

REVIEW

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

A Meta-analysis

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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.¹ Catheter-related bloodstream infection (CR-BSI) can be a serious complication, leading to increases in mortality, hospital stay, and medical costs.²

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.³ 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 cefazolin⁴ and minocycline-rifampin.^{5,6} 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.

JAMA. 1999;281:261-267

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sulfadiazine do not require coating before insertion and may be less susceptible to antibiotic resistance.⁷ Several recent randomized trials⁸⁻²² 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 study⁹ has shown a significant reduction in the clinically more important

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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.^{23,24}

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.^{3,25,26} In the analysis of catheter colonization, all studies that defined catheter colonization as growth from a catheter segment using semiquantitative²⁷ or quantitative²⁸ culture techniques were included. One study²¹ 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.³ 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 study²² that reported the incidence of CR-BSI based on paired blood cultures²⁹ 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.³⁰ 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.³¹ Tests for heterogeneity of the ORs were performed using the Woolf method.³² 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.^{14-16,19,20} 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 al¹⁶ (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^{21,22} 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 studies³³⁻⁴¹ were not randomized and 2 studies^{21,22} were excluded

based on criteria for defining catheter colonization and CR-BSI. Of the remaining 13 studies, 4^{11,12,18,19} 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^{8-16,18-20} were used in the analysis of catheter colonization (2611 catheters), and 11 studies^{8,9,11,13-20} 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^{16,17} 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.^{9,13-17,20} Five studies allowed catheter exchange using a guide wire.^{9,14-16,19} 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, ⁸ 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, ⁹ 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, ¹⁰ 1996¶	3	ICU	No	28 (28)	26 (26)	6.6	6.8	SQ (IV, >15 CFU)	NR
Hannan et al, ¹¹ 1996	3	ICU	NR	68 (NR)	60 (NR)	7	8	SQ (IV, >10 ³ CFU)#	SQ (IV, >10 ³ CFU), NS
Bach et al, ¹² 1994¶	3	ICU	No	14 (14)	12 (12)	7.0	7.0	QN (IV, >10 ³ CFU)	NR
Bach et al, ¹³ 1996¶	2, 3	Surgical	No	116 (116)	117 (117)	7.7	7.7	QN (IV, >10 ³ CFU)	SO (IV)
Heard et al, ¹⁴ 1998¶	3	SICU	Yes	151 (107)	157 (104)	8.5	9	SQ (IV, SC, >14 CFU)	SO (IV, SC, >4 CFU)
Collin, ¹⁵ 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, ¹⁶ 1996¶	3	TPN	Yes	124 (92)	127 (99)	9.6	9.1	SQ (IV, SC, >15 CFU)	SO (IV, SC)
Pemberton et al, ¹⁷ 1996	3	TPN	No	32 (32)	40 (40)	10	11	NR	SO (IV), res, NS
Ramsay et al, ¹⁸ 1994¶	3	Hospital	No	199 (199)	189 (189)	10.9	10.9	SQ (IV, SC, >15 CFU)	SO (IV, SC)
Trazzera et al, ¹⁹ 1995¶	3	ICU/BMT	Yes	123 (99)	99 (82)	11.2	6.7	SQ (IV, >15 CFU)	SO (IV, >15 CFU)
George et al, ²⁰ 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.

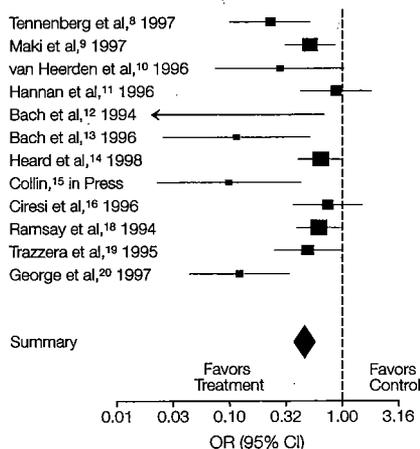
cutaneous segments and 3 studies used quantitative culture methods (Table 1). In the studies of CR-BSI, 2 studies required either the presence of clinical symptoms of bloodstream infection⁸ or resolution of symptoms on catheter removal¹⁷ and 3 studies required no other sources of infection.^{8,11,17} Five studies explicitly stated that peripheral blood cul-

tures were drawn only when there were clinical symptoms suggesting bloodstream infection.^{9,14-16,18}

A variety of randomization procedures were used in the studies. Three trials randomized catheters,^{9,11,13} while the other trials randomized patients. Three trials^{14,16,19} 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^{9,12,13,16,18} (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.^{8-10,14,16,17,20}

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^{14-16,19,20} 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, ⁹ 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, ⁹ 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, ¹⁰ 1996	4 (14.3)	10 (38.5)	0.27 (0.07-1.00)
Hannan et al, ¹¹ 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, ¹² 1994†	0 (0)	4 (33.3)	0 (0-0.65)
Bach et al, ¹³ 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, ¹⁴ 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, ¹⁵ 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, ¹⁶ 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, ¹⁷ 1996	2 (6.3)	3 (7.5)	0.82 (0.13-5.24)
Ramsay et al, ¹⁶ 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, ¹⁹ 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, ²⁰ 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^{14,16,19} 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^{9-12,14,16-20} 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 al²⁰ 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^{8-10,14-16,18,19} using standard semi-quantitative culture methods²⁷ 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 trial²⁰ 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^{8,17} or in which blood cultures were drawn only when there were clinical symptoms of bloodstream infection^{9,14-16,18} gave a summary OR for CR-BSI of 0.60 (95% CI, 0.37-0.97; $P = .03$). Including the study²² 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

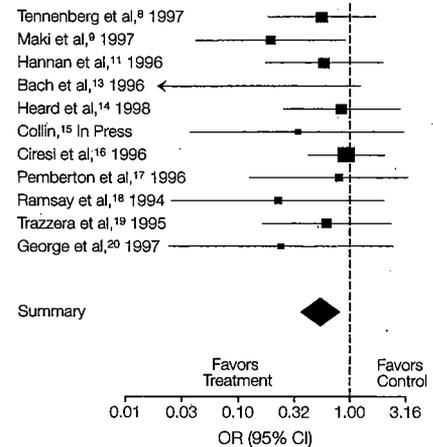
The findings of this quantitative review indicate that central venous catheters impregnated with chlorhexidine-silver sulfadiazine are effective in reducing the incidence of catheter colonization and CR-BSI compared with nonimpregnated catheters. The reduction in the odds of catheter colonization and 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.⁹ 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,^{9,42} with an attributable patient mortality of 10% to 35% and associated costs of up to \$30 000 per episode.^{2,9} 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.⁵ 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.⁶

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 study²¹ 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 study²² 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.^{3,43} It was not possible to study this effect without both catheter- and patient-based data or data for initial catheters

only. However, Maki et al⁹ 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^{14,16,19} had a quasi-randomized design because patients were randomized by record number, possibly introducing bias through unblinding of the randomization schedule.⁴⁴ 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,^{9,14-16,18} however, blood cultures were drawn only when bloodstream infection was suspected because of clinical symptoms. Two more studies^{8,17} 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^{8,11,17} 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.²⁰ 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.⁴⁵ 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^{11,17,20} do not show a large treatment effect, whereas the 2 largest trials^{9,18} 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 study⁴⁶ 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.⁴⁷ 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.⁴⁸ Importantly, however, the US Food and Drug Administration has recently issued a notice concerning hypersensitivity reactions to chlorhexidine-impregnated medical devices,⁴⁸ and there have been reports of immediate hypersensitivity reactions to chlorhexidine-silver sulfadiazine-impregnated central venous catheters in Japan, including 1 potentially associated death.^{49,50} 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.³ Despite these precautions, central venous catheters remain a significant source of nosocomial infections.⁵¹ 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.

Funding/Support: Dr Veenstra is supported by a Roche Pharmaceuticals (Palo Alto, Calif) postdoctoral fellowship; Drs Saint and Saha were Robert Wood Johnson clinical scholars at the time this work was con-

ducted; Dr Lumley was supported by a Howard Hughes Medical Institute predoctoral fellowship; and Dr Sullivan is supported by National Institutes of Health grants HS/HL08368-01A1 and HS07834-03S1.

Acknowledgment: We thank Roxie Albrecht, MD, Alfons Bach, MD, Stephen Heard, MD, L. Beaty Pemberton, MD, and P. Vernon van Heerden, MD, for providing citations of additional studies; Roxie Albrecht, MD, Alfons Bach, MD, Stephen Heard, MD, James Ramsay, MD, Salvatore Trazzera, MD, and P. Vernon van Heerden, MD, for providing additional information from their studies; Gary Collin, MD, for providing a copy of his manuscript; and Alfons Bach, MD, for helpful discussion.

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ORIGINAL CONTRIBUTION

Cost-Effectiveness of Antiseptic-Impregnated Central Venous Catheters for the Prevention of Catheter-Related Bloodstream Infection

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CENTRAL VENOUS CATHETERS are essential in caring for many hospitalized patients who are critically ill and those requiring repeated venous access. Despite the advantages of their use, such as the ability to administer medications and large fluid volumes, central venous catheters are associated with mechanical and significant infectious complications.¹ Catheter-related bloodstream infection (CR-BSI) occurs with 3% to 7% of catheters and affects more than 200 000 patients per year in the United States.^{2,3} The attributable mortality of CR-BSI ranges from approximately 10% to 25%, and CR-BSI has been associated with significant increases in the length of hospitalization and medical care costs.⁴⁻⁷

Strategies have been evaluated to decrease the incidence of CR-BSI, including the use of transparent dressings,^{8,9} strict adherence to proper aseptic technique and handwashing,^{10,11} silver-impregnated catheter cuffs,^{12,13} topical antiseptic solutions,^{14,15} and routine catheter changes.^{16,17} Some of these interventions have shown promise, but CR-BSI remains a significant cause of morbidity and mortality in hospitalized patients.^{18,19}

A novel strategy for the prevention of CR-BSI is the use of central venous catheters impregnated with the antiseptic combination of chlorhexidine

Context A recent randomized controlled trial and meta-analysis indicated that central venous catheters impregnated with an antiseptic combination of chlorhexidine and silver sulfadiazine are efficacious in reducing the incidence of catheter-related bloodstream infection (CR-BSI); however, the ultimate clinical and economic consequences of their use have not been formally evaluated.

Objective To estimate the incremental clinical and economic outcomes associated with the use of antiseptic-impregnated vs standard catheters.

Design Decision analytic model using data from randomized controlled trials, meta-analyses, and case-control studies, as well as safety data from the US Food and Drug Administration.

Setting and Patients A hypothetical cohort of hospitalized patients at high risk for catheter-related infections (eg, patients in intensive care units, immunosuppressed patients, and patients receiving total parenteral nutrition) requiring use of a central venous catheter.

Intervention Short-term use (2-10 days) of chlorhexidine-silver sulfadiazine-impregnated multilumen central venous catheters and nonimpregnated catheters.

Main Outcome Measures Expected incidence of CR-BSI and death attributable to antiseptic-impregnated and standard catheter use; direct medical costs for both types of catheters.

Results In the base-case analysis, use of antiseptic-impregnated catheters resulted in a decrease in the incidence of CR-BSI of 2.2% (5.2% for standard vs 3.0% for antiseptic-impregnated catheters), a decrease in the incidence of death of 0.33% (0.78% for standard vs 0.45% for antiseptic-impregnated), and a decrease in costs of \$196 per catheter used (\$532 for standard vs \$336 for antiseptic-impregnated). The decrease in CR-BSI ranged from 1.2% to 3.4%, the decrease in death ranged from 0.09% to 0.78%, and the costs saved ranged from \$68 to \$391 in a multivariate sensitivity analysis.

Conclusion Our analyses suggest that use of chlorhexidine-silver sulfadiazine-impregnated central venous catheters in patients at high risk for catheter-related infections reduces the incidence of CR-BSI and death and provides significant saving in costs. Use of these catheters should be considered as part of a comprehensive nosocomial infection control program.

JAMA. 1999;282:554-560

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and silver sulfadiazine (antiseptic-impregnated catheters).²⁰ These catheters are designed to reduce the incidence of CR-BSI by inhibiting bacterial colonization of the catheter surface.²¹ Almost all of the randomized controlled trials evaluating these cath-

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eters²²⁻³⁶ have reported reductions in the incidence of CR-BSI, but there has been some uncertainty regarding their efficacy because only 1 of these trials²³ reported a statistically significant reduction. However, a recent meta-analysis of these studies found a statistically significant reduction in the incidence of CR-BSI, and suggests that the majority of previous trials were underpowered to evaluate CR-BSI incidence.³⁷

The clinical and economic effects of using antiseptic-impregnated central venous catheters have not been formally evaluated. Given the results of the recent meta-analysis summarizing the evidence from randomized controlled trials, new reports of hypersensitivity reactions to these catheters in Japan,³⁸⁻⁴⁰ and the current interest in their use, a cost-effectiveness analysis is warranted to assist decision making regarding adoption of this new technology.¹⁹ We used decision-analytic techniques to evaluate the incremental clinical and economic outcomes associated with the use of antiseptic-impregnated vs standard central venous catheters in hospitalized patients.

METHODS

Decision Model

A decision model was created to evaluate the outcomes associated with the use of antiseptic-impregnated catheters vs standard catheters (FIGURE 1). The time horizon for the analysis was the period of hospitalization and the perspective was that of the health care payer. In the decision model, either an antiseptic-impregnated or standard catheter could be used in a patient requiring a central venous catheter. The use of either catheter type could lead to (1) CR-BSI (defined as an identical organism isolated from a peripheral blood culture and a colonized catheter),³⁷ (2) catheter colonization without bloodstream infection, or (3) no infectious complications. We assumed that some colonized catheters (without bloodstream infection) would be associated with signs of local infection such as purulence or erythema at the insertion site and thus require replacement; we did not include

this outcome for catheters that were not colonized based on preliminary calculations indicating the incremental effect was small. Hypersensitivity reaction was included as a potential adverse event associated with antiseptic-impregnated catheters. The final outcome for all patients was life or death.

The hypothetical patient cohort in the model consisted of hospitalized patients at high risk for catheter-related infections requiring the short-term use (2 to 10 days) of multilumen central venous catheters. We chose this cohort because the majority of patients in the clinical trials evaluating antiseptic-impregnated catheters were from high-risk populations such as patients in intensive care units (ICUs), immunosuppressed patients, and patients receiving total parenteral nutrition,³⁷ and these patients are the primary recipients of central venous catheters in clinical practice. The majority (99%) of patients in the trials received multilumen catheters. A duration of catheterization of 2 to 10 days was chosen because some trials excluded catheters in place for less than 1 day, the mean duration of catheterization in the trials was 7.9 days, and the efficacy of these catheters beyond 10 days has not been well studied.^{23,37}

Likelihood of Events

The probabilities of clinical events used in the decision model are shown in TABLE I. The probability of CR-BSI and of catheter colonization were based on a meta-analysis³⁷ of 13 randomized controlled trials²²⁻³⁴ comparing antiseptic-impregnated with standard central venous catheters. Rather than use the summary odds ratios from that study, we calculated summary risk ratios (RRs) because decision analysis uses probability estimates, or risks, rather than odds.⁴¹ The odds ratios and RRs differ slightly because the odds ratio is an estimate of RR and is dependent on the prevalence of infection. The summary RR for CR-BSI, calculated using Mantel-Haenszel methods,⁴² was 0.58 (95% confidence interval [CI], 0.40-0.85). A test for heterogeneity of treatment effect among the trials was not significant ($P = .80$), indicating the individual trials were measuring a similar treatment effect. The summary RR for catheter colonization (0.61; 95% CI, 0.51-0.73) was determined in a slightly different fashion than in the meta-analysis: only occurrences of catheter colonization without associated bloodstream infection were included, and a subset of trials^{22-24,28,30,32,33} that pro-

Figure 1. Decision Tree Used to Evaluate Antiseptic-Impregnated Central Venous Catheters

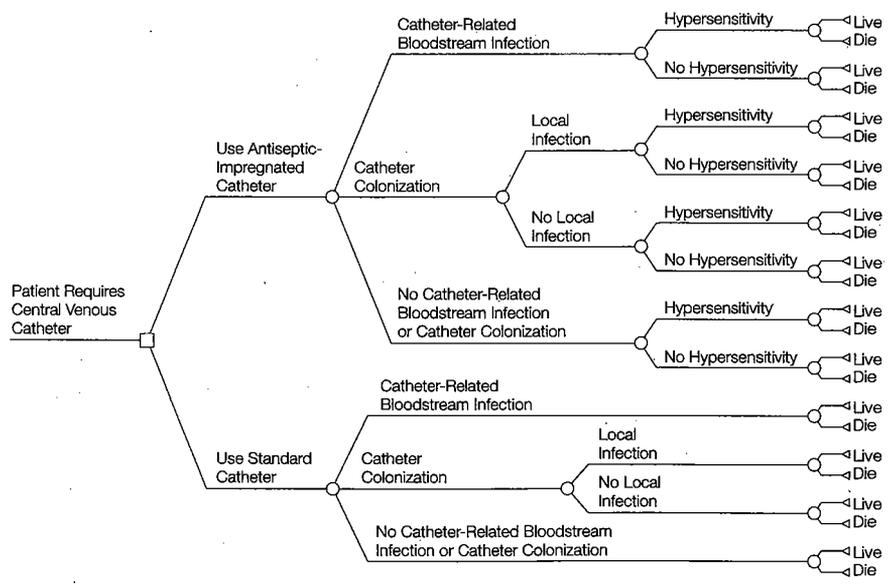


Table 1. Parameters Used in Decision Analysis Model*

	Base-Case Value (Range)	Reference
CR-BSI		
Standard catheter, %	5.2 (3.9-6.5)	37
Risk ratio†	0.582 (0.398-0.851)	37
Catheter colonization		
Standard catheter, %	24.7 (22.0-27.5)	37
Risk ratio†	0.61 (0.51-0.73)	37
Death attributable to CR-BSI, %	15.0 (5.0-25.0)	4-7, 44
Hypersensitivity reaction, %‡	0.0111 (0.0056-0.0222)	38
Death from hypersensitivity reaction, %	7.7 (3.9-15.4)	38
Local infection if colonization, %	50.0 (25.0-75.0)	31
Costs for 1998, \$		
Additional cost of antiseptic catheter	25 (20-30)	23, 29, 47
CR-BSI§	9738 (4869-19 476)	6, 44
Hypersensitivity reaction	1192 (596-2384)	..
Cost of managing local infection	210 (105-315)	47

*CR-BSI indicates catheter-related bloodstream infection.

†Probability for antiseptic-impregnated catheters was calculated by multiplying the RR by the probability for standard catheters.

‡Based on incidence in Japan.

§Six and a half days in the intensive care unit (\$1152/d) and 6 ward days (\$375/d).

||See "Methods" section.

duced a summary measure with no statistical evidence of heterogeneity ($P = .10$) or publication bias was used.

The probability of CR-BSI with standard catheters (the baseline risk) was derived by statistically pooling the proportion of standard catheters associated with CR-BSI.⁴³ The probability of catheter colonization with standard catheters was derived in a similar fashion. The probability of CR-BSI with antiseptic-impregnated catheters was determined by multiplying the RR for CR-BSI with antiseptic-impregnated catheters by the probability of CR-BSI with standard catheters (Table 1). The probability of catheter colonization with antiseptic-impregnated catheters was derived similarly. We estimated that half of colonized catheters were associated with signs of local infection.³¹

The probability of death attributable to CR-BSI was based on previous reports. A matched case-control study by Pittet et al⁶ of 86 cases of bloodstream infection in a surgical ICU found an attributable mortality of 35% (95% CI, 25%-45%). However, attributable mortality in a subset of 20 patients with bloodstream infection associated with central venous catheters was 25%.⁴⁴ Other reports of excess mortality due to CR-BSI range from 28% for critically ill

patients⁷ to 10% to 25% for patients hospital-wide.^{4,23} We used a 15% attributable mortality for the base-case scenario and explored a range from 5% to 25% in sensitivity analyses.

Although there have been no reports of hypersensitivity reactions to chlorhexidine-silver sulfadiazine-impregnated central venous catheters in the United States (P. Johnson, Arrow International, written communication, March 18, 1999), 13 cases of immediate hypersensitivity reaction were reported in Japan, including 1 potentially associated death.³⁸⁻⁴⁰ There were 117 000 antiseptic-impregnated catheters sold in Japan before their use was halted because of these cases. Assuming that all reported cases were caused by antiseptic-impregnated catheters, the approximate incidence in Japan per catheter sold was 11.1 cases per 100 000. We used this estimate in our base-case analysis to ensure that potential risks from antiseptic-impregnated catheters were adequately captured (Table 1). The probability of death due to a hypersensitivity reaction was based on the 1 death in 13 cases in Japan. High and low estimates were obtained by doubling and halving the probability, respectively. We assumed the incidence of mechanical complications was the same for both catheter types.

Costs

Pittet et al⁶ reported an average additional charge for patients with nosocomial bacteremia in the ICU in 1990 of \$33 268 and an excess hospital stay of 8 days in the ICU and 6 days in the general ward. The excess ICU stay for patients with CR-BSI who survived was 6.5 days, and their average additional charge was \$28 690.⁴⁴ We chose to estimate the current attributable cost of CR-BSI by multiplying the excess hospital stay for these patients by current per diem hospital costs. The costs at the University of Washington Medical Center for a day in the ICU and a day in the ward (\$1152 and \$375, respectively) were estimated by multiplying the per diem room charges by the appropriate cost-to-charge ratio (0.631).⁴⁵ These per diem costs do not include procedural costs or professional fees. The per diem hospital costs, multiplied by the additional days of stay (6.5 ICU days, 6 ward days), give a total additional cost for CR-BSI of \$9738, which was used in the base-case analysis (Table 1). The low estimate for the cost of CR-BSI, \$4869, was obtained by halving the base-case cost, and is similar to an inflation-adjusted⁴⁶ cost estimate for CR-BSI of \$6005 in hospital-wide patients reported by Arnov and colleagues.⁵ The high estimate, \$19 476, is double the base-case cost, but is significantly less than Pittet and Wenzel's⁴⁴ estimate converted to cost and adjusted for inflation⁴⁶ (\$44 864).

The additional cost of an antiseptic-impregnated catheter compared with a standard catheter for an averaged-sized hospital is approximately \$25.^{23,29,47} We estimated that a hypersensitivity reaction would require subcutaneous epinephrine and intravenous corticosteroids, diphenhydramine, and cimetidine. The treatment costs for these items at the University of Washington Medical Center is approximately \$40. We assumed that 1 additional day in the ICU would be required for a total cost of \$1192. High and low estimates were derived by doubling and halving the treatment cost for the base case. It was assumed that a locally infected catheter insertion site

without signs of bloodstream infection would be managed by inserting a new catheter. The cost of managing this complication (\$210) was estimated by adding the cost of a blood culture at University of Washington Medical Center (\$24) to the cost of replacing a central venous catheter (\$186) derived from an infection-control study that used antiseptic-impregnated catheters.⁴⁷

Outcome Assessment and Sensitivity Analyses

The following primary outcome measures were calculated for each catheter type: incidence of CR-BSI, incidence of death attributable to CR-BSI and/or hypersensitivity reaction, and direct medical costs. The incremental value for each of these measures was determined by subtracting the result for standard catheters from that for antiseptic-impregnated catheters. Local infection associated with catheter colonization was also determined.

We performed a series of sensitivity analyses to evaluate the uncertainty in our analysis. To evaluate the impact of the uncertainty in all of the parameters in the model, we performed a multivariate sensitivity analysis by conducting a Monte Carlo simulation.⁴⁸ Such a calculation provides an estimate of the overall uncertainty by simulating the use of multiple catheters in which the clinical probabilities and costs are randomly drawn from probability distributions that represent the uncertainty of each of the parameters. The probability distributions for the parameters were fit so that the means were similar to the base case and the central ranges corresponded with the ranges in Table 1. In general, logistic normal distributions were used to model clinical probabilities and gamma distributions were used to model costs.⁴⁹ The use of 10 000 catheters was simulated, and the mean and the central range containing 95% of the values for the incremental costs, incidence of CR-BSI, and incidence of death were determined.

We also conducted a series of 1-way sensitivity analyses to evaluate the effect of varying individual probabilities

Table 2. Results of Decision Analysis Comparing Antiseptic-Impregnated With Standard Central Venous Catheters

	Direct Medical Costs for 1998, \$	Incidence of Catheter-Related Bloodstream Infection, %	Incidence of Death Due to Catheter-Related Bloodstream Infection or Hypersensitivity, %
Antiseptic-impregnated catheter	336	3.0	0.45
Standard catheter	532	5.2	0.78
Difference (range) between 2 catheter types*	-196 (-391 to -68)	-2.2 (-3.4 to -1.2)	-0.33 (-0.78 to -0.09)

*From multivariate sensitivity analysis.

and costs. These analyses were performed by varying 1 parameter at a time while holding the others fixed. Finally, to test further the robustness of the results, we set all parameters in the model to favor standard catheters more than antiseptic-impregnated catheters in a worst-case scenario.

RESULTS

Costs and Outcomes

In the base-case analysis, use of an antiseptic-impregnated catheter compared with a standard catheter resulted in an expected saving of costs of \$196 per catheter (TABLE 2). The expected incidence of CR-BSI decreased from 5.2% for standard catheters to 3.0% for antiseptic-impregnated catheters, an absolute decrease of 2.2% and a relative decrease of 42%. The expected incidence of death attributable to the combination of CR-BSI and/or hypersensitivity reaction decreased from 0.78% to 0.45%, an absolute decrease of 0.33% and a relative decrease of 42%. The incidence of local infections decreased from 12.4% to 7.5%. The calculation of an incremental cost-effectiveness ratio (eg, cost per death avoided) was not conducted because the intervention is dominant: greater efficacy and lower costs.^{50,51}

Sensitivity Analyses

Antiseptic-impregnated catheters remained the dominant strategy (decreased costs and increased efficacy) over the central range of values calculated in the multivariate sensitivity analysis (Table 2). These results held for the worst-case scenario, in which antiseptic catheters resulted in equal costs

(incremental cost of \$0), decreases in the incidence of CR-BSI (0.6%) and death (0.03%).

The impact on the incremental cost of the most influential individual parameters is shown in a series of 1-way sensitivity analyses in FIGURE 2. The greatest variation in the results was associated with the cost of CR-BSI; the results ranged from -\$408 to -\$91. The threshold value for the cost of CR-BSI was \$687. In other words, in the base-case scenario, antiseptic-impregnated catheters would save costs as long as the attributable cost of an episode of CR-BSI is more than \$687. The other most influential variables were the RR for CR-BSI and the incidence of CR-BSI. The additional cost of an antiseptic-impregnated catheter had only a small impact on the incremental cost; the threshold value was \$221 in the base-case scenario and \$30 in the worst-case scenario. When the RR for CR-BSI was set to 1.0 but the RR for catheter colonization remained unchanged, use of an antiseptic-impregnated catheter resulted in an expected cost \$15 higher than for a standard catheter.

The incremental incidence of death was dependent on the probability of death attributable to CR-BSI (FIGURE 3); the results ranged from -0.54% to -0.11%; the parameter threshold value was 0.2%. The RR for CR-BSI was also influential, producing results from -0.47% to -0.12%. In addition, the baseline risk of CR-BSI had a significant impact, -0.41% to -0.25%. The probability of hypersensitivity reaction, explored over the ranges given in Table 1, had little discernable effect on the incremental incidence of death. Hyper-

sensitivity reaction would have to occur with 4.2% of antiseptic-impregnated catheters to produce equal incidences of death for both catheter types; this is more than 350 times the base-case value. The equivalent threshold value in the worst-case scenario was 0.2%.

COMMENT

We used decision analytic techniques to evaluate the clinical and economic

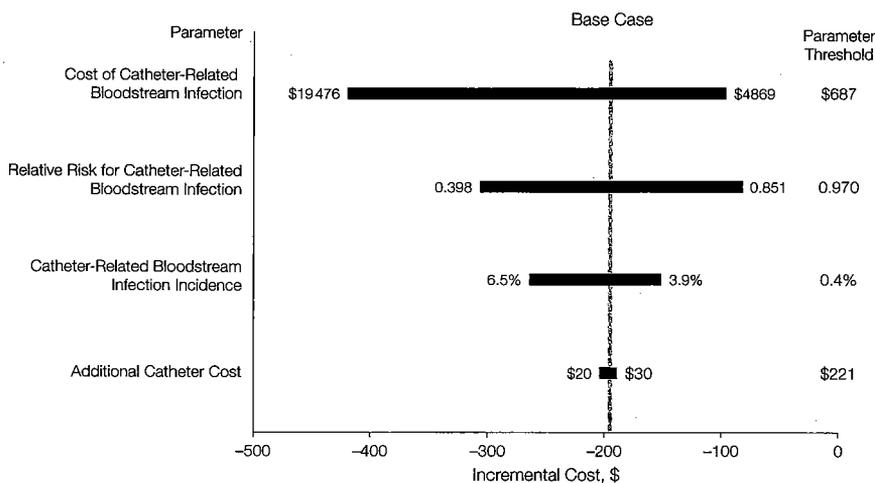
consequences of using antiseptic-impregnated central venous catheters in hospitalized patients at high risk for CR-BSI. Our analysis indicates that the use of antiseptic-impregnated catheters in this patient population results in decreased medical care costs, a reduction in the incidence of CR-BSI, and a decrease in the incidence of death compared with use of standard catheters. These results hold true over a wide range

of clinical and economic assumptions. The base-case analysis suggests that for every 300 antiseptic-impregnated catheters used, approximately \$59 000 will be saved, 7 cases of CR-BSI avoided, and 1 death prevented.

The analysis presented here differs from previous informal cost estimates^{23,29,47,52} of antiseptic-impregnated central venous catheters in several ways. First, we used decision analytic techniques to provide a formal framework for our analysis. Second, we evaluated the incidence of death associated with the use of central venous catheters. Third, the estimates used for the efficacy of antiseptic-impregnated catheters were based on evidence from a series of randomized controlled trials rather than a single study. Fourth, we included hypersensitivity reaction as a potential adverse event associated with antiseptic-impregnated catheters. Finally, a wide range of costs and probabilities were explored in 1-way and multivariate sensitivity analyses. Clinical trials confirming the results reported here are needed but may be costly; for example, a randomized trial with 90% power to detect a statistically significant decrease in mortality would require more than 10 000 patients in each study arm based on the effect size and incidence estimates in this study.

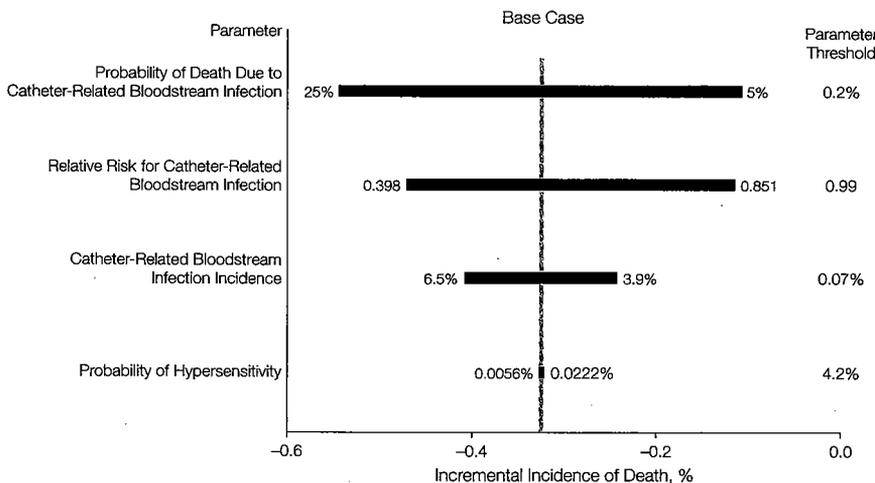
Why do antiseptic-impregnated catheters result in such significant cost saving? The use of these catheters is essentially a disease-prevention strategy. The disease in this case, CR-BSI, has an incidence of about 5% and leads to additional medical care costs of about \$10 000. The intervention costs an additional \$25, reduces the incidence of disease by about 40%, and unlike many prevention strategies, the benefits of its use are seen almost immediately. An equivalent pharmaceutical intervention would be highly valued. In addition to the costs saved from preventing CR-BSI, there are costs saved because of the decreased need for placing new catheters.^{23,29,47} In our model, we estimate that the decrease in local infections alone results in a costs saving of approximately \$10 per catheter. Although an-

Figure 2. One-way Sensitivity Analyses for Incremental Cost: Effect of Varying Individual Parameters



Threshold values represent parameter values that result in no difference in cost between catheter types.

Figure 3. One-way Sensitivity Analyses for Incremental Incidence of Death: Effect of Varying Individual Parameters



Threshold values represent parameter values that result in no difference in the incidence of death between catheter types.

tiseptic-impregnated catheters appear to be effective for the primary prevention of CR-BSI, it is critical that proper infection-control practices¹⁸ be followed, as in the clinical trials, to observe the expected benefits.

The results of our study are not generalizable to all patients requiring a central venous catheter. The meta-analysis on which our study was based included the results from clinical trials in which the majority of patients were from groups at high risk for catheter-related infections such as patients in the ICU, patients receiving total parenteral nutrition, and immunosuppressed patients. The parameters in our analysis for the baseline risk of CR-BSI and the attributable mortality and costs of CR-BSI are also reflective of this patient population. Therefore, the policy implications of this analysis should be limited to similar patient populations. If the hospital policy were to provide these catheters to all patients requiring central venous catheters, the costs saved may not offset the additional cost of antiseptic-impregnated catheters. Further studies are needed to identify more clearly high-risk patients and the appropriate duration of catheterization for antiseptic-impregnated catheters.

The baseline risk of CR-BSI used in our analysis is similar to published rates. The Centers for Disease Control and Prevention reported average CR-BSI rates of 2.8 to 12.8 infections per 1000 catheter-days (median, 1.8-7.1) for all ICU types and average rates of 4.5 to 6.1 infections per 1000 catheter-days (median, 4.6-5.3) for medical/surgical ICUs.⁵³ The range of values for the baseline risk of CR-BSI explored in our analysis was 4.9 to 8.2 infections per 1000 catheter-days (based on an average duration of catheterization of 7.9 days), and the cost threshold value was 0.4 infections per 1000 catheter-days. These results suggest that antiseptic-impregnated catheters are likely to save costs in other high-risk, ICU settings. However, hospitals in the Centers for Disease Control and Prevention sample tended to be large teaching hospitals that are not representative of most US

hospitals, and the benefits reported in this analysis may not be seen for institutions in which CR-BSI rates for central lines are significantly lower.

The uncertainty in several of the parameters used in our study merits discussion. The attributable cost of CR-BSI has a significant effect on the results of the analysis. Because we based our estimate on the excess ICU stay reported in a study using 1988-1990 data, and because the average length of hospitalization has decreased by 15% to 25% over the past 5 to 10 years,⁵⁴ this cost could be overestimated, favoring antiseptic-impregnated catheters. However, the per diem hospital costs we used do not include procedure costs or professional fees, and are thus likely conservative enough to compensate for a moderate decrease in the length of hospitalization. We used a conservative estimate for the attributable mortality of CR-BSI (15% vs 25% reported in the study by Pittet and Wenzel⁴⁴) and explored a wide range of values to account for the uncertainty in this estimate. The attributable cost and mortality of CR-BSI have not been adequately studied, and a well-designed case-control study that matches patients for length of catheterization in addition to parameters such as disease severity is required. In the meantime, our results suggest that antiseptic-impregnated catheters should save costs for reasonable ranges of CR-BSI attributable costs and mortality found in high-risk patients.

The occurrence of immediate hypersensitivity reaction in association with the use of chlorhexidine-silver sulfadiazine-impregnated catheters is of potential concern. There have been 4 reports of hypersensitivity reactions in Japan, 3 in the United Kingdom, and none in the United States since a Food and Drug Administration warning letter³⁸ was issued in March 1998 (P. Johnson, Arrow International, written communication, March 18, 1999). The higher incidence of hypersensitivity reaction in Japan may be caused by a higher previous exposure of patients in Japan to chlorhexidine or by a genetic predisposition.³⁸ The lack of any re-

cent reports of hypersensitivity reactions in the United States suggests the difference between the United States and Japan is not due to different levels of clinician awareness. Because we used the incidence of hypersensitivity reaction in Japan as our base-case estimate, our results could be considered conservative for patients in the United States.

Finally, our analysis was conducted from the perspective of a health care payer. An analysis from the societal perspective, which might include indirect costs such as patient's time lost from work, would result in even greater costs saved than reported here. In addition, we limited the time frame of analysis to the period of hospitalization. If this time frame were extended to include medical costs after hospitalization, a decreased incidence of CR-BSI might result in additional costs saving due to decreased health care needs such as home nursing.

The application of advanced catheter technologies such as antiseptic-impregnation and antibiotic-coating⁵⁵⁻⁵⁷ may save costs or be cost-effective for a variety of catheter types and patient populations and warrants research. Importantly, careful patient monitoring is needed to determine the risk factors and frequency of hypersensitivity reactions to chlorhexidine-silver sulfadiazine-impregnated catheters. Also, although there has been no evidence for the development of bacterial resistance,²³ the use of antiseptic-impregnated catheters should be monitored for this potentially serious complication that could offset the benefits of their use in the long-term.

Our analysis indicates that the use of antiseptic-impregnated central venous catheters results in both decreased costs and decreased morbidity and mortality in hospitalized patients at high risk for catheter-related infections. This conclusion holds true over a wide range of clinical and economic assumptions. The use of antiseptic-impregnated central venous catheters in high-risk patients should thus be considered as part of a comprehensive nosocomial infection control program.

PREVENTION OF BLOODSTREAM INFECTION

Funding/Support: Dr Veenstra was supported by a Roche postdoctoral fellowship, Dr Saint was a Robert Wood Johnson Clinical Scholar at the time this work was conducted, and Dr Sullivan was supported by grants HS/HL08368-01A1 and HS07834-03S1 from the National Institutes of Health. None of the authors has received financial support from or holds any personal financial interest in the manufacturer of chlorhexidine-silver sulfadiazine-impregnated catheters, Arrow International (Reading, Pa).

Acknowledgment: We thank Walter E. Stamm, MD, for an early review of the manuscript and the 3 anonymous reviewers for their comments.

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