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Prevention of intravascular catheter-related infection with newer chlorhexidine-silver sulfadiazine-coated catheters: a randomized controlled trial

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Abstract *Background:* The indication of antiseptic-coated catheters remains debated. *Objective:* To test the ability of the new generation of chlorhexidine-silver and sulfadiazine-coated catheters, with enhanced antiseptic coating, to reduce the risk of central venous catheter (CVC)-related infection in ICU patients. *Design:* Multicentre randomized double-blind trial. *Patients and setting:* A total of 397 patients from 14 ICUs of university hospitals in France. *Intervention:* Patients were randomized to receive an antiseptic-coated catheter (ACC) or a standard non-coated catheter (NCC). *Measurements:* Incidence of CVC-related infection. *Results:* Of 367 patients having a successful catheter insertion, 363 were analysed (175 NCC and 188 ACC). Patients had one (NCC=162, ACC=180) or more (NCC=13, ACC=11) CVC inserted. The two groups were similar for insertion site [subclavian (64 vs 69)] or jugular (36 vs 31%)], and type of catheters (single-lumen 18 vs 18%; double-lumen 82 vs 82%), and mean (median) duration of catheterisation [12.0±11.7 (9) vs 10.5±8.8 (8) days in the NCC and ACC groups, respectively]. Significant colonisation of the catheter occurred in 23 (13.1%) and 7 (3.7%) patients, respectively, in the NCC and ACC groups (11 vs 3.6 per 1000 catheter-days; p=0.01); CVC-related infection (bloodstream infection) occurred in 10 (5) and 4 (3) patients in the NCC and CC groups, respectively (5.2 vs 2 per 1000 catheter days; p=0.10). *Conclusions:* In the context of a low baseline infection rate, ACC were associated with a significant reduction of catheter colonisation and a trend to reduction of infection episodes, but not of bloodstream infection.

Keywords Intensive care · Catheter-associated infection · Bacteraemia · Prevention · Antiseptics

Introduction

Central venous catheter (CVC) infections are one of the major causes of infections acquired in intensive care unit (ICU) patients. About 25% of bloodstream infections recorded in ICUs are secondary to proven catheter-related infection [1, 2] and up to 80% of the so-called primary bacteraemia may be caused by catheter infection [3]. Although catheter-related bacteraemia is associated with the lowest attributable mortality compared with other sources [2], the burden of such infections is high in critically ill patients [2, 3, 4]. An estimated 80,000 bacteraemias occur annually as a result of central venous catheter-related infection in U.S. hospitals, with associated fatalities ranging from 2400 to 20,000 per year [5]. Pittet et al. have estimated that nosocomial bloodstream infection, irrespective of its source, was associated with an overall 35% attributable mortality and a prolonged hospital stay of 32 days, including 8 days in the ICU [6]. We recorded similar results in a French multicentre study [2], where we found catheter-related bacteraemia associated with an estimated 11.5% (95% CI: −14 to 37.5%) attributable mortality.

Prevention of catheter-related infections is therefore a priority for infection control programs. Recognized preventive measures include strict ("maximal") barrier precautions during insertion and careful aseptic techniques during subsequent manipulations of catheters [7]. Other preventive measures, including the use of catheters specifically designed to oppose colonisation, such as antimicrobial-coated catheters, are not universally accepted or recommended for routine use. Because of their limited efficacy demonstrated only in large trials, and the concern of emergence of resistance to the antimicrobial agents used, their use is currently restricted to settings where persistently high infection rates are recorded despite adherence to other preventive measures [7, 8].

Previous trials have demonstrated a 50% risk reduction of infection rates when using antiseptic-coated catheters [9, 10, 11, 12]; however, their efficacy to reduce catheter-related bloodstream infection has been questioned [13]. In addition, one trial suggests lower efficacy of chlorhexidine-silver sulfadiazine-coated (CH-SS) catheters compared with antibiotic-impregnated catheters [14]. In that trial, the first-generation of antiseptic-coated catheters was used. The lower apparent efficacy of these catheters was ascribed to antiseptics not being present on the internal lumen of the catheter, and to the limited duration of antiseptic efficacy [8].

A new generation of chlorhexidine-silver sulfadiazine-coated catheters, featuring higher concentration of antiseptics and enhanced bonding to both the internal and external surface of the catheter, has become recently available (ArrowGard Blue Plus, Arrow International, Reading, Pa.), but no clinical trial documenting their preventive efficacy has been published. In this trial, we assessed the ability of this new generation of catheters to prevent short-term (<30 days) catheter-related infection in critically ill patients, as compared with standard non-antiseptic coated catheters.

Patients and methods

The study was conducted over a 4-year period (June 1998 to January 2002) in 14 ICUs in France. The study protocol was approved by our institution Review Board and written informed consent was required. Patients were eligible when insertion of a central venous catheter (CVC) at a new site (subclavian or internal jugular) was planned for therapy or monitoring of at least 3-day duration (see the ESM for details on exclusion criteria).

Randomisation and blinding

Catheters, whether or not antiseptic-coated, were provided with identical appearance. The randomisation procedure ensured that patients included remained in the same allocation group, when guide-wire exchange was performed (see the ESM for details).

Insertion and maintenance of catheters

Recommendations were provided to study centres to comply with maximal barrier precautions [15] during insertion and repositioning of catheters, if indicated (see the ESM for details on catheter maintenance). Catheters were removed when no longer required, or because of malfunction, when suspicion of infection or otherwise unexplained bloodstream infection occurred; and in the presence of gross inflammation or pus at the catheter insertion site.

Guide-wire exchange

Catheter exchange over a guide wire was allowed only in cases of low to moderate suspicion of catheter infection, in the absence of severe sepsis or with obvious signs of infection at the catheter insertion site. After exchange, the second catheter was removed if the first one proved to be colonized.

Data recorded

Patients were followed up to 48 h after catheter removal. In addition to admission characteristics of patients (see the ESM for details), data recorded included: (a) mechanical complication occurring during insertion (number of venipunctures, arterial puncture, haematoma, pneumothorax); (b) presence of local signs suggesting infection (erythema at the catheter skin entry site, scored as 0: absence; 1+: <5 mm; 2+: 5–10 mm; 3+: >10 mm; presence of induration or purulence); (c) presence of a systemic inflammatory response syndrome or of symptoms characterizing severe sepsis [16]; (d) presence of other documented infection; (e) other intravascular devices in place or inserted each day; (f) dressing changes; (g) results of blood and catheter-tip cultures, and of other clinically significant microbiological samplings; and (h) antibiotics administered.

Microbiological data

Blood cultures were obtained when temperature was >38.2° or <36.5°C. Diagnostic samples of any other suspected infection foci were taken as clinically indicated. Upon catheter removal, the in-

travascular catheter tip was cultured using the quantitative culture described by Cleri et al. [17], modified by Brun-Buisson et al. [18] (see the ESM for details).

Definitions and measurements

Bloodstream infection was defined as secondary when growing the same organism as that recovered from another site of infection than the catheter, and as primary (non-catheter-related) when no other site, including the catheter, was found growing in the same microorganism. The comparability of microorganisms was based on speciation and antibiotic susceptibility profile.

Catheters were classified as infected or colonized according to the following definitions: catheter colonisation was defined as a catheter tip culture yielding $\geq 10^3$ cfu/ml. When the catheter tip culture grew $<10^3$ cfu/ml, in the absence of the other criteria of probable infection defined below, the catheter was classified as contaminated.

Catheter-related infection included one of the three following case definitions [18, 19, 20]:

1. Probable catheter-related bloodstream infection was defined as blood culture growing an organism commonly associated with catheter colonisation such as *Staphylococci, Candida* or *Corynebacterium spp.*, in the absence of other sites of infection apparently causing bloodstream infection.
2. Definite catheter-related bloodstream infection was defined as a positive peripheral blood culture, regardless of the organism, associated with a positive catheter tip culture or presence of pus at the insertion site growing the same organism as in blood.
3. Non-bacteraemic catheter-related sepsis was defined as catheter colonisation associated with otherwise unexplained signs and symptoms of sepsis [16], in the absence of bacteraemia, which resolved within 48 h after catheter removal, in the absence of change in antibiotic therapy.

All three case definitions of infection were included in the primary efficacy analysis.

Data analysis

A Clinical Evaluation Committee composed of the two coordinating investigators (C.B.B., G.N.) and the statistician (F.D.) assessed, blindly to the randomisation group, the evaluability of catheters and the classification of all episodes of bloodstream infection and of catheters having a positive culture, according to the above definitions. Catheters were excluded from the analysis when insertion had failed. Catheters that had not been adequately followed-up until the time of removal (transfer to another unit or hospital) were censored on the last day of follow-up in the ICU and classified by the committee as infected or uninfected using the data available up to the last day of follow-up and bacteriological data were subsequently received.

Sample size

The anticipated catheter-related infection rate was estimated at 10% in the control group. Assuming a 50% relative reduction (to 5%) in the antiseptic-coated catheter group, the study was initially planned to include 500 patients per group, with a 5% alpha risk and a 80% power.

Statistical analysis

The primary end point was the rate of catheter-related infection, including catheter-related bacteraemia and non-bacteraemic catheter-related sepsis, in each group. All cases of catheter-related infection recorded from all evaluable catheters were included in the primary efficacy analysis. The secondary end points were the incidence of CVC-related bloodstream infection and of catheter colonisation. Incidence rates of catheter-related infection and colonisation are reported per 1000 catheter-days and compared between groups using Wald statistics. All tests were two-sided. Value of $p \leq 0.05$ were considered statistically significant. Statistical analyses were performed using EPI-Info (CDC, Atlanta, Ga.) and S-Plus package.

Results

All 14 participating ICUs were in university hospitals. There were two medical, nine surgical and three mixed units. The trial was stopped after 42 months because of the slow enrolment rate and lower than expected infection rate, which did not allow reaching the pre-specified objectives within a reasonable time frame. At termination of the study, 397 patients had been randomized (Fig. 1). Of the 366 patients included in the analysis, 175 received a non-coated catheter and 191 an antiseptic-coated catheter. The clinical characteristics of the two groups were similar (Table 1).

Double-lumen catheters were mostly used (82%), and the majority of catheters (67%) were inserted in the subclavian vein. The characteristics of catheters were similar in the two groups but more mechanical complications occurred at insertion of coated catheters (10 vs 2; R=4.5; 95% CI: 1.02–20; Table 2). A similar proportion of catheters were subsequently exchanged over a guide wire (7 and 6%, respectively, in the non-coated and coated catheter group).

Catheter tip culture was not available for 3 patients, so the analysis of infection rates was performed on only 363 patients. Of the 3 patients with missing catheter cultures, one catheter was withdrawn by the patient and two ca-

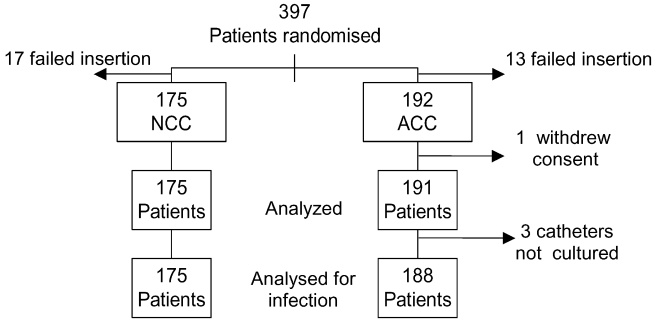

Fig. 1 Flow chart of patients enrolled in the trial and reasons for exclusion. *NCC* non-coated catheters, *ACC* antiseptic-coated catheters

Table 1 Patients characteristics at ICU admission or randomisation. *CH–SS* chlorhexidine–silver sulfadiazine. *SAPS II* Simplified Acute Physiology Score [25]; *LOD* Logistic Organ Dysfunction Score [26]

	Non-coated catheters	CH–SS-coated catheters
No. of patients	175	191
Age (mean, SD)	58 (18.0)	59.2 (17.8)
Admission category (*n*, %)		
Medical	68 (39)	88 (46)
Surgical scheduled	23 (13)	19 (10)
Surgical emergency	48 (27)	51 (27)
Non-operative trauma	36 (21)	33 (17)
Underlying disease severity (*n*, %)		
None or non-fatal	115 (66)	128 (67)
Ultimately fatal	53 (30)	55 (29)
Rapidly fatal	7 (4)	8 (4)
Severity score at ICU admission		
SAPS II (median, range)	37 (6, 118)	40 (6, 85)
Severity scores at randomization		
SAPS II (median, range)	33 (6, 118)	36 (6, 85)
LOD (median, range)	4 (0, 17)	4 (0, 17)
Days from ICU admission to inclusion (median, range)	3 (0, 112)	2 (0, 97)
Ongoing antibiotics at inclusion (*n*, %)	115 (66)	111 (58)
Other infectious focus (*n*, %)	119 (68)	111 (58)

There were 2 patients in each group with a LOD score $\geq$15, and 13 and 11 patients with a SAPS II >60, respectively, in the coated and non-coated catheters groups

Table 2 Characteristics of catheters included in the study

	Non-coated catheters (*n*=175)	CH–SS-coated catheters (*n*=191)
No. lumen (*n*, %)		
Single	31 (18)	35 (18)
Double	144 (82)	156 (82)
Condition of insertion (*n*, %)		
Unplanned	16 (9)	21 (11)
Scheduled	159 (91)	170 (89)
Order of catheter, second or more (*n*, %)	64 (37)	57 (30)
Insertion site (*n*, %)		
Internal jugular	63 (36)	59 (31)
Subclavian	112 (64)	132 (69)
Mechanical complications (*n*)[a]		
Pneumothorax	0	1
Arterial puncture	2	9
Subsequent catheter exchange (%)		
None	162 (93)	180 (94)
One or more	13 (7)	11 (6)

[a] The overall rate of mechanical complications was higher in the coated catheter group (10 vs 2; R=4.54; 95% CI: 1.02–20)

theters were not submitted for culture (one upon death of the patient, and another after transfer to another ward). In the remaining 363 patients (175 in the uncoated and 188 in the coated group), the mean (median) duration of catheterisation was similar, respectively of 12±11.7 (9) days and 10.5±8.9 (8) days; catheters remained in place for $\geq$7 days in 73 (42%) and 86 (43%) patients, respectively. Twenty-four (14%) catheters were removed for suspected infection in the uncoated catheter group, and 38 (20%) catheters in the coated group (p=0.13). Overall, 310 of 363 (85%) catheters were sterile, and 53 grew microorganisms. A similar proportion of catheters were classified as contaminated in both groups, with 11 (6.3%) and 12 (6.4%) contaminated catheters, respectively, in the non-coated and the coated group. Catheter colonisation was recorded in 23 of 175 (13.1%) uncoated catheters and 7 of 188 (3.7%) coated catheters, for an incidence of 11 and 3.6 per 1000 catheter-days (p=0.01), respectively (Table 3). Catheter-related infection occurred in 11 (6.3%) patients receiving uncoated catheters and 4 (2.1%) receiving coated catheters, i.e., 5.2 and 2.0 per 1000 catheter-days (RR=0.39; 95% CI: 0.12–1.22; p=0.10),

Table 3 Catheter colonisation/infection and associated bloodstream infections

	Non-coated catheters (n=175)	CH–SS-coated catheters (n=188)	RR (95% CI)
No. of catheter-days	2099	1971	
Duration of catheterisation (days; median, range)	9 (1–108)	8 (0–83)	
Catheter colonisation			
No. of catheters (%)	23 (13.1)	7 (3.7)	0.32 (0.14–0.76)[a]
Incidence, per 1000 catheter-days	11	3.6	
Catheter-related non-bacteraemic sepsis	6 (3.4)	1 (0.5)	
Bloodstream Infections (*n*, %)			
Catheter-related	36 (20.6)	35 (18.6)	
Incidence, per 1000 catheter-days	5 (2.9)	3 (1.6)	
Non-catheter-related	2.4	1.5	
Primary	12 (6.9)	14 (7.4)	
Secondary	19 (10.9)	18 (9.6)	
Catheter-related infections			
No. of catheters infected	11 (6.3%)	4 (2.1%)	0.39 (0.12–1.22)[b]
Incidence, per 1000 catheter-days	5.2	2.0	

[a] P=0.03
[b] P=0.10

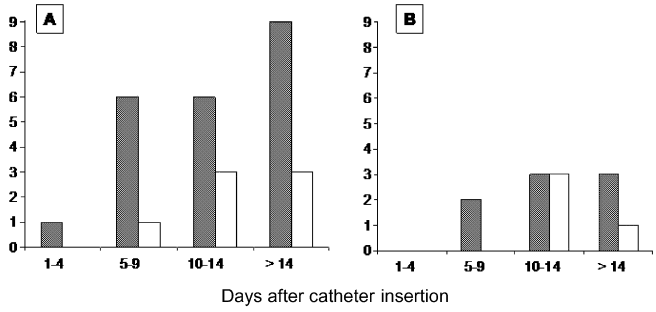

Fig. 2A,B Number of catheter colonized (**A**) or infected (**B**) for uncoated (*black bars*) or coated (*light bars*) catheters according to number of days of catheterisation

respectively. Definite catheter-related bloodstream infection occurred in only 5 (2.9%) and 3 (1.6%) patients, for an incidence of 2.4 and 1.5 per 1000 catheter-days, respectively (p=0.64).

Colonisation and infection occurred earlier in the non-coated group (Fig. 2): infection occurred after 5 days or more and 10 days or more, respectively, in the non-coated and coated group, although the difference was not significant by log-rank analysis (data not shown). Infection tended to be more frequent for catheters inserted at the jugular site (6.6 vs 2.9%; p=0.10), and when the catheter was the second or more catheter inserted in a given patient as opposed to being the first one (5.3 vs 1.7%; p=0.16). The number of lumen was not associated with infection (4.4% for double-lumen vs 3.1% for single-lumen catheters; p=0.64).

Microorganisms causing infection are shown Table 4. Gram-positive organisms were associated with 40% catheter colonisation or infection in the non-coated group and all such cases in the coated group. It is noteworthy that there were no cases of colonisation/infection with Gram-negative bacilli or *Candida* in the coated-catheter group. Polymicrobial infection occurred in 4 and 0 catheters, respectively, in the uncoated and coated groups.

One patient in the antiseptic-coated group experienced shock 1 h after catheter insertion, which led to withdrawal of the catheter for a suspected allergic reaction. This episode was subsequently attributed to sepsis unrelated to the catheter.

Discussion

In this double-blinded randomized controlled trial, we found that the second generation of central venous catheters coated with chlorhexidine and silver sulfadiazine were associated with a relative reduction of catheter-related infection rate of about 60%, but could not demonstrate a significant decrease of bloodstream infection rate. A number of trials have been performed to test the effectiveness of the first generation of chlorhexidine-silver sulfadiazine-coated catheters. In the largest clinical trial published to date comparing antiseptic-coated with conventional non-coated catheters [9], which included 405 CVC, Maki et al. observed that CVC colonisation rate (as defined by catheter tip cultures yielding >15 cfu) was reduced from 24.1 to 13.5% (p=0.005); more importantly, catheter-related bloodstream infection were also reduced from 4.7 to 1.0% (p=0.03). Clinical trials performed up to 1998 comparing antiseptic-coated catheters to non-coated catheters have been reviewed in a meta-analysis by Veenstra et al. [11]. In that analysis, the summary odds ratio for the risk reduction of infection rates associated with antiseptic-coated catheters was estimated at 0.56 (95% CI: 0.37–0.84).

However, several studies did not document such an effect, especially when focusing on blood stream infection [8]. For example, in a randomized controlled study of 233 catheters, Bach et al. found no significant reduction in catheter-related bloodstream infection (0 vs 3, p=0.25), despite a significant reduction in catheter colonisation rate (31 vs 18%; p=0.036) and persistent antiseptic activity of catheters for up to 15 days [21]. Moreover, in the trial comparing antiseptic- to antibiotic-coated catheters [14], infection rates recorded in the former group were high, comparable to those of the control group of the trial reported by Maki et al. in 1997 [9]; however, all infections

Table 4 Microorganisms associated with colonisation or infection of catheters

	Non-coated catheters		Antiseptic-coated catheters	
	Infected[b]	Colonised	Infected[a]	Colonised
Gram-positive cocci				
Coagulase-negative staphylococci	5 (2)	3	3 (2)	1
S. aureus	1 (1)	1	1 (1)	2
Enterococci	3 (1)	–	–	–
Gram-negative bacilli				
Enterobacteriaceae	5 (0)	2	–	–
Aerobic gram-negative bacilli	1 (1)	5	–	–
Candida sp.	0	2	–	–
Total[a]	15 (5)	13	4 (3)	3

[a] Four infections and one colonisation in the non-coated catheter group were polymicrobial; none was polymicrobial in the coated group

[b] Microorganisms associated with bacteraemia are shown in parentheses

in the antiseptic-coated catheter group occurred after 7 days or more. These results suggested suboptimal efficacy of the antiseptic-coated catheters compared with antibiotic-bonded catheters, especially for catheters remaining in place for over 1 week. In that trial, the first generation of antiseptic-coated catheters were used, which may have provided insufficient protection duration for catheters remaining in place for relatively long periods.

The new generation of antiseptic-coated catheters has two distinctive features from the previous generation: (a) the entire lumen track is coated with antiseptics; and (b) the concentration of antiseptics on the external surface is approximately three times higher than that coating catheter of the first-generation. These features should provide enhanced protection against colonisation of the catheter and further reduce the infection risk.

In this trial, we have tested the preventive efficacy of this new generation of antiseptic-coated catheters, and found that infection rate was reduced by about 60% (RR=0.39; 95% CI: 0.12–1.22) as compared with standard non-coated catheters; however, this reduction did not reach statistical significance (p=0.10), because of the relatively small sample size in regard of the overall low infection rate in our study population.

It is noteworthy that the overall catheter-related infection rate was 5.2/1000 catheter-days in the control group, with only 4 (2.0 per 1000 catheter-days) catheter-related bloodstream infection, despite a relatively long median duration of catheterisation of 8–9 days. This rate is much lower than anticipated and previously reported from epidemiological and surveillance studies [5, 7], and from that reported in the control groups of previous clinical trials testing antiseptic- or antibiotic-coated catheters. Our low baseline infection rate may be due in part to the criteria for inclusion in the study, resulting in exclusion of patients and catheters at higher risk of infection (e.g., inserted as an emergency procedure). It was also possibly due the organisational constraints associated with obtaining written informed consent, which may have been difficult to seek when central venous catheterisation is needed in a critically ill patient, resulting in a bias toward including low-risk patients with planned catheter insertion, and in the slow enrolment rate of the trial. It is noteworthy that 90% of catheter insertions in our study were planned catheterisation. In addition, progress made in preventive measures, which appear to have substantially lowered catheter-related infection rates in the past decade [22], is another likely explanation for our low baseline infection rate. Finally, inclusion in a clinical trial may result in better adherence to prevention protocols and guidelines and a better outcome. Whatever the respective contribution of these factors to our low baseline infection rate, this resulted in large part in the early termination of the trial after 42 months, when it was apparent that a much larger population would be needed to demonstrate an effect on infection rates.

There was a consistent and similar reduction of infection and colonisation rates in our trial (Table 3); however, the reduced catheter colonisation rate must be interpreted with caution. We made no attempt to antagonize the antiseptics when culturing catheter tips, and some residual antiseptic may have shed from the catheter to the culture medium, thus inhibiting growth of microorganisms. Bach et al. [21] have shown that a substantial antiseptic activity is retained for up to 2 weeks, which may inhibit growth of organisms adherent to the catheter [23]. Since catheter colonisation was part of the definition for infection, this may have artificially reduced the infection rate in the coated-catheter group, especially for non-bacteraemic sepsis. It is noteworthy that the incidence of non-catheter related bloodstream infection did not differ between the two groups (31 and 32 episodes, respectively, in the uncoated and antiseptic-coated groups, respectively; Table 3). Specifically, the incidence of primary bloodstream infection, which often are not individualized from proven catheter-related bloodstream infection in surveillance studies, was similar (12 and 14 episodes, respectively).

Our results are consistent with those of another randomized trial recently conducted in the United States and testing the new generation of antiseptic-coated catheters [24]. In this trial including 777 catheters, the colonisation rate was 23.3 and 12.8 per 1000 catheter-days, respectively, in the non-coated catheter and the coated-catheter group; however, similarly to our study, the incidence of bloodstream infection was very low (1.2 vs 0.4 per 1000 catheter-days, respectively). In the current context of decreasing infection rates, especially of bacteraemia [22], the design and conduct of clinical trials of new devices is a difficult challenge.

The point estimate of the risk reduction afforded by the new generation of chlorhexidine-silver sulfadiazine-coated catheters is in the low range of estimates provided by previous studies with the first generation of such catheters [11], suggesting these catheters may afford enhanced protection for a longer period, and could be useful in ICU patients at high risk of infection and receiving central venous catheterisation for periods of 1–2 weeks; however, a comparison between the two generations of catheters has not been performed.

Conclusion

In conclusion, using the new generation of chlorhexidine-silver sulfadiazine-coated catheters was associated with a strong trend toward reduction in infection rates of central venous catheters. Protection against infection appeared to extend up to 10 days in our study. Although our study failed to demonstrate a statistically significant reduction of catheter-related infection, because of the low baseline infection rate and insufficient power of the study, our

results are consistent with another similar trial recently conducted in the U.S. Whether the reduction is larger than that provided by the first generation of antiseptic-coated catheters or equivalent to that afforded by antibiotic-bonded catheters would need a randomized trial comparing the two types of catheters. Such a trial would be extremely difficult to perform, except in settings with very high baseline infection rates.

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