Comparison of triple-lumen central venous catheters impregnated with silver nanoparticles (AgTive®) vs conventional catheters in intensive care unit patients

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SUMMARY

Background: Silver-impregnated central venous catheters (CVCs) have been proposed as a means for preventing CVC colonization and related bloodstream infections (CRBSIs).
Aim: To evaluate the efficacy of CVCs impregnated with silver nanoparticles in a large group of critically ill patients.
Methods: A prospective, randomized clinical trial was conducted in five intensive care units (ICUs). Three hundred and thirty-eight adult patients requiring CVCs between April 2006 and November 2008 were randomized to receive AgTive silver-nanoparticle-impregnated (SC) or conventional (CC) CVCs. Primary endpoints were CVC colonization (growth of $\geq$15 colony-forming units from the catheter tip) and incident CRBSIs (meeting the definitions of the Centers for Disease Control and Prevention). Infection-free time (days from initial CVC insertion to initial blood culture positivity) and ICU mortality rates were measured as secondary endpoints.
Findings: The SC group ($N = 135$) and CC group ($N = 137$) were similar in terms of clinical and laboratory parameters at baseline, reasons for ICU admission, complications during CVC insertion, and total time with CVC (mean $\pm$ standard deviation; SC 13 $\pm$ 24 vs CC 15 $\pm$ 37 days). No significant intergroup differences were found in CVC colonization rates (SC 32.6% vs CC 30%; $P = 0.7$), CRBSI incidence rates (3.36 infections per 1000 catheter-days in both groups), infection-free times (SC 13 $\pm$ 34 vs CC 12 $\pm$ 12 days; $P = 0.85$) or ICU mortality (SC 46% vs CC 43%; $P = 0.7$).

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Conclusion: In critically ill patients, use of AgTive® silver-nanoparticle-impregnated CVCs had no significant effect on CVC colonization, CRBSI incidence or ICU mortality. These CVCs cannot be recommended as an adjunctive tool for control of CRBSIs.

Introduction

Central venous catheters (CVCs) are indispensable for managing most critical illnesses, but their use is associated with an increased risk of bloodstream infections (BSIs). In the USA, where the use of CVCs in intensive care units (ICUs) has been estimated at one million catheter-days per year, approximately 80,000 cases of CVC-related BSIs are reported annually.[1–6] Biomaterial technology has developed a number of strategies aimed at reducing these complications,[7,8] including the use of catheters coated or impregnated with anti-infective agents (e.g. antiseptics, antimicrobials, antimetabolite substances and silver ions). Studies on the efficacy of these devices have yielded conflicting results.[9–13] Silver-ion-eluting CVCs have been tested in critically ill and cardiac surgery patients, but — with rare exceptions[14,15] — the results have been unconvincing.

A newer generation of silver-impregnated CVCs (LogiCath AgTive®, MedeX Medical Inc., Naseby, Northants, UK) has been marketed with the claim of enhanced bactericidal activity. AgTive catheters are made of polyurethanes impregnated with silver nanoparticles, and their interaction with body fluids and intravenous solutions results in the release of significantly larger amounts of silver ions from the inner and outer surfaces of the catheter.[16] In a single-centre, prospective trial conducted in a mixed population of ICU and non-ICU patients, these silver nanoparticle-impregnated catheters markedly reduced CVC colonization rates and catheter-associated infection rates compared with non-antiseptic CVCs.[17] This article reports the results of a multi-centre, randomized, controlled trial to assess the efficacy of CVCs impregnated with silver nanoparticles in a large population of critically ill patients in ICUs.

Methods

Patients

Patients were recruited in the ICUs of five Italian university hospitals from April 2006 to November 2008. The study protocol was approved by the institutional review board of the coordinating centre (Università Cattolica del Sacro Cuore, Protocol No. 254 A.474/C.E./2005) on behalf of all participating centres. Adult patients ($\geq$ 18 years) scheduled to undergo central venous catheterization (via subclavian or internal jugular route) were enrolled with informed consent. Exclusion criteria were a history of unsuccessful attempts at catheterization or evidence of previous surgery, skeletal deformity and/or scarring involving the catheterization site.

Endpoints

The primary endpoints were crude CVC colonization rates and the incidence of catheter-related bloodstream infections (CRBSIs) (number of infections per 1000 catheter-days). Infection-free time (measured in days from the time of initial

catheterization to the time of initial blood culture positivity) and ICU mortality rates were secondary endpoints.

CVC insertion, care and removal

All CVCs were inserted at subclavian or jugular sites in accordance with the recommendations of O'Grady *et al.*[5] The insertion site was covered with a transparent, semi-permeable dressing that was inspected daily and changed when necessary. Tubing and three-way stopcocks were changed according to local protocols or when needed. Catheters remained in place as long as required, and this need was assessed regularly. Whenever a CVC was removed (because it was no longer needed, not functioning properly or thought to be infected), the tip was submitted for semi-quantitative culture[18] and antimicrobial susceptibility studies. Blood cultures and other microbiological studies were ordered as indicated. Catheter removal was not standardized, but physicians were advised to make every effort to avoid tip contamination. Catheter exchange over a guidewire was only allowed in the absence of severe sepsis or signs of local infection, and replacement catheters were removed promptly if the previous catheter's tip was found to be colonized.

Definitions

As recommended by the Centers for Disease Control and Prevention,[5] catheter colonization was defined as growth of $\geq$15 colony-forming units from a distal catheter segment, and exit site infection was defined as erythema or induration within 2 cm of the catheter exit site in the absence of concomitant BSI and without concomitant purulence. The relationship between BSIs and CVCs was based on clinical and microbiological data, and classified as follows:

- probable — blood culture growing an organism commonly associated with catheter colonization in the absence of other sources of bacteraemia/fungaemia;
- definite — bacteraemia/fungaemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein, clinical manifestations of infection and no apparent source for the BSI except the catheter, and at least one of the following: positive semi-quantitative cultures of peripheral blood and CVC tip yielding identical organisms (at species and antibiogram levels), or positivity for the same organism in blood cultures drawn simultaneously from the CVC and from a peripheral site, where the latter culture became positive >2 h after that drawn from the central line; or
- none (in the absence of the above findings).

Randomization and blinding

Patients were randomized to Group A [standard triple-lumen, non-medicated CVC; conventional catheter (CC)] or Group B

[AgTive triple-lumen, silver-nanoparticle-impregnated CVC; silver catheter (SC)] using an Internet-based scheme, stratified by centre, patient age and gender. The key was held by the data manager. For data collection purposes, patients were identified solely as members of Group A or B. When catheter replacement was necessary, the new catheter was the same type as the catheter being removed. Therefore, the physicians performing catheterization were aware of the type of catheter being used in each case, but this information was not available to the institutional review board that decided whether the study should be terminated or to the statisticians who analysed the data.

Data collection

Upon enrolment (i.e. at the time of catheterization), the patient's Sequential Organ Failure Assessment (SOFA) score[19] was calculated, and the following information was recorded: age; sex; dates of hospital and ICU admission; nature and severity of underlying disease; reason for ICU admission; clinical/laboratory findings and treatments already being administered at ICU admission (details in Table I); and the Simplified Acute Physiology Score II (SAPS II, calculated within 24 h of ICU admission).[20] The number of venepunctures performed during every catheterization procedure and any complications that occurred were noted.

Statistical analysis

Assuming a conventional CVC colonization rate of 10% and a 50% reduction of this rate with test catheters, it was initially calculated that a sample size of 848 patients (424 patients per group) would be necessary to ensure adequate (0.8) power to detect intergroup differences at a two-sided α-level of 0.05. However, after observing that the colonization rate was higher than initially expected (around 30%), the sample size was recalculated, estimating that 118 patients per group would be necessary to detect a 50% intergroup difference with a power of 0.8.

Intergroup differences involving primary endpoints were evaluated using Fisher's exact test. Kaplan−Meier survival curves and relative log-rank tests were used to assess the effect of catheter type on secondary endpoints. Statistical analyses were performed using R 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

In total, 338 patients were randomized during the study period, but important microbiological and/or clinical data were missing in 66 cases (Figure 1). Data were thus analysed for 272 patients [mean age ± standard deviation (SD): 63.9 ± 17 years; 61% males; mean SAPS II score ± SD: 49.5 ± 18.6; mean SOFA score ± SD: 7 ± 3]. The SC ($N = 135$) and CC groups ($N = 137$) were not significantly different in terms of clinical characteristics at baseline (Table I), total number of CVCs, percentage of patients who had intravascular devices other than CVCs, multiple venepunctures during CVC insertion, and catheter removal without replacement (Table II).

Microbiological outcomes in the two groups were also similar (Table III). On the whole, CVC colonization was documented in almost one-third of all patients, with a slightly (but not significantly) higher incidence in the SC group. A minimal difference emerged for probable CRBSIs, whereas the incidence of definite CRBSIs was identical in the two groups (3.36 events per 1000 catheter-days). The most common catheter tip isolates in both groups were Gram-negative bacteria (Table IV).

There were no significant intergroup differences in terms of the estimated risk of CRBSIs (Figure 2) ($P = 0.39$, log-rank test) or ICU mortality (Figure 3) ($P = 0.68$, log-rank test). On the whole, 121 of the 272 (44.5%) patients died in the ICUs [62 (46%) in the SC group, 59 (43%) in the CC group].

Table I
Baseline characteristics of the two groups

	Conventional CVCs ($N = 137$)	AgTive CVCs ($N = 135$)	P-values[a]
Males, *N* (%)	78 (57)	87 (64)	0.3
Age, years	62.9 ± 17.3	64.8 ± 16.6	0.36
SOFA score at enrolment	7.16 ± 3.7	6.84 ± 3.6	0.54
Reason for ICU admission			
Medical, *N* (%)	80 (60)	90 (71)	0.2
Surgical, *N* (%)	31 (23)	22 (17)	0.2
Non-scheduled intervention, *N* (%)	13 (10)	13 (10)	0.9
Scheduled intervention, *N* (%)	18 (13)	9 (7)	0.1
Trauma, *N* (%)	22 (17)	14 (11)	0.1
Clinical/laboratory findings and treatment underway at ICU admission			
SAPS II[b]	50.0 ± 18.6	49.0 ± 18.7	0.66
Fever, *N* (%)	32 (23)	25 (18)	0.4
Phlebitis, *N* (%)	0 (0)	2 (1)	0.2
Body temperature, °C	37 ± 1	37 ± 1	1
Fibrinogen, mg/dL	548 ± 3	567 ± 3	1
Serum albumin, g/dL	2.6 ± 0.7	2.8 ± 0.8	0.2
Antibiotic therapy, *N* (%)	76 (55)	64 (47)	0.2
Vasoactive drug support, *N* (%)	31 (23)	35 (26)	0.6

CVC, central venous catheter; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; SD, standard deviation; SAPS II, Simplified Acute Physiology Score II. Data are shown as means ± SD, until otherwise indicated.
[a] Intergroup differences tested by analysis of variance and Kruskal-Wallis sum rank procedures (quantitative variables) or Fisher's exact test (counts).
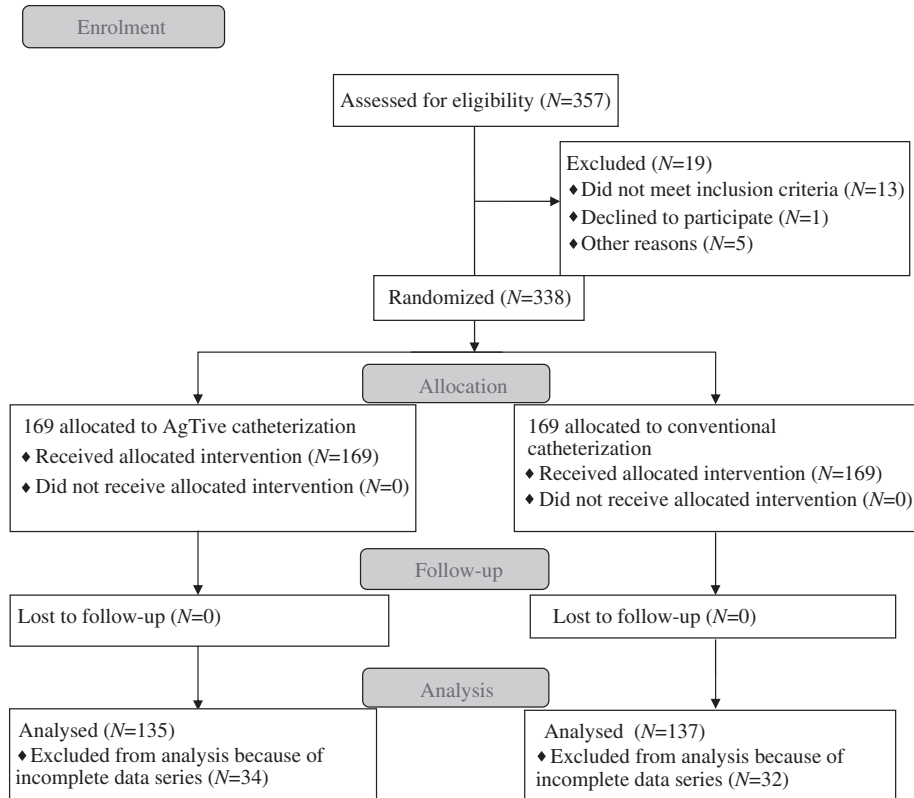[b] Calculated within 24 h of ICU admission.

Figure 1. Flow diagram of participants' passage through the study.

Discussion

On the basis of data collected in 272 patients, the AgTive CVC appears to have little impact on the incidence of CVC colonization and CRBSIs in critically ill patients. The overall rates of catheter colonization (31.2%) and CRBSIs (4.8%) in the study population are consistent with previous reports,[21–24] but neither variable was significantly influenced by use of the silver-eluting catheters. Indeed, the incidence of CRBSIs was identical in the two treatment arms (3.36 events /1000 catheter-days).

Various techniques are used to incorporate silver into CVCs. Claims that silver alloy coatings protect CVCs against bacterial adhesion have not been confirmed in clinical settings,

Table II
Central venous catheterization procedures in the two groups[a]

	Conventional CVCs (N = 137)	AgTive CVCs (N = 135)	P-values[b]
No. of venepunctures for CVC insertion			
1	103 (75)	111 (82)	0.3
≥2	34 (25)	24 (18)	0.2
Complications			
Arterial puncture	1 (1)	1 (1)	1
Haematoma	0 (0)	0 (0)	—
Pneumothorax	0 (0)	0 (0)	—
Patients with other catheters at CVC insertion			
Second CVC	4 (3)	5 (4)	0.7
Arterial catheter	91 (66)	85 (63)	0.6
Dialysis catheter	10 (7)	13 (10)	0.6
Swan-Ganz catheter	1 (1)	1 (1)	1
Total	106 (77)	104 (77)	1
Original CVC outcome			
Replacement	16 (12)	15 (11)	0.9
Replacement over guidewire	6 (4)	8 (6)	0.6
Removal without replacement	35 (26)	39 (29)	0.6
Time with CVC, days (mean ± SD)	15 ± 37	13 ± 24	0.6

CVC, central venous catheter; SD, standard deviation.
[a] Data are presented as N (%) unless otherwise indicated.
[b] Fisher's exact test for intergroup differences.

Table III
Central venous catheterization outcomes in the two groups

	Conventional CVCs (N = 137)	AgTive CVCs (N = 135)	P-values[b]
Catheter-days (total)[a]	2081	1784	—
Microbiological outcomes — N (%)/N per 1000 catheter-days			
CVC colonization	41 (30)/19.7	44 (32.6)/24.6	0.7
CRBSI			
Probable	25 (18)/12	16 (12)/8.9	0.2
Definite	7 (5)/3.36	6 (4)/3.36	1

CVC, central venous catheter; CRBSI, catheter-related bloodstream infection.
[a] Includes time with original and replacement CVCs.
[b] Fisher's exact test for intergroup differences.

Table IV
Micro-organisms isolated from colonized central venous catheters[a]

	Conventional CVCs (N = 137)	AgTive CVCs (N = 135)	P-values[d]	Conventional CVCs (N = 137)	AgTive CVCs (N = 135)	P-values[d]
	Colonization			CRBSI[b]		
Gram-positive bacteria						
Staphylococcus spp.	10	11	1	11	12	0.4
Enterococci	3	3	1	4	2	0.7
Gram-negative bacteria						
Pseudomonas aeruginosa	13	8	0.3	3	3	1
Acinetobacter baumannii	1	4	0.2	3	2	1
Other[c]	10	16	0.2	6	2	0.3
Fungi						
Candida spp.	5	5	1	5	4	1
Total isolates	42	47	0.5	32	25	0.4

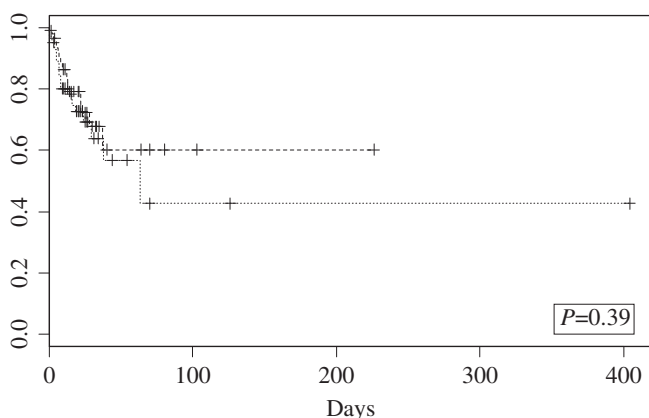CVC, central venous catheter; CRBSI, catheter-related bloodstream infection.
[a] Some colonizations/infections were polymicrobial.
[b] Includes probable and definitive CRBSIs.
[c] *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Serratia marcescens*, *Enterobacter cloacae*.
[d] Fisher's exact test for intergroup differences involving colonization rates/CRBSI rates.

especially those with low baseline colonization rates and catheter indwelling times exceeding 10 days.[25,26] More encouraging results have been obtained with oligon, a polyurethane matrix impregnated with silver, carbon and platinum. Contact with body fluids or infusates results in prolonged release of silver ions from both the inner and outer surfaces of oligon catheters. Two studies in high-risk patients found that these CVCs reduced catheter colonization, especially by coagulase-negative staphylococci and Gram-negative bacilli.[14,15] However, in a third study, they produced no significant benefits,[27] and a fourth study found that they were associated with significantly higher colonization rates than those observed with catheters coated with rifampicin plus minocycline (14.6% and 8.9%, respectively; P = 0.039).[28]

The performance of silver-impregnated catheters also seems to depend on baseline rates of CVC tip colonization. For example, in one study, standard catheter colonization rates (11.2 per 1000 catheter-days) were already quite low (despite the median

indwelling time of 10 days), and they were not significantly reduced by catheters made of a mixture of silver zeolite powder and polyurethane (9.4 per 1000 catheter-days).[29] In another study, however, zeolite-impregnated CVCs significantly lowered the frequency of positive CVC tip cultures in a setting where rates of colonization for untreated catheters were quite high (73%).[30]

The only other study that specifically examined CVCs impregnated with silver nanoparticles is that of Boswald *et al.*, who found that they significantly reduced rates of CVC colonization (−37.7%) and catheter-associated infection (−71.3%).[17] The discrepancy between their findings and the present findings may reflect different levels of infection risk and case mixes in the two study populations. The study by Boswald *et al.* involved a single centre, and <20% of the patients were in an ICU when the CVCs were inserted. Furthermore, >50% had malignancy and over half had undergone elective surgery. In the present population, elective surgery was rare, and most (77%) patients had other intravascular catheters in addition to the CVC. Finally, the two studies

Figure 2. Kaplan–Meier curves show no significant intergroup difference in the risk of catheter-related bloodstream infections [adjusted for total times with central venous catheter (CVC), P = 0.39, log-rank test]. Dashed line, conventional CVCs; dotted line, silver-nanoparticle-impregnated CVCs.
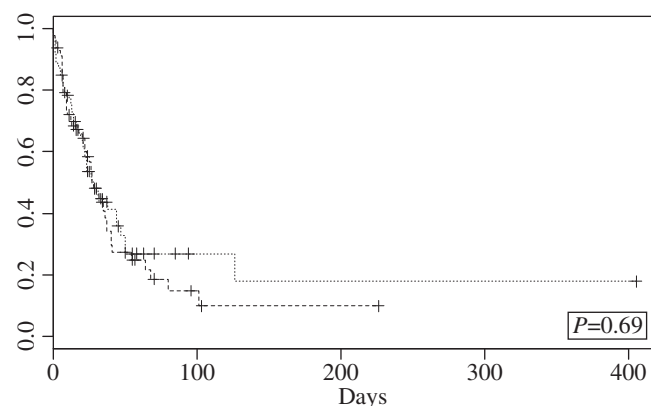
Figure 3. Kaplan–Meier curves show no significant intergroup difference in intensive care unit survival rates. Dashed line, conventional central venous catheters (CVCs); dotted line, silver-nanoparticle-impregnated CVCs.

used different criteria to identify CRBSIs. Meaningful comparison of the results is thus quite difficult.

Migration of skin microbes from the insertion site or from a contaminated hub appears to be the main cause of CVC colonization and subsequent BSI, but it is not clear whether or not catheter colonization is a reliable surrogate marker of CRBSI. A retrospective analysis of 29 selected reports revealed solid linear correlation between catheter colonization and CRBSI rates ($r = 0.69$, $r^2 = 0.48$, $P < 0.001$).[31] As others have noted, however, antiseptic particles released by the catheter tip into the culture medium could reduce microbial growth, increasing the risk of false-negative tip culture.[31–33] This may explain why some antimicrobial CVCs have been reported to lower catheter colonization rates but not the incidence of CRBSIs.[9,10,15,29] Meta-analyses have yielded conflicting conclusions on this point. Casey *et al.* found that silver-treated catheters (alloy-coated, impregnated, iontophoretic) did not improve colonization or CRBSI rates, whereas a more recent analysis revealed borderline reductions in both rates ($P = 0.04$ and $P = 0.07$, respectively).[13,34]

The overall colonization rate (31.2%), which was essentially the same in all centres, is slightly higher than rates reported in large, prospective, randomized trials (22.8–26%).[21–23] The possibility of protocol violations during catheterization, especially when less-experienced physicians were operating without ultrasound guidance or after two or more venepunctures (21.3%), cannot be excluded.

The baseline rate of definite CRBSIs was fairly low in the present study (4.8%). Under these circumstances, a much larger population would have been needed to analyse the potentially beneficial effects of the AgTive catheters reliably. However, in light of the slow recruitment, the trial was terminated after 32 months. Nonetheless, the results shed doubt on the antimicrobial efficacy of the AgTive catheters. *In vitro*, these catheters have displayed prolonged release of silver ions,[16] but this may have been insufficient in the study population, where total mean catheter days were 15.4 days in the CC group and 13.3 days in the SC group.

The CVC tip and blood cultures in the present study yielded similarly high rates of Gram-negative bacteria in the two groups. This might reflect the characteristics of the study population, which mainly consisted of critically ill patients requiring prolonged catheterization. In this setting, hub colonization, intraluminal migration and subsequent infection by Gram-negative organisms are distinct risks.[6,16] Certain Gram-negative rods are constitutively resistant to silver,[16] but concentrations of ≥ 5–10 μg/mL have proved to be highly effective against the biofilms produced by *Pseudomonas aeruginosa*. The fact that the concentration produced on the surface of AgTive catheters is below the bactericidal threshold[35] may explain the high number of *P. aeruginosa* isolates recovered.

This study has several limitations. Most importantly, the physicians involved in catheterization were aware of the catheter type used in each case, and this may have biased decisions (e.g. whether an infection was CVC-related when criteria for definite CRBSIs were not met). In addition, the catheter removal process was not standardized. Tip contamination may have occurred during some of these procedures, and if so, the colonization rates may have been overestimated. Furthermore, the roll-plate method used to culture catheter tips reduces the chances of isolating micro-organisms colonizing the catheter lumen (a common finding with long-dwelling CVCs). Finally, the microbial isolates were not characterized molecularly (e.g. by pulsed-field gel electrophoresis). This may have revealed additional cases of clonal identity between bloodstream and catheter isolates, increasing the number of definite CRBSIs observed. However, all of these shortcomings would have had similar effects in both groups, so they cannot explain why results in the SC group were no lower than those in the CC group, as expected on the basis of previous reports.[17]

In conclusion, in international guidelines, the use of antimicrobial or antiseptic CVCs is only considered to be cost-effective when CRBSI rates remain high after rigorous application of all other preventive measures.[7,36] The study findings indicate that the LogiCath AgTive CVC is unlikely to have a significant impact, even in this setting. Staff compliance with recommended infection control protocols (hand hygiene, maximal barrier precautions, asepsis during catheter insertion, daily monitoring) thus remains the mainstay of our defence against CRBSIs.

Acknowledgements

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