

# PREVENTION OF BLOODSTREAM INFECTIONS WITH CENTRAL VENOUS CATHETERS TREATED WITH ANTI-INFECTION 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<sub>95%</sub>).

**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.<sup>1</sup> Infection may be local or systemic, including thrombophlebitis, bloodstream infection (BSI), endocarditis, and metastatic distribution (eg, osteomyelitis, endophthalmitis, or arthritis).<sup>2,3</sup> CVC-related bacteremia is a major cause of nosocomial BSI,<sup>4,5</sup> with a reported incidence of approximately 5%.<sup>6</sup> The consequences of these infections, in terms of morbidity, mortality, and additional healthcare costs, are of major importance.<sup>7</sup>

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.<sup>8,9</sup> 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,<sup>10</sup> 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.<sup>11,12</sup> 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.<sup>13</sup> 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.<sup>14</sup>

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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,<sup>10</sup> and meta-analyses<sup>11,15</sup> 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<sup>16</sup> or more than 10<sup>3</sup> CFU in a quantitative culture.<sup>2</sup> 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.<sup>5</sup> 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.<sup>17</sup> 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 per-

formed 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<sub>95</sub>).<sup>18</sup> For BSI, which happens rarely, we calculated Peto odds ratio (OR); this is a more appropriate model when many trials show no events.<sup>19</sup> 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.<sup>20</sup>

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<sup>21</sup> of 50 or fewer) was a clinically relevant result<sup>2</sup> 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<sup>22</sup>; one used historical controls<sup>23</sup>; one had inadequate endpoints<sup>24</sup>; and one<sup>25</sup> described the same cohort reported in a previous article.<sup>26</sup> Finally, 23 trials<sup>8,9,26-46</sup> 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 ceftazidime (5 trials, 329 catheters); and silver coating (2 trials, 206 catheters). One trial compared two devices with an inactive control group<sup>41</sup>; 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 Colonization	Bloodstream Infection	Insertion Time (d)		Score (Random/Blinding/Dropouts)
						Mean	Range	
Bach et al., <sup>26</sup> 1996	Major abdominal surgery	1. Catheter in teicoplanin bath for 15 min (10) 2. Normal catheter (10)	1	3/10		2		2/1/0
Bach et al., <sup>28</sup> 1996	Cardiac surgery	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (116) 2. Normal catheter (117)	2 or 3	48/116	0/116	7.5 to 8.1	0.95 to 22.9	1/2/0
Boswald et al., <sup>29</sup> 1999	Different populations	1. Silver-impregnated catheter (86) 2. Normal catheter (79)	Different	12/86	3/117	8 to 9	5 to 51	2/0/1
Ciresi et al., <sup>30</sup> 1996	Total parenteral nutrition	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (124) 2. Normal catheter (127)	3	10/124	8/124	11.5 to 12.9		0/0/1*
Dahlberg et al., <sup>31</sup> 1995	Dialysis	1. Silver-impregnated collagen cuff catheter (47) 2. Normal catheter (54)	2	12/127	8/124	34.8 to 41.5		1/0/0
Flowers et al., <sup>32</sup> 1989	Surgical ICU	1. Silver-impregnated collagen cuff catheter (26) 2. Normal catheter (29)	3	11/54	2/54	4.4 to 5.6	2.0 to 16.9	0/0/1†
George et al., <sup>33</sup> 1997	Immunocompromised transplant patients	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (35) 2. Normal catheter (44)	3	10/29	4/29	No data		2/0/1
Goldschmidt et al., <sup>34</sup> 1995	Oncology	1. Silver-impregnated catheter (120) 2. Normal catheter (113)	1	25/35	3/35	12.7 to 13.3	3 to 61	0/0/1†
Groeger et al., <sup>35</sup> 1993	Oncology	1. Silver-impregnated collagen cuff catheter, tunnel (92) 2. Dacron cuff catheter, tunnel (108)	2	53/120	10/120	143 to 147		1/0/0
Hannan et al., <sup>36</sup> 1999	ICU	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (174) 2. Normal catheter (177)	2 or 3	51/113	18/113	7.5 to 7.6	1 to 32	1/0/0
Heard et al., <sup>37</sup> 1998	Surgical ICU	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (151) 2. Normal catheter (157)	3	33/92	3/177	8.5 to 9.0	1 to 65	0/0/1*
Kamal et al., <sup>38</sup> 1991	Surgical ICU	1. Catheter in ceftazolin bath for 15 min (60) 2. Normal catheter (33)	3	82/157	6/157	4.1 to 5.0		0/0/1*
Logghe et al., <sup>8</sup> 1997	Hematologic malignancies	1. Silver sulfadiazine + chlorhexidine-impregnated catheter (338) 2. Normal catheter (342)	2 or 3	4/33	0/33	20		1/1/0

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

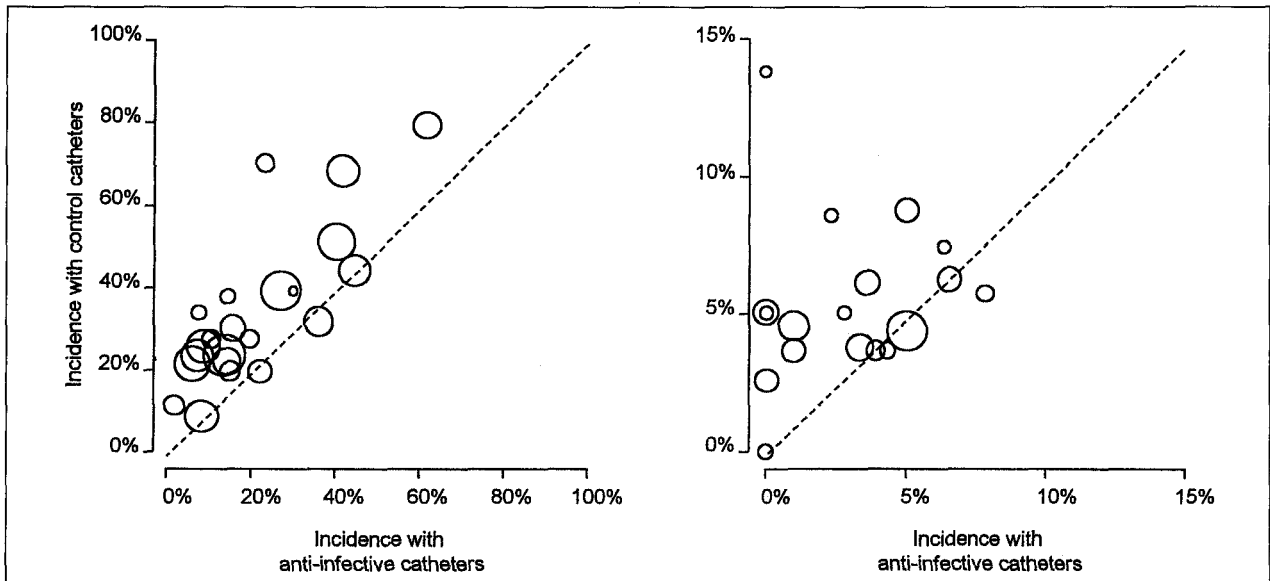
Reference	Setting	Anti-infective Catheter and Control Catheter (No. of Catheters)	No. of Lumens	No. With Colonization	Bloodstream Infection	Insertion Time (d)		Score (Random/Blinding/Dropouts)
						Mean	Range	
Loo et al., <sup>39</sup> 1997	ICU	1. Silver sulfadiazine + chlorhexidine-impregnated catheter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

ICU = intensive care unit.

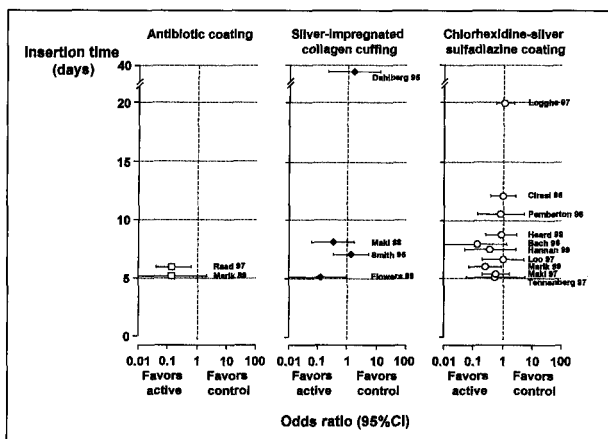
\*Randomization according to patient's medical record number.

†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<sup>38</sup> 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.<sup>32</sup> 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<sup>33</sup> did not report on the average insertion time, one<sup>34</sup> tested silver coating (ie, a technique that was not tested in any other trial reporting on BSI), and in one<sup>38</sup> 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.<sup>26,41</sup> 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).<sup>32,40,43</sup> 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.<sup>31</sup> 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.<sup>40</sup> When data from this trial were pooled with the data from the trial with the longest average insertion time,<sup>31</sup> 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).<sup>9,36,39,41,44</sup> The combined risk of BSI decreased from 4.1% with control to 1.9% with anti-infective catheters (OR, 0.48; CI<sub>95</sub>, 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).<sup>8,28,30,37,42</sup> The combined risk of BSI was 4.5% with control and 4.2% with anti-infective catheters (OR, 0.94; CI<sub>95</sub>, 0.58 to 1.54).

### Adverse Events

Twelve trials reported the presence or absence of adverse events.<sup>9,26,27,31-34,38,40,42,43,45</sup> There was some evidence that cuffed catheters were more difficult to insert than control catheters,<sup>31</sup> and that they extruded more often.<sup>32,40,43</sup> 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.<sup>9,26,29,32,34,36,38-41,43,45</sup> In ten, they questioned the usefulness of such devices. The authors of one trial did not draw any conclusions.<sup>46</sup>

### DISCUSSION

One of the proposed strategies to prevent CVC-related infection is the antiseptic or antimicrobial coating or cuffing of catheters.<sup>47</sup> 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<sub>95</sub>, 0.37 to 0.84).<sup>11,12,47</sup> 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<sub>95</sub>, 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.<sup>48</sup> 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.<sup>13,28</sup> *In vitro*, a steep exponential decrease in antimicrobial activity was shown during the

**TABLE 2**  
EFFICACY OF ANTI-INFECTION 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 <sub>95</sub> )	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	
Silver-impregnated collagen cuff	Long term†	No data	No data	No data	No data	No data		
	All	4	8	2/236 (3.4%)	15/287 (5.2%)	0.62 (0.27 to 1.43)	0.22	
Chlorhexidine–silver sulfadiazine coating	Short term†	3	7	6/189 (3.2%)	13/233 (5.6%)	0.54 (0.21 to 1.36)	0.14	32, 40, 43
	Long term	1	38	2/47 (4.3%)	2/54 (3.7%)	1.15 (0.16 to 8.49)	N/A	
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	
	Long term	5	12	32/761 (4.2%)	35/783 (4.5%)	0.94 (0.58 to 1.54)	0.52	8, 28, 30, 37, 42

OR = odds ratio; CI<sub>95</sub> = 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.

§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.<sup>28</sup> In vivo, the antimicrobial activity of CVCs treated with chlorhexidine–silver sulfadiazine was shown to be time dependent.<sup>13</sup>

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<sup>13</sup> 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<sup>13</sup> 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,<sup>13</sup> 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.<sup>27</sup> Catheters treated with minocycline and rifampin may have antimicrobial activity extending up to 2 and possibly up to 4 to 6 weeks.<sup>25</sup> 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.<sup>32</sup> 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.<sup>49</sup> 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.<sup>50</sup> 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,<sup>13,25</sup> 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,<sup>1</sup> allergic reactions, and resistance acquisition. Insertion of cuffed catheters may be more difficult, and extrusion may occur.<sup>32,40,43</sup> Severe allergic reactions related to catheters coated with chlorhexidine–silver sulfadiazine have been described<sup>51,52</sup>; 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.<sup>53</sup>

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).<sup>12</sup> Antibiotic-coated catheters were recommended for infection control in critically ill patients.<sup>14</sup> 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.<sup>54</sup> Stringent application of guidelines to prevent catheter infection has been recognized as highly efficacious in critically ill patients.<sup>55</sup> 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.

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