PREVENTION OF BLOODSTREAM INFECTIONS WITH CENTRAL VENOUS CATHETERS TREATED WITH ANTI-INFECTIVE AGENTS DEPENDS ON CATHETER TYPE AND INSERTION TIME: EVIDENCE FROM A META-ANALYSIS

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ABSTRACT

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

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

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

RESULTS: Two trials on antibiotic coating (343 CVCs) had an average insertion time of 6 days; the risk of BSI decreased from 5.1% with control to 0% with anti-infective catheters. There were no trials with longer average insertion times. In three trials on silver collagen cuffs (422 CVCs), the average insertion time ranged from 5 to 8.2 days (median, 7 days); the risk of BSI was 5.6% with control and 3.2% with anti-infective catheters. In another trial on silver collagen cuffs (101 CVCs), the average insertion time was 38 days;

the risk of BSI was 3.7% with control and 4.3% with anti-infective catheters. In five trials on chlorhexidine–silver sulfadiazine coating (1,269 CVCs), the average insertion time ranged from 5.2 to 7.5 days (median, 6 days); the risk of BSI decreased from 4.1% with control to 1.9% with anti-infective catheters. In five additional trials on chlorhexidine–silver sulfadiazine coating (1,544 CVCs), the average insertion time ranged from 7.8 to 20 days (median, 12 days); the risk of BSI was 4.5% with control and 4.2% with anti-infective catheters.

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

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

A novel technologic approach to reduce CVC-related infection is the impregnation of catheters with antiseptic or antimicrobial agents, but clinical trials to assess the efficacy of these agents have produced inconsistent results.[8,9] Guidelines for the prevention of intravascular device–related infections published by the Centers for Disease Control

and Prevention proposed the use of impregnated catheters for adults with an unacceptably high rate of infection,[10] but no consensus has been reached about the definition of such a rate.

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

We undertook this study of randomized, controlled trials to quantify the relative efficacy of CVCs treated with different anti-infective agents and to identify factors that have an impact on the efficacy of these devices.

METHODS
Search Strategy

An extensive search of the relevant literature in all languages was performed using MEDLINE (Data Star, PubMed, and KnowledgeFinder 4.19 to January 20, 2000), EMBASE (to January 12, 2000), and Cochrane Library (2000, issue I). Key words used alone or in combination included central venous catheter, infection, coated, impregnated, subcutaneous cuff, antibiotic bonding, antibiotic-coated, silver-sulfadiazine, chlorhexidine, and random. Reference lists of retrieved reports, review articles,[10] and meta-analyses[11,15] were checked. Data from abstracts, letters, review articles, and animal studies were not considered.

Inclusion Criteria, Endpoints, and Definitions

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

One of two endpoints had to be reported in dichotomous form according to the definitions provided by the original authors: catheter colonization per 100 catheters inserted and BSI per 100 catheters inserted. Catheter colonization was considered as less important. It was defined as a documented growth from a proximal or distal catheter segment of either 15 or more colony-forming units (CFU) in a semiquantitative culture[16] or more than 10^3 CFU in a quantitative culture.[2] This definition was valid for the purpose of this study regardless of whether cultures were obtained from the external surface only or from both the internal and the external surfaces of the catheters. BSI was considered as the primary endpoint in this context. It was defined as the presence of the same organism isolated from a (semi)quantitative culture of a catheter segment and from the patient's blood in the absence of another source of infection.[5] This subgroup included patients with or without accompanying clinical symptoms (ie, sepsis).

Scoring and Data Extraction

All authors independently read the included articles and assessed their methodologic quality using the validated Oxford scale.[17] There was a pre hoc agreement to include trials with randomization according to the patients' date of birth, hospital chart number, or alternate allocation, but to exclude trials without randomization (eg, historical controls). Allocated scores were compared, and consensus was reached by discussion. Data abstraction was performed by one of the authors (BW) and independently cross-checked by the other two.

Qualitative, Quantitative, and Subgroup Analyses

For colonization, we calculated relative risk (RR) with 95% confidence interval (CI_{95}).[18] For BSI, which happens rarely, we calculated Peto odds ratio (OR); this is a more appropriate model when many trials show no events.[19] We tested for statistical heterogeneity using a chi-square test. A fixed effect model was used throughout because we combined data only when they were clinically homogeneous.[20]

There was a pre hoc agreement that an absolute risk reduction of 2% or more to prevent BSI (corresponding to a number-needed-to-treat[21] of 50 or fewer) was a clinically relevant result[2] and, therefore, would justify the use of anti-infective CVCs.

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

RESULTS
Trial Characteristics

A total of 103 reports were screened. Twenty-seven were considered for inclusion and 4 were subsequently excluded due to the following: one had an inadequate control group[22]; one used historical controls[23]; one had inadequate endpoints[24]; and one[25] described the same cohort reported in a previous article.[26] Finally, 23 trials[8,9,26-46] published between 1988 and 1999 including data on 4,660 catheters (2,319 anti-infective and 2,341 control) were analyzed (Table 1). Eleven were conducted in an intensive care unit setting, four were conducted among oncologic patients, two were conducted among surgical patients, two were conducted among patients receiving total parenteral nutrition, and four were conducted among other patient populations. The average number of catheters per trial was 194 (range, 20 to 680). The dropout rate of catheters varied between 0% and 49%. Average observation periods ranged from 2 to 147 days. The median Oxford score was 2 (range, 1 to 5). In 18 trials, no attempt was made at blinding.

Anti-infective catheters were treated with chlorhexidine–silver sulfadiazine coating (12 trials, 1,456 catheters); silver-impregnated collagen cuffing (5 trials, 328 catheters); antibiotic coating with teicoplanin, minocycline plus rifampin, vancomycin, or cefazolin (5 trials, 329 catheters); and silver coating (2 trials, 206 catheters). One trial compared two devices with an inactive control group[41]; all other trials compared one device with a control.

Qualitative and Quantitative Analyses

Catheter Colonization. Catheter colonization was reported in 22 trials (3,902 CVCs) (Table 1). There was a large variability in event rates with both anti-infective and control catheters: 1.7% to 62% (average, 22%) for anti-infec-

TABLE 1
ANALYZED TRIALS OF CENTRAL VENOUS CATHETERS WITH COATING OR CUFFING

Reference	Setting	Anti-Infective Catheter and Control Catheter (No. of Catheters)	No. of Lumens	No. With Endpoint/Total No.		Insertion Time (d)		Score (Random/ Blinding/ Dropouts)
				Coloni-zation	Bloodstream Infection	Mean	Range	
Bach et al.,[28] 1996	Major abdominal surgery	1. Catheter in teicoplanin bath for 15 min (10) 2. Normal catheter (10)	1	3/10 4/10		2		2/1/0
Bach et al.,[28] 1996	Cardiac surgery	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (116) 2. Normal catheter (117)	2 or 3	48/116 81/117	0/116 3/117	7.5 to 8.1	0.95 to 22.9	1/2/0
Boswald et al.,[29] 1999	Different populations	1. Silver-impregnated catheter (86) 2. Normal catheter (79)	Different	12/86 18/79		8 to 9	5 to 51	2/0/1
Ciresi et al.,[30] 1996	Total parenteral nutrition	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (124) 2. Normal catheter (127)	3	10/124 12/127	8/124 8/124	11.5 to 12.9		0/0/1*
Dahlberg et al.,[31] 1995	Dialysis	1. Silver-impregnated collagen cuff catheter (47) 2. Normal catheter (54)	2	7/47 11/54	2/47 2/54	34.8 to 41.5		1/0/0
Flowers et al.,[32] 1989	Surgical ICU	1. Silver-impregnated collagen cuff catheter (26) 2. Normal catheter (29)	3	2/26 10/29	0/26 4/29	4.4 to 5.6	2.0 to 16.9	0/0/1†
George et al.,[33] 1997	Immunocompro-mised transplant patients	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (35) 2. Normal catheter (44)	3	10/44 25/35	1/44 3/35	No data		2/0/1
Goldschmidt et al.,[34] 1995	Oncology	1. Silver-impregnated catheter (120) 2. Normal catheter (113)	1	53/120 51/113	10/120 18/113	12.7 to 13.3	3 to 61	0/0/1†
Groeger et al.,[35] 1993	Oncology	1. Silver-impregnated collagen cuff catheter, tunnel (92) 2. Dacron cuff catheter, tunnel (108)	2	33/92 35/108		143 to 147		1/0/0
Hannan et al.,[36] 1999	ICU	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (174) 2. Normal catheter (177)	2 or 3	47/174 71/177	1/174 3/177	7.5 to 7.6	1 to 32	1/0/0
Heard et al.,[37] 1998	Surgical ICU	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (151) 2. Normal catheter (157)	3	60/151 82/157	5/151 6/157	8.5 to 9.0	1 to 65	0/0/1*
Kamal et al.,[38] 1991	Surgical ICU	1. Catheter in cefazolin bath for 15 min (60) 2. Normal catheter (33)	3	1/60 4/33	0/60 0/33	4.1 to 5.0		0/0/1*
Logghe et al.,[8] 1997	Hematologic malignancies	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (338) 2. Normal catheter (342)	2 or 3		17/338 15/342	20		1/1/0

TABLE 1 (cont'd)
ANALYZED TRIALS OF CENTRAL VENOUS CATHETERS WITH COATING OR CUFFING

Reference	Setting	Anti-Infective Catheter and Control Catheter (No. of Catheters)	No. of Lumens	No. With Endpoint/Total No. Colonization	No. With Endpoint/Total No. Bloodstream Infection	Insertion Time (d) Mean	Insertion Time (d) Range	Score (Random/ Blinding/ Dropouts)
Loo et al.,[39] 1997	ICU	1. Silver sulfadiazine + chlorhexidine–impregnated catheter (77) 2. Normal catheter (81)	3	12/77 25/81	3/77 3/81	6.6	0 to 18	0/0/1[‡]
Maki et al.,[40] 1988	Medical, surgical, and ICU patients without granulocytopenia	1. Silver-impregnated collagen cuff catheter (99) 2. Normal catheter (135)	Different	7/99 33/135	1/99 51/135	7.2 to 9.1	1 to 73	2/0/0
Maki et al.,[9] 1997	Medical and surgical ICU patients	1. Silver sulfadiazine + chlorhexidine–impregnated catheter (208) 2. Normal catheter (195)	3	28/208 47/195	2/208 9/195	6		1/2/1
Marik et al.,[41] 1999	Medical ICU patients	1. Silver sulfadiazine + chlorhexidine–impregnated catheter 2. Minocycline + rifampin–impregnated catheter (38) 3. Normal catheter (39)	3	7/36 4/38 11/39	1/36 0/38 2/39	4 to 6		2/0/1
Pemberton et al.,[42] 1996	Total parenteral nutrition	1. Silver sulfadiazine + chlorhexidine–impregnated catheter (32) 2. Normal catheter (40)	3		2/32 3/40	10 to 11		2/0/0
Raad et al.,[26] 1997	Different populations	1. Minocycline + rifampicin–impregnated catheter (130) 2. Normal catheter (136)	3	11/130 36/136	0/130 7/136	6	1 to 28	2/2/1
Smith et al.,[43] 1995	Gynecologic oncology	1. Silver-impregnated collagen cuff catheter (64) 2. Normal catheter (69)	3	14/63 13/64	5/64 4/69	8.2 to 6.1		1/0/1
Tennenberg et al.,[44] 1997	Medical, surgical, and ICU patients	1. Silver sulfadiazine + chlorhexidine–impregnated catheter (137) 2. Normal catheter (145)	2 or 3	8/137 32/145	5/137 9/145	5.1 to 5.3		2/0/0
Thornton et al.,[45] 1996	ICU	1. Catheter in vancomycin bath for 5 min (91) 2. Normal catheter (85)	3	56/91 68/85		≤ 7		1/0/0
van Heerden et al.,[46] 1996	ICU	1. Silver sulfadiazine + chlorhexidine–impregnated catheter (28) 2. Normal catheter (26)	2 or 3	4/28 10/26		7		1/0/0

ICU = intensive care unit.
*Randomization according to patient's medical record number.
†Initially randomized, controlled trial, subsequently alternately allocation.
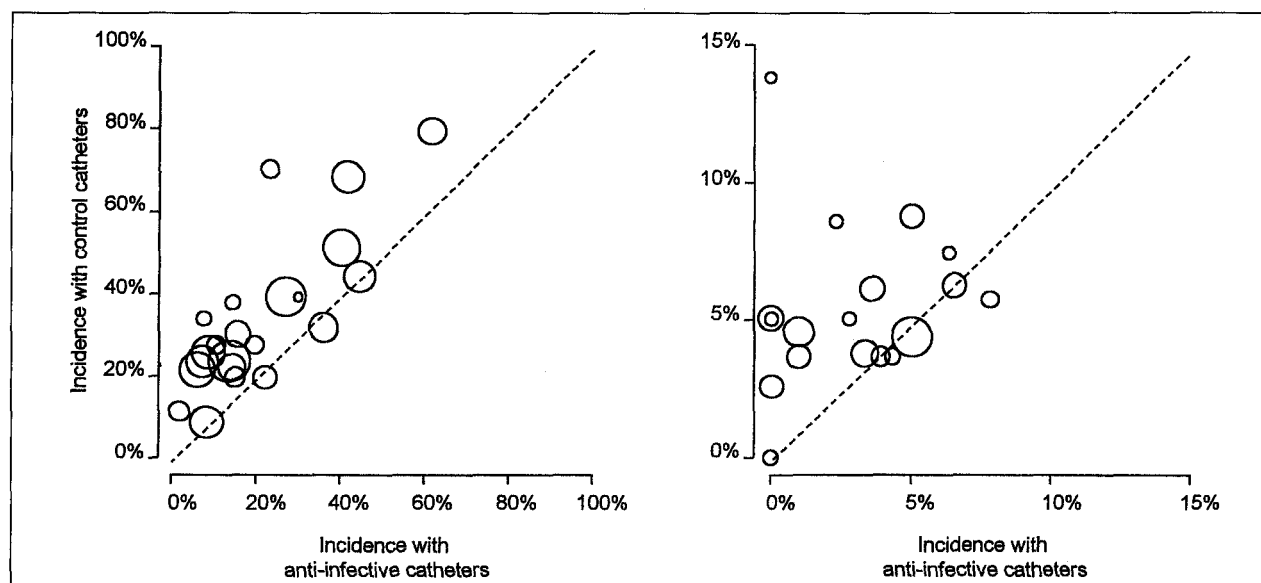‡Treatment allocation alternately (bimonthly).

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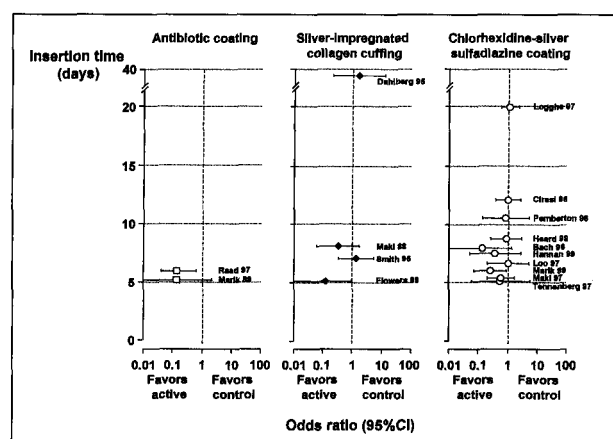

FIGURE 2. Impact of the average insertion times as reported in the original trials on the efficacy of anti-infective catheters to prevent bloodstream infection in the respective study. One study[38] with no events has been excluded. 95% CI = 95% confidence interval.

tive catheters and 9.4% to 80% (average, 35%) for control catheters (Fig. 1, left). The scatter suggested improvement with anti-infective catheters. The data were heterogeneous ($P < .001$). When data from all trials were combined, the difference in favor of anti-infective catheters was statistically significant (RR, 0.61; CI_{95}, 0.51 to 0.72).

BSI. BSI was reported in 18 trials (4,045 CVCs) (Table 1). There was a large variability in event rates with both anti-infective and control catheters: 0% to 7.8% (average, 2.9%) for anti-infective catheters and 0% to 13.8% (average, 4.7%) for control catheters (Fig. 1, right). In one trial, 4 (13.8%) of 29 patients receiving an inactive control catheter had a BSI, whereas none of 26 receiving a silver-impregnated collagen cuff catheter did.[32] The scatter suggested improvement with anti-infective catheters. The data

were homogeneous ($P = .329$). When data from all trials were combined, the difference in favor of anti-infective catheters was statistically significant (OR, 0.63; CI_{95}, 0.45 to 0.87).

Impact of Insertion Time on Anti-Infective Efficacy. Of all 18 trials that reported on BSI, one[33] did not report on the average insertion time, one[34] tested silver coating (ie, a technique that was not tested in any other trial reporting on BSI), and in one[38] there was no BSI (ie, 0 events). Thus, sensitivity analyses to quantify the impact of insertion time on anti-infective efficacy could be performed with data from 15 trials (16 comparisons) that tested antibiotic coating, silver-impregnated collagen cuffing, and chlorhexidine–silver sulfadiazine coating (Fig. 2; Table 2).

In both relevant trials on antibiotic coating (343 CVCs), the average insertion time was 6 days.[26,41] The combined risk of BSI decreased from 5.1% with control to 0% with anti-infective catheters (OR, 0.14; CI_{95}, 0.04 to 0.51). There were no trials with longer average insertion times.

In three of four trials on silver-impregnated collagen cuffs (422 CVCs), the average insertion time ranged from 5 to 8.2 days (median, 7 days).[32,40,43] The combined risk of BSI was 5.6% with control and 3.2% with anti-infective catheters (OR, 0.54; CI_{95}, 0.21 to 1.36). In the fourth trial on silver-impregnated collagen cuffs (101 CVCs), the average insertion time was 38 days.[31] The risk of BSI was 3.7% with control and 4.3% with anti-infective catheters (OR, 1.15; CI_{95}, 0.16 to 8.49). One trial reported an average insertion time of 8.2 days.[40] When data from this trial were pooled with the data from the trial with the longest average insertion time,[31] long-term efficacy was still not statistically significant (incidence of BSI, 3.7% with control vs 2.1% with anti-infective catheters [OR, 0.56; CI_{95}, 0.16 to 1.98]).

In five of 10 trials on chlorhexidine–silver sulfadiazine coating (1,269 CVCs), the average insertion time

ranged from 5.2 to 7.5 days (median, 6 days).[9,36,39,41,44] The combined risk of BSI decreased from 4.1% with control to 1.9% with anti-infective catheters (OR, 0.48; CI_{95}, 0.25 to 0.91). In the five other trials on chlorhexidine–silver sulfadiazine coating (1,544 CVCs), the average insertion time ranged from 7.8 to 20 days (median, 12 days).[8,28,30,37,42] The combined risk of BSI was 4.5% with control and 4.2% with anti-infective catheters (OR, 0.94; CI_{95}, 0.58 to 1.54).

Adverse Events

Twelve trials reported the presence or absence of adverse events.[9,26,27,31-34,38,40,42,43,45] There was some evidence that cuffed catheters were more difficult to insert than control catheters,[31] and that they extruded more often.[32,40,43] No systemic allergic reaction or local hypersensitivity was reported in any trial.

Conclusions of the Original Authors

In 12 studies (52%), the original authors concluded from their data that anti-infective catheters were useful.[9,26,29,32,34,36,38-41,43,45] In ten, they questioned the usefulness of such devices. The authors of one trial did not draw any conclusions.[46]

DISCUSSION

One of the proposed strategies to prevent CVC-related infection is the antiseptic or antimicrobial coating or cuffing of catheters.[47] BSI is the most relevant endpoint in this context. Two factors can be identified that have a major impact on the prevention of BSI with these catheters: insertion time and type of anti-infective method. In previous meta-analyses on the antimicrobial efficacy of catheters treated with chlorhexidine–silver sulfadiazine, and from data on short-term trials only (2 to 10 days), there was a statistically significant decrease in BSI compared with control catheters (OR, 0.56; CI_{95}, 0.37 to 0.84).[11,12,47] The authors concluded that these devices were effective in decreasing BSI. In our analysis, the result was similar for the subgroup of catheters treated with chlorhexidine–silver sulfadiazine and having short-term insertion (OR, 0.48; CI_{95}, 0.25 to 0.91). However, one additional important conclusion from this systematic review is that first-generation chlorhexidine–silver sulfadiazine catheters are not efficacious when the average insertion time is longer than 8 days.

Microorganisms in contact with plastic surfaces produce a protective, multi-layer biofilm within which they can survive.[48] It is tempting to speculate that such a biofilm could suppress the anti-infective action of the treated catheters. Indeed, with average insertion times of approximately 1 week, 1 in approximately 50 catheters treated with chlorhexidine–silver sulfadiazine will not lead to a BSI, which would have been the case with inactive devices (absolute risk reduction, 2.2%) (Table 2). When average insertion times were twice as long (approximately 12 days), this number was 1 in approximately 300 (absolute risk reduction, 0.3%). These results are in agreement with both in vitro and in vivo studies.[13,28] In vitro, a steep exponential decrease in antimicrobial activity was shown during the

TABLE 2
EFFICACY OF ANTI-INFECTIVE CENTRAL VENOUS CATHETERS IN THE PREVENTION OF BLOODSTREAM INFECTIONS (SENSITIVITY ANALYSES)

Anti-Infective Intervention	Average Insertion Time	No. of Trials	Insertion Time (d)	No. of Bloodstream Infections/Total No.		OR (CI_{95})	Heterogeneity* (P)	References
				Anti-Infective Catheter	Control Catheter			
Antibiotic coating	All	2	6	0/168 (0%)	9/175 (5.1%)	0.14 (0.04 to 0.51)	N/A	26, 41
	Short term	2	6	0/168 (0%)	9/175 (5.1%)	0.14 (0.04 to 0.51)	N/A	
	Long term[†]	No data	No data	No data	No data	No data		
Silver-impregnated collagen cuff	All	4	8	2/236 (3.4%)	15/287 (5.2%)	0.62 (0.27 to 1.43)	0.22	32, 40, 43
	Short term[†]	3	7	6/189 (3.2%)	13/233 (5.6%)	0.54 (0.21 to 1.36)	0.14	
	Long term	1	38	2/47 (4.3%)	2/54 (3.7%)	1.15 (0.16 to 8.49)	N/A	31
Chlorhexidine–silver sulfadiazine coating	All	10	8	44/1,393 (3.2%)	61/1,420 (4.3%)	0.73 (0.50 to 1.09)	0.52	9, 36, 39 41, 44
	Short term[§]	5	6	12/632 (1.9%)	26/637 (4.1%)	0.48 (0.25 to 0.91)	0.7	8, 28, 30, 37, 42
	Long term	5	12	32/761 (4.2%)	35/783 (4.5%)	0.94 (0.58 to 1.54)	0.52	

OR = odds ratio; CI_{95} = 95% confidence interval; N/A = not applicable.
*Result is shown when there were data from three or more trials.
[†]There were no trials with average insertion times longer than 7 days.
[‡]Excluding one trial with an insertion time of 38 days.[31]
[§]Trials with insertion times shorter than the median of the average insertion times of all chlorhexidine trials.

first week of insertion for devices treated with chlorhexidine–silver sulfadiazine.[28] In vivo, the antimicrobial activity of CVCs treated with chlorhexidine–silver sulfadiazine was shown to be time dependent.[13]

With antibiotic coating, there was not one single case of BSI. The absolute risk reduction compared with inactive control catheters was 5.1%, suggesting that approximately 20 patients need to receive an antibiotic-coated CVC for one patient not to develop a BSI who would have done so had they received inactive catheters. Thus, for short insertion times (ie, no longer than approximately 1 week), there was some evidence from indirect comparisons that antibiotic coating was more efficacious than chlorhexidine–silver sulfadiazine impregnation. These data are consistent with the results of a recently published large, randomized trial[13] in which CVC-related BSI was less likely in catheters coated with minocycline–rifampin (incidence, 0.3%) compared with catheters treated with chlorhexidine–silver sulfadiazine (incidence, 3.4%) with a median insertion time of 6 to 7 days. For both devices, the degree of short-term antimicrobial efficacy falls into our pre hoc definition of worthwhile prevention (ie, absolute risk reduction of $\geq$ 2% corresponding to a number-needed-to-treat of $\leq$ 50). However, data from the randomized trial[13] and from our meta-analysis suggest that twice as many catheters treated with chlorhexidine–silver sulfadiazine, compared with antibiotic-coated catheters, need to be inserted to prevent one BSI. We do not know whether the difference in efficacy between these catheter types is due to the anti-infective substances per se, different methods of coating, or both. Impregnation with chlorhexidine–silver sulfadiazine covers only the external surface of catheters. Some antibiotic coatings cover both the external and the internal surfaces of catheters. This may be associated with enhanced efficacy, as previously suggested,[13] but needs to be formally tested.

No long-term data on antibiotic-treated CVCs were available. In one study, a complete loss of activity for teicoplanin-coated catheters within 36 hours was reported.[27] Catheters treated with minocycline and rifampin may have antimicrobial activity extending up to 2 and possibly up to 4 to 6 weeks.[25] This inconsistency may be interpreted as evidence of specific antibiotic activities. Further randomized trials are needed to establish the effect of different antibiotic coating methods on the long-term anti-infective efficacy of CVCs.

Silver-impregnated collagen cuffing did not prevent BSI, although one small trial with a short insertion time (average, 5 days) reported a borderline significant result in favor of the anti-infective catheters.[32] In that trial, almost 14% of patients who received a control catheter had a BSI, a rate that was much higher than that in any other trial (Fig. 1, right). Because we have to assume that there is a relationship between the event rate in control catheters and the true underlying risk, it may be speculated that that trial studied patients at a particular high risk of infection. This was not the case (Table 1). However, small trials have been shown in other settings to overestimate the effect of an intervention.[49] Because that trial was of limited size, it had no important weight in the combined analysis.

We had to rely on average insertion times as reported in the original studies to estimate the potential impact of insertion time on the efficacy of anti-infective CVCs. In some, the range of catheter duration for individual patients was wide. This is a limitation of our study. However, in the absence of valid randomized trials comparing different insertion times, these analyses remain the best we have. It would be helpful to confirm our results using individual patient data.

Assuming that some anti-infective catheters prevent BSI if they are kept in situ for less than 1 week, we have to ask whether it is worthwhile to exchange these catheters regularly in chronically catheterized patients. There are three issues here: device, risk, and cost. Within the limitations of our analysis, there was evidence for time dependency with catheters coated with chlorhexidine–silver sulfadiazine. Thus, if those devices are to be used, there is an argument to replace them regularly, although it is not known whether one replacement per week is optimal. Systematic replacement of conventional CVCs through guidewire exchange every 3 days did not seem to reduce the risk of infection in a randomized trial.[50] There was no evidence for time dependency of antibiotic-coated devices because no trials reporting on longer average insertion times could be retrieved. If the antimicrobial efficacy of antibiotic-coated catheters should indeed extend to 2 to 4 weeks,[13,25] an exchange of them after 7 days might not be necessary. However, this needs to be confirmed in randomized, controlled trials.

Risk includes mechanical complications during insertion,[1] allergic reactions, and resistance acquisition. Insertion of cuffed catheters may be more difficult, and extrusion may occur.[32,40,43] Severe allergic reactions related to catheters coated with chlorhexidine–silver sulfadiazine have been described[51,52]; however, no systemic allergic reactions were reported in the analyzed trials, most likely due to their low incidence. It is likely that the issue of increased risk of resistance concerns mostly antibiotic-coated catheters. Furthermore, whether long-term exposure of bacteria to disinfectants is associated with increasing resistance or possible selective pressure to become antibiotic resistant remains to be determined.[53]

Anti-infective catheters cost approximately twice as much as conventional catheters. To justify a change in clinical practice, the increased cost incurred by a more frequent use of a more expensive device must be balanced against the savings obtained by preventing BSIs. Catheters coated with chlorhexidine–silver sulfadiazine appeared to be cost-effective for short-term insertion (2 to 10 days).[12] Antibiotic-coated catheters were recommended for infection control in critically ill patients.[14] However, the economic impact of these CVCs should be evaluated to enable policy decisions to be made regarding their implementation in clinical practice.

When inserted for no longer than 1 week, 1 in approximately 20 antibiotic-coated catheters and 1 in

approximately 50 catheters coated with chlorhexidine–silver sulfadiazine will not lead to a BSI, which would have occurred had they not been coated. As recently emphasized, this novel technology should be viewed as an adjunct to, rather than a substitute for, good infection control practices.[54] Stringent application of guidelines to prevent catheter infection has been recognized as highly efficacious in critically ill patients.[55] Anti-infective catheters are important in reducing the incidence of CVC-related infection, but further research is required to define the most efficacious method and the optimal time for device replacement and to identify subgroups of patients who might benefit most from this protective measure. Cost-effectiveness analyses of such interventions are also required.

REFERENCES

1. Ruesch S, Walder B, Tramèr MR. Complications of central venous catheters: internal jugular versus subclavian access—a systematic review. *Crit Care Med* 2002;30:454-460.
2. Maki DG, Mermel LA. Infections due to infusion therapy. In: Bennett JV, Brachman PS, eds. *Hospital Infections*, 4th ed. Philadelphia: Lippincott-Raven; 1998:689-724.
3. Arnow PM, Quimosing EM, Beach M. Consequences of intravascular catheter sepsis. *Clin Infect Dis* 1993;16:778-784.
4. Jarvis W, Edwards J, Culver D, et al. Nosocomial infection rates in adults and pediatric intensive care units in the United States: the National Nosocomial Infections Surveillance System. *Am J Med* 1991;91:185S-191S.
5. Pittet D. Nosocomial bloodstream infections. In: Wenzel RP, ed. *Prevention and Control of Nosocomial Infections*, 3rd ed. Baltimore: Williams and Wilkins; 1997:711-769.
6. Richet H, Hubert B, Nitemberg G, et al. Prospective multicenter study of vascular-catheter-related complications and risk factors for positive central-catheter cultures in intensive care unit patients. *J Clin Microbiol* 1990;28:2520-2525.
7. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA* 1994;271:1598-1601.
8. Logghe C, Van Ossel C, D'Hoore W, Ezzedine H, Wauters G, Haxhe JJ. Evaluation of chlorhexidine and silver-sulfadiazine impregnated central venous catheters for the prevention of bloodstream infection in leukaemic patients: a randomized controlled trial. *J Hosp Infect* 1997;37:145-156.
9. Maki DG, Stolz SM, Wheeler S, Mermel LA. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized, controlled trial. *Ann Intern Med* 1997;127:257-266.
10. Pearson ML. Guideline for prevention of intravascular device-related infections: Part I. Intravascular device-related infections: an overview. The Hospital Infection Control Practices Advisory Committee. *Am J Infect Control* 1996;24:262-277.
11. Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection. *JAMA* 1999;281:261-267.
12. Veenstra DL, Saint S, Sullivan SD. Cost-effectiveness of antiseptic-impregnated central venous catheters for the prevention of catheter-related bloodstream infection. *JAMA* 1999;282:554-560.
13. Darouiche RO, Raad I, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 1999;340:1-8.
14. Wenzel RP, Edmond MB. The evolving technology of venous access. *N Engl J Med* 1999;340:48-50.
15. Haxhe JJ, D'Hoore W. A meta-analysis dealing with the effectiveness of chlorhexidine and silver-sufhadiazine impregnated central venous catheters. *J Hosp Infect* 1998;40:166-168.
16. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med* 1977;296:1305-1309.
17. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.
18. Morris JA, Gardner MJ. Statistics with confidence: confidence intervals and statistical guideline. In: Gardner MJ, Altman DG, eds. *Calculating Confidence Intervals for Relative Risk, Odds Ratios, and Standardised Ratios and Rates*. London: British Medical Journal; 1995:50-63.
19. Yusuf S, Peto R, Lewis J. Beta blockade during and after myocardial infarction: an overview of the randomized trials. *Progress in Cardiovascular Research* 1985;27:335-371.
20. Gavaghan DJ, Moore RA, McQuay HJ. An evaluation of homogeneity tests in meta-analyses in pain using simulations of individual patient data. *Pain* 2000;85:415-424.
21. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318:1728-1733.
22. Babycos CR, Barrocas A, Webb WR. A prospective randomized trial comparing the silver-impregnated collagen cuff with the bedside tunneled subclavian catheter. *JPEN J Parenter Enteral Nutr* 1993;17:61-63.
23. Hasaniya NW, Angelis M, Brown MR, Yu M. Efficacy of subcutaneous silver-impregnated cuffs in preventing central venous catheter infections. *Chest* 1996;109:1030-1032.
24. Bambauer R, Schiel R, Mestres P, Klinkmann J, Sioshansi P. Scanning electron microscopic investigation of catheters for blood access. *Blood Purif* 1996;14:249-256.
25. Raad II, Darouiche RO, Hachem R, et al. Antimicrobial durability and rare ultrastructural colonization of indwelling central catheters coated with minocycline and rifampin. *Crit Care Med* 1998;26:219-224.
26. Raad I, Darouiche R, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. The Texas Medical Center Catheter Study Group. *Ann Intern Med* 1997;127:267-274.
27. Bach A, Darby D, Bottiger B, Bohrer H, Motsch J, Martin E. Retention of the antibiotic teicoplanin 'on a hydromer-coated central venous catheter to prevent bacterial colonization in postoperative surgical patients. *Intensive Care Med* 1996;22:1066-1069.
28. Bach A, Schmidt H, Bottiger B, et al. Retention of antibacterial activity and bacterial colonization of antiseptic-bonded central venous catheters. *J Antimicrob Chemother* 1996;37:315-322.
29. Boswald M, Lugauer S, Regenfus A, et al. Reduced rates of catheter-associated infection by use of a new silver-impregnated central venous catheter. *Infection* 1999;27:S56-S60.
30. Ciresi DL, Albrecht RM, Volkers PA, Scholten DJ. Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. *Am Surg* 1996;62:641-646.
31. Dahlberg PJ, Agger WA, Singer JR, et al. Subclavian hemodialysis catheter infections: a prospective, randomized trial of an attachable silver-impregnated cuff for prevention of catheter-related infections. *Infect Control Hosp Epidemiol* 1995;16:506-511.
32. Flowers RH 3rd, Schwenzer KJ, Kopel RF, Fisch MJ, Tucker SI, Farr BM. Efficacy of an attachable subcutaneous cuff for the prevention of intravascular catheter-related infection: a randomized, controlled trial. *JAMA* 1989;261:878-883.
33. George SJ, Vuddamalay P, Boscoe MJ. Antiseptic-impregnated central venous catheters reduce the incidence of bacterial colonization and associated infection in immunocompromised transplant patients. *Eur J Anaesthesiol* 1997;14:428-431.
34. Goldschmidt H, Hahn U, Salwender HJ, et al. Prevention of catheter-related infections by silver coated central venous catheters in oncological patients. *Zentralbl Bakteriol* 1995;283:215-223.
35. Groeger JS, Lucas AB, Coit D, et al. A prospective, randomized evaluation of the effect of silver impregnated subcutaneous cuffs for preventing tunneled chronic venous access catheter infections in cancer patients. *Ann Surg* 1993;218:206-210.
36. Hannan M, Juste RN, Umasanker S, et al. Antiseptic-bonded central venous catheters and bacterial colonisation. *Anaesthesia* 1999;54:868-872.
37. Heard SO, Wagle M, Vijayakumar E, et al. Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. *Arch Intern Med* 1998;158:81-87.
38. Kamal GD, Pfaller MA, Rempe LE, Jebson PJ. Reduced intravascular catheter infection by antibiotic bonding: a prospective, randomized, controlled trial. *JAMA* 1991;265:2364-2368.
39. Loo S, VanHerden PV, Gollege CL, et al. Infection in central lines: antiseptic-impregnated vs standard non-impregnated catheters. *Anaesth Intensive Care* 1997;25:637-639.
40. Maki DG, Cobb L, Garman JK, Shapiro JM, Ringer M, Helgerson RB. An attachable silver-impregnated cuff for prevention of infection with central venous catheters: a prospective randomized multicenter trial. *Am J Med* 1988;85:307-314.
41. Marik PE, Abraham G, Careau P, Varon J, Fromm RE Jr. The ex vivo antimicrobial activity and colonization rate of two antimicrobial-bonded central venous catheters. *Crit Care Med* 1999;27:1128-1131.
42. Pemberton LB, Ross V, Cuddy P, Kremer H, Fessler T, McGurk E. No difference in catheter sepsis between standard and antiseptic central

venous catheters: a prospective randomized trial. *Arch Surg* 1996;131:986-989.

43. Smith HO, DeVictoria CL, Garfinkel D, et al. A prospective randomized comparison of an attached silver-impregnated cuff to prevent central venous catheter-associated infection. *Gynecol Oncol* 1995;58:92-100.

44. Tennenberg S, Lieser M, McCurdy B, et al. A prospective randomized trial of an antibiotic- and antiseptic-coated central venous catheter in the prevention of catheter-related infections. *Arch Surg* 1997;132:1348-1351.

45. Thornton J, Todd NJ, Webster NR. Central venous line sepsis in the intensive care unit: a study comparing antibiotic coated catheters with plain catheters. *Anaesthesia* 1996;51:1018-1020.

46. van Heerden PV, Webb SA, Fong S, et al. Central venous catheters revisited: infection rates and an assessment of the new Fibrin Analysing System Brush. *Anaesth Intensive Care* 1996;24:330-333.

47. Raad I. Intravascular-catheter-related infections. *Lancet* 1998;351:893-898.

48. Lew DP, Pittet D, Waldvogel FA. Infections that complicate the insertion of prosthetic devices. In: Mayhall CG, ed. *Hospital Epidemiology and Infection Control*, 2nd ed. Baltimore: Williams and Wilkins; 1996:731-748.

49. Moore RA, Tramèr MR, Carroll D, Wiffen PJ, McQuay HJ. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ* 1998;316:333-338.

50. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med* 1992;327:1062-1068.

51. Oda T, Hamasaki J, Kanda N, Mikami K. Anaphylactic shock induced by an antiseptic-coated central nervous catheter. *Anesthesiology* 1997;87:1242-1244.

52. Terazawa E, Shimonaka H, Nagase K, Masue T, Dohi S. Severe anaphylactic reaction due to a chlorhexidine-impregnated central venous catheter. *Anesthesiology* 1998;89:1296-1298.

53. Sivaji Y, Mandal A, Agarwal DS. Disinfectant induced changes in the antibiotic sensitivity and phage typing pattern in *Staphylococcus aureus*. *J Hosp Infect* 1986;7:236-243.

54. Pearson ML, Abrutyn E. Reducing the risk for catheter-related infections: a new strategy. *Ann Intern Med* 1997;127:304-306.

55. Eggimann P, Harbarth S, Constantin MN, Touveneau S, Chevrolet JC, Pittet D. Impact of a prevention strategy targeted at vascular-access care on incidence of infections acquired in intensive care. *Lancet* 2000;355:1864-1868.