calculated using Mantel-Haenszel methods under a fixed-effects model.<sup>31</sup> Tests for heterogeneity of the ORs were performed using the Woolf method.<sup>32</sup> Publication bias was investigated with tests for association between effect size and study size.

Some studies allowed subjects to receive more than 1 catheter during the study period but used the patient as the unit of randomization.<sup>14-16,19,20</sup> The resulting within-patient correlation leads to underestimation of the SE of the OR. To investigate the effect of this correlation, a sensitivity analysis was performed using a conservative estimate of the variance obtained by multiplying the variance of the OR for each of these studies by the average number of catheters per patient. We used catheter-based results rather than patient-based results from the study by Ciresi et al<sup>16</sup> (Roxie Albrecht, MD, written communication, January 1998) for consistency with the analysis of the other studies. Although this results in a slight decrease in the study OR (from 1.08 to 0.95), the effect on the summary results is small and not significant.

In addition to the sensitivity analyses incorporating increased variance estimates and the 2 studies<sup>21,22</sup> not meeting

the outcome definition criteria, the following sensitivity analyses were planned a priori: exclusion of studies with quasi-randomized design, exclusion of studies that did not use only triple-lumen catheters, and investigation of any sources of heterogeneity. The effect of the duration of catheterization was examined by plotting the study ORs in order of increasing treatment catheter duration.

**RESULTS**

**Study Selection**

A total of 215 articles were located from all sources. No unpublished studies were found. Twenty-four studies were comparative studies of chlorhexidine–silver sulfadiazine–impregnated vs nonimpregnated central venous catheters in humans. Nine studies<sup>33-41</sup> were not randomized and 2 studies<sup>21,22</sup> were excluded

based on criteria for defining catheter colonization and CR-BSI. Of the remaining 13 studies, 4<sup>11,12,18,19</sup> were published in abstract form. Ten studies examined both catheter colonization and CR-BSI, 2 examined only catheter colonization, and 1 reported only CR-BSI. Thus, 12 studies<sup>8-16,18-20</sup> were used in the analysis of catheter colonization (2611 catheters), and 11 studies<sup>8,9,11,13-20</sup> were used in the analysis of CR-BSI (2603 catheters). A summary of the 13 studies is given in TABLE 1.

**Study Characteristics**

The majority of studies used triple-lumen catheters; of 2830 catheters in the 13 studies, 2494 were triple-lumen, 306 were double-lumen, and 30 were single-lumen (Table 1). Most patients were from populations at high risk for catheter-

related infections; approximately one third of catheters were from patients in the intensive care unit, and 2 studies<sup>16,17</sup> exclusively examined patients receiving total parenteral nutrition. The remaining patients were from a variety of hospital settings. The mean duration of treatment catheter placement ranged from 5.1 to 11.2 days. There was no significant difference in catheter location between treatment and control groups in studies reporting catheter insertion site.<sup>9,13-17,20</sup> Five studies allowed catheter exchange using a guide wire.<sup>9,14-16,19</sup> There were no reports of adverse effects from the treatment catheters in any of the studies.

The majority of studies cultured an intravascular catheter segment using semiquantitative methods; several studies cultured both intravascular and sub-

**Table 1.** Characteristics of Studies Comparing Antiseptic-Impregnated With Control Catheters\*

Study, y	No. of Catheter Lumens	Patient Population	Catheter Exchange†	No. of Catheters (No. of Patients)		Catheter Duration, Mean, d		Outcome Definitions	
				Treatment Group	Control Group	Treatment Group	Control Group	Catheter Colonization‡	Catheter-Related Bloodstream Infection§
Tennenberg et al, <sup>8</sup> 1997	2, 3	Hospital	No	137 (137)	145 (145)	5.1	5.3	SQ (IV, SC, >15 CFU)	SO (IV, SC, site), CS, NS
Maki et al, <sup>9</sup> 1997	3	ICU	Yes	208 (72)	195 (86)	6.0	6.0	SQ (IV, >15 CFU)	SO (>15 CFU, IV, hub, inf)
van Heerden et al, <sup>10</sup> 1996¶	3	ICU	No	28 (28)	26 (26)	6.6	6.8	SQ (IV, >15 CFU)	NR
Hannan et al, <sup>11</sup> 1996	3	ICU	NR	68 (NR)	60 (NR)	7	8	SQ (IV, >10 <sup>3</sup> CFU)#	SQ (IV, >10 <sup>3</sup> CFU), NS
Bach et al, <sup>12</sup> 1994¶	3	ICU	No	14 (14)	12 (12)	7.0	7.0	QN (IV, >10 <sup>3</sup> CFU)	NR
Bach et al, <sup>13</sup> 1996¶	2, 3	Surgical	No	116 (116)	117 (117)	7.7	7.7	QN (IV, >10 <sup>3</sup> CFU)	SO (IV)
Heard et al, <sup>14</sup> 1998¶	3	SICU	Yes	151 (107)	157 (104)	8.5	9	SQ (IV, SC, >14 CFU)	SO (IV, SC, >4 CFU)
Collin, <sup>15</sup> in press	1, 2, 3	ED/ICU	Yes	98 (58)	139 (61)	9.0	7.3	SQ (IV, SC, >15 CFU)	SO (IV, SC)
Ciresi et al, <sup>16</sup> 1996¶	3	TPN	Yes	124 (92)	127 (99)	9.6	9.1	SQ (IV, SC, >15 CFU)	SO (IV, SC)
Pemberton et al, <sup>17</sup> 1996	3	TPN	No	32 (32)	40 (40)	10	11	NR	SO (IV, res, NS)
Ramsay et al, <sup>18</sup> 1994¶	3	Hospital	No	199 (199)	189 (189)	10.9	10.9	SQ (IV, SC, >15 CFU)	SO (IV, SC)
Trazzera et al, <sup>19</sup> 1995¶	3	ICU/BMT	Yes	123 (99)	99 (82)	11.2	6.7	SQ (IV, >15 CFU)	SO (IV, >15 CFU)
George et al, <sup>20</sup> 1997	3	Transplant	No	44 (NR)	35 (NR)	NR	NR	SQ (IV, >5 CFU)	SO (IV)

\*NR indicates not reported; ICU, intensive care unit; SICU, surgical intensive care unit; TPN, total parenteral nutrition; BMT, bone marrow transplant; ED, emergency department; hospital, hospitalwide or a variety of settings; SQ, semiquantitative culture; QN, quantitative culture; CFU, colony-forming units; IV, intravascular catheter segment; SC, subcutaneous catheter segment; site, catheter insertion site; hub, catheter hub; inf, catheter infusate; SO, same organism isolated from blood and catheter; CS, clinical symptoms of systemic infection; res, resolution of symptoms on catheter removal; and NS, no other sources of infection.

†Catheter exchange was performed using a guide wire.

‡Catheter segments cultured and criteria for positive culture are given in parentheses.

§Catheter segment or site cultured and criteria for positive culture are given in parentheses.

||Organism identity was confirmed by restriction-fragment subtyping.

¶Additional information was provided by author (personal communications, Jan 1998-Mar 1998).

#Culture method is reported as semiquantitative; criteria for culture growth suggest quantitative method.

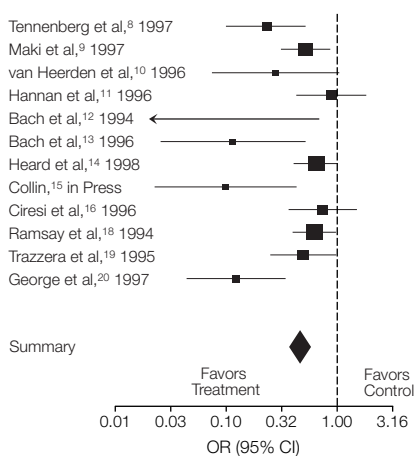
cutaneous segments and 3 studies used quantitative culture methods (Table 1). In the studies of CR-BSI, 2 studies required either the presence of clinical symptoms of bloodstream infection<sup>8</sup> or resolution of symptoms on catheter removal<sup>17</sup> and 3 studies required no other sources of infection.<sup>8,11,17</sup> Five studies explicitly stated that peripheral blood cul-

tures were drawn only when there were clinical symptoms suggesting bloodstream infection.<sup>9,14-16,18</sup>

A variety of randomization procedures were used in the studies. Three trials randomized catheters,<sup>9,11,13</sup> while the other trials randomized patients. Three trials<sup>14,16,19</sup> randomized patients by patient record number (Salvatore Trazzera, MD, written communication, January 1998). The investigators were blinded to catheter type in 5 of the studies<sup>9,12,13,16,18</sup> (Roxie Albrecht, MD, written communication, January 1998; Alfons Bach, MD, written communication, February 1998; James Ramsay, MD, written communication, January 1998; P. Vernon van Heerden, MD, written communication, January 1998). Patient eligibility and study dropouts were adequately described in 7 of the studies.<sup>8-10,14,16,17,20</sup>

cause the smaller trials tend to show a greater reduction in the odds of catheter colonization. However, there was no evidence of correlation of the logarithm of the OR (log[OR]) with the number of events, ranked number of events, or SE of log(OR). There is no obvious trend in the study ORs with duration of catheterization (Figure 1).

**Figure 1.** Analysis of Catheter Colonization in Trials Comparing Chlorhexidine–Silver Sulfadiazine–Impregnated Central Venous Catheters With Nonimpregnated Catheters



The diamond indicates summary odds ratio (OR) and 95% confidence interval (CI). Studies are ordered by increasing mean duration of catheterization in the treatment group. The size of the squares is inversely proportional to the variance of the studies.

**Catheter Colonization**

The summary results from the 12 studies examining catheter colonization indicate a significant reduction in the odds of catheter colonization in the treatment group (OR, 0.44; 95% CI, 0.36-0.54;  $P < .001$ ) (FIGURE 1 and TABLE 2). The test for heterogeneity of treatment effect for catheter colonization among the studies was significant ( $P = .005$ ). There is some evidence of publication bias be-

**Catheter-Related Bloodstream Infection**

Pooling the results from the 11 studies examining the incidence of CR-BSI revealed a significant reduction in the odds of CR-BSI in the treatment group (OR, 0.56; 95% CI, 0.37-0.84;  $P = .005$ ) (FIGURE 2 and Table 2). There is no evidence of heterogeneity among the study ORs ( $P = .81$ ). Tests of publication bias were not significant. There is no clear relationship between the mean duration of catheterization and the study ORs (Figure 2).

**Sensitivity Analyses**

Increasing the variance of the 5 studies<sup>14-16,19,20</sup> that had more than 1 catheter per patient and were randomized by patient did not substantially change the CI of the summary OR for catheter colonization (OR, 0.45; 95% CI, 0.36-0.55;  $P < .001$ ) or CR-BSI (OR, 0.54; 95% CI, 0.35-0.84;  $P = .005$ ). Exclusion of the 3

**Table 2.** Results for Trials Examining Catheter Colonization and Catheter-Related Bloodstream Infection\*

Study, y	Catheter Colonization			Catheter-Related Bloodstream Infection		
	Positive Cultures, No. (%)		OR (95% CI)	Positive Cultures, No. (%)		OR (95% CI)
	Treatment Group	Control Group		Treatment Group	Control Group	
Tennenberg et al, <sup>8</sup> 1997	8 (5.8)	32 (22.1)	0.22 (0.10-0.49)	5 (3.6)	9 (6.2)	0.57 (0.19-1.75)
Maki et al, <sup>9</sup> 1997	28 (13.5)	47 (24.1)	0.49 (0.29-0.82)	2 (1.0)	9 (4.6)	0.20 (0.04-0.94)
van Heerden et al, <sup>10</sup> 1996	4 (14.3)	10 (38.5)	0.27 (0.07-1.00)	...	...	...
Hannan et al, <sup>11</sup> 1996	22 (32.4)	22 (36.7)	0.83 (0.40-1.72)	5 (7.4)	7 (11.7)	0.60 (0.18-2.00)
Bach et al, <sup>12</sup> 1994†	0 (0)	4 (33.3)	0 (0-0.65)	...	...	...
Bach et al, <sup>13</sup> 1996†	2 (1.7)	16 (13.7)	0.11 (0.02-0.49)	0 (0)	3 (2.6)	0 (0-1.28)
Heard et al, <sup>14</sup> 1998	60 (39.7)	82 (52.2)	0.60 (0.38-0.95)	5 (3.3)	6 (3.8)	0.86 (0.26-2.89)
Collin, <sup>15</sup> in press	2 (2.0)	25 (18.0)	0.10 (0.02-0.41)	1 (1.0)	4 (2.9)	0.35 (0.04-3.16)
Ciresi et al, <sup>16</sup> 1996†	15 (12.1)	21 (16.5)	0.69 (0.34-1.42)	13 (10.5)	14 (11.0)	0.95 (0.43-2.10)
Pemberton et al, <sup>17</sup> 1996	...	...	...	2 (6.3)	3 (7.5)	0.82 (0.13-5.24)
Ramsay et al, <sup>18</sup> 1994	45 (22.6)	63 (33.3)	0.58 (0.37-0.92)	1 (0.5)	4 (2.1)	0.23 (0.03-2.11)
Trazzera et al, <sup>19</sup> 1995†	16 (13.0)	24 (24.2)	0.47 (0.23-0.94)	4 (3.3)	5 (5.1)	0.63 (0.17-2.42)
George et al, <sup>20</sup> 1997	10 (22.7)	25 (71.4)	0.12 (0.04-0.33)	1 (2.3)	3 (8.6)	0.25 (0.02-2.50)

\*OR indicates odds ratio; CI, confidence interval; ellipses, data not applicable.  
†Additional information provided by author (personal communications, Jan 1998-Mar 1998).

trials<sup>14,16,19</sup> randomized by patient record number produced a summary OR of 0.37 (95% CI, 0.29-0.48;  $P < .001$ ) for catheter colonization and 0.39 (95% CI, 0.22-0.69;  $P = .001$ ) for CR-BSI. Analysis of the studies<sup>9-12,14,16-20</sup> that exclusively used triple-lumen catheters gave a summary OR of 0.52 (95% CI, 0.42-0.64;  $P < .001$ ) for catheter colonization and 0.60 (95% CI, 0.38-0.95;  $P = .03$ ) for CR-BSI.

A sensitivity analysis to investigate possible sources of heterogeneity in the studies examining catheter colonization indicated that the trial by George et al<sup>20</sup> was the most important source of heterogeneity. Exclusion of this study increased the  $P$  value for the test of heterogeneity from .005 to .04. An analysis of the trials<sup>8-10,14-16,18,19</sup> using standard semiquantitative culture methods<sup>27</sup> to define catheter colonization showed no significant heterogeneity ( $P = .10$ ) and had little effect on the summary results (OR, 0.47; 95% CI, 0.38-0.59;  $P < .001$ ). Including the trial<sup>20</sup> that did not define catheter colonization did not noticeably change the summary results.

Analysis of the 7 studies either that required clinical symptoms for the definition of CR-BSI<sup>8,17</sup> or in which blood cultures were drawn only when there were clinical symptoms of bloodstream infection<sup>9,14-16,18</sup> gave a summary OR for CR-BSI of 0.60 (95% CI, 0.37-0.97;  $P = .03$ ). Including the study<sup>22</sup> that used paired blood cultures to define CR-BSI with the studies in the main analysis increased the summary OR for CR-BSI, but the results remained statistically significant (OR, 0.67; 95% CI, 0.47-0.95;  $P = .02$ ).

## COMMENT

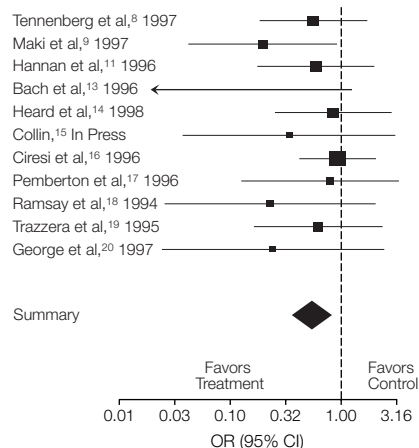
The findings of this quantitative review indicate that central venous catheters impregnated with chlorhexidine-silver sulfadiazine are effective in reducing the incidence of catheter colonization and CR-BSI compared with nonimpregnated catheters. The reduction in the odds of catheter colonization and CR-BSI in the treatment group is significant in the main analyses and in all of the sensitivity analyses.

The individual trials provided fairly strong evidence of the efficacy of

chlorhexidine-silver sulfadiazine-impregnated catheters in preventing catheter colonization, but the evidence for the outcome of primary clinical and economic interest, CR-BSI, was less compelling. Although all of the trials showed a reduction in the odds of CR-BSI using catheter-based data, 10 of the 11 trials failed to show a statistically significant reduction, possibly because of the lack of adequate power. Thus, the only statistically significant evidence of a reduction in CR-BSI was provided by 1 single-center trial.<sup>9</sup> This meta-analysis serves to reconcile the lack of significant treatment effect found for CR-BSI in previous trials and provides further evidence for the effectiveness of central venous catheters impregnated with chlorhexidine-silver sulfadiazine.

The summary effect size found for CR-BSI in the main analysis and the sensitivity analyses suggests that impregnated catheters reduce the risk of bloodstream infection associated with central venous catheters by about 40%. These results are applicable only for similar patient populations and interventions (ie, patients at high risk for developing CR-BSI that require a short-term, multilumen central venous catheter). There are important clinical and economic implications of a 40% reduction in the incidence of CR-BSI. This is particularly true for intensive care units, where 3% to 7% of central venous catheters lead to CR-BSI,<sup>9,42</sup> with an attributable patient mortality of 10% to 35% and associated costs of up to \$30 000 per episode.<sup>2,9</sup> The potential benefit of chlorhexidine-silver sulfadiazine-impregnated catheters in lower-risk populations, however, remains to be determined. The effectiveness of chlorhexidine-silver sulfadiazine-impregnated catheters in preventing catheter-related infections found in this analysis is similar to results for central venous catheters coated with minocycline-rifampin.<sup>5</sup> A recent preliminary report of a direct comparison of the 2 catheter types suggests that minocycline-rifampin-treated catheters may be more efficacious for preventing CR-BSI than chlorhexidine-silver sulfadiazine-impregnated catheters.<sup>6</sup>

**Figure 2.** Analysis of Catheter-Related Bloodstream Infection in Trials Comparing Chlorhexidine-Silver Sulfadiazine-Impregnated Central Venous Catheters With Nonimpregnated Catheters



The diamond indicates summary odds ratio (OR) and 95% confidence interval (CI). Studies are ordered by increasing mean duration of catheterization in the treatment group. The size of the squares is inversely proportional to the variance of the studies.

No conclusions can be made regarding the relationship between duration of catheterization and reduction of catheter colonization or CR-BSI because there is no clear trend in the study ORs with duration of catheterization. It is also difficult to make conclusions about the use of a specific outcome definition because of the small size of the resulting pooled studies. Including the study<sup>21</sup> that did not report a definition for catheter colonization did not significantly affect the summary results because of its small size (19 catheters). Including the study<sup>22</sup> that used paired blood cultures to define CR-BSI, however, increased the summary OR because of its size (680 catheters) and study OR (1.15), although the change was not significant.

Several important limitations of this meta-analysis should be discussed in regard to study design of the individual trials. Studies with multiple catheters per patient may measure different treatment effects because subsequent catheters likely have a higher risk of infection.<sup>3,43</sup> It was not possible to study this effect without both catheter- and patient-based data or data for initial catheters

only. However, Maki et al<sup>9</sup> analyzed their results using both catheter- and patient-based data and compared initial and subsequent catheters and found comparable results. In studies with multiple catheters per patient that were randomized by patient number, the catheters were not independent, so the SE of the OR was underestimated. A sensitivity analysis conducted to investigate this effect by increasing the variance of these studies found no significant change in the summary OR for either outcome. Several studies<sup>14,16,19</sup> had a quasi-randomized design because patients were randomized by record number, possibly introducing bias through unblinding of the randomization schedule.<sup>44</sup> Exclusion of these studies in a sensitivity analysis, however, also did not have a significant effect on the summary OR for catheter colonization or CR-BSI.

The definition of CR-BSI used in many of the trials did not explicitly require the presence of clinical symptoms of bloodstream infection or the lack of other sources of infection. In 5 of the studies,<sup>9,14-16,18</sup> however, blood cultures were drawn only when bloodstream infection was suspected because of clinical symptoms. Two more studies<sup>8,17</sup> required clinical symptoms for the definition of CR-BSI. A subset analysis of these 7 studies produced results similar to the main analysis and a statistically significant reduction in the odds of developing CR-BSI. The 3 studies<sup>8,11,17</sup> that required there be no other sources of infection reported ORs similar to the summary results, but the pooled results of this small subset were not significant. Although it appears that our findings are consistent with clinically relevant episodes of bloodstream infection, the incidence of CR-BSI could have been overestimated in some of the studies because the catheters may not have been the primary source of infection in some patients.

The statistically significant test of heterogeneity for catheter colonization in the main analysis suggests that different trials are measuring different treatment effects for the impregnated catheters. The heterogeneity in the study OR for catheter colonization appears to arise mainly from the study by George et al.<sup>20</sup> The cri-

teria for a positive catheter culture used in this study were atypically low and, in combination with an immunocompromised patient population, may have led to the high incidence of catheter colonization found in the control group (71.4%) and the introduction of heterogeneity. Subset analysis of studies with standard definitions of catheter colonization resulted in a significant summary OR and a nonsignificant test of heterogeneity. Of note, no statistical evidence of heterogeneity was found in any of the analyses of the primary outcome of interest, CR-BSI.

The possibility of publication bias is a concern in the meta-analytic framework.<sup>45</sup> We have attempted to address this bias with a thorough search for both published and unpublished studies in any language using a variety of sources, including experts in the field and the catheter manufacturer. If publication bias was present, it would be expected that smaller trials would tend to report a greater treatment effect because smaller trials with positive results are more likely to be published than those with negative results. As can be seen in Figure 2, the ORs for CR-BSI for the 3 smallest trials<sup>11,17,20</sup> do not show a large treatment effect, whereas the 2 largest trials<sup>9,18</sup> show a greater treatment effect than most other studies. Although there is no clear evidence of publication bias for CR-BSI, it must be recognized that 1 or more unpublished studies may not have been located despite an extensive search strategy.

A recent study<sup>46</sup> indicated that the results of meta-analyses may not be predictive of the results of large clinical trials, although this issue has been explored in greater detail in a more recent analysis.<sup>47</sup> The results of our study thus suggest that a large, multicenter clinical trial may be warranted to confirm the results presented here. Such a trial, however, will be expensive and time-consuming. Inferences regarding trial design can be made based on our analysis. A trial with adequate power to investigate the outcome of CR-BSI would require 2115 catheters in both treatment and control groups to have 90% power to detect a reduction in inci-

dence of CR-BSI from 5% to 3%, a reasonable level of effect given the results of this meta-analysis. In the meantime, given the homogeneity of the results of the trials examining CR-BSI, the results of our study provide a quantitative assessment of the summary treatment effect found in the studies reported to date.

Further research is needed to investigate the efficacy of antiseptic-impregnated catheters in other patient populations and catheter types such as peripheral venous catheters and tunneled catheters, which are at lower risk for catheter-related infections. No adverse effects were reported in any of the trials or have been reported to date in patients in the United States.<sup>48</sup> Importantly, however, the US Food and Drug Administration has recently issued a notice concerning hypersensitivity reactions to chlorhexidine-impregnated medical devices,<sup>48</sup> and there have been reports of immediate hypersensitivity reactions to chlorhexidine-silver sulfadiazine-impregnated central venous catheters in Japan, including 1 potentially associated death.<sup>49,50</sup> Further investigation is required to evaluate the risk of hypersensitivity reactions to these catheters.

Prevention of catheter-related infections has focused on the essential measures of aseptic insertion technique and proper catheter care.<sup>3</sup> Despite these precautions, central venous catheters remain a significant source of nosocomial infections.<sup>51</sup> The findings of our meta-analysis indicate that central venous catheters impregnated with chlorhexidine-silver sulfadiazine are effective in reducing CR-BSI in high-risk patients requiring short-term catheterization and may provide a strategy for decreasing the overall incidence and cost of catheter-related infections. The decision to use these catheters should be made based on considerations of the baseline risk of CR-BSI in specific patient populations, potential reductions in morbidity and mortality, economic costs, and the risk of adverse events.

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