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Veerle ELM Gillis MD , Marijn J van Es MSc , Yannick Wouters MD PhD , Geert JA Wanten MD PhD

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Highlights

- A safe and reliable central venous access is the cornerstone of treatments in numerous clinical settings.
- Antiseptic barrier caps seems an effective strategy to reduce CLABSI
- Antiseptic barrier caps are safe, timesaving and highly appreciated by health care workers for their ease of use.
- Monitoring of ABC use, and availability of caps is key to improve and maintain compliance.

Antiseptic barrier caps to prevent central line-associated bloodstream infections: a systematic review and meta-analysis

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Type of article: Systematic review and meta-analysis

Veerle ELM Gillis, MD[1]*, Marijn J van Es, MSc*[1]*, Yannick Wouters, MD PhD*[1]*, Geert JA Wanten, MD PhD*[1]

[1]*Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands.*

Corresponding author:

Veerle E.L.M. Gillis, MD

Department of Gastroenterology and Hepatology

Radboud University Medical Centre

PO Box 9101, code 455

Geert Grooteplein Zuid 10

6500 HB Nijmegen, The Netherlands

Tel: +316 50008466

Fax: +31 243694296

E-mail: veerle.gillis@radboudumc.nl

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MvE: None

YW: None

GW: reports grants from Geistlich Pharma, and consulting fees from Geistlich Pharma and Zealand outside the submitted work.

Author contributions:

VG: Conceptualization, methodology, validation, formal analysis, investigation, data curation, writing - original draft, writing - review and editing, visualization, project administration

MvE: Conceptualization, methodology, validation, investigation, data curation, writing - original draft, writing - review and editing

YW: Conceptualization, methodology, validation, writing - review and editing

GW: Conceptualization, methodology, validation, writing - review and editing, supervision

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Abstract

Background: Reliable and safe venous access is crucial for patients using central venous catheters (CVC). However, such CVCs carry a risk for central line-associated bloodstream infections (CLABSIs). Antiseptic barrier caps (ABCs) are a novel tool in the armamentarium for CVC disinfection. Our aim was to review the efficacy and safety of ABCs.

Method: A literature search was conducted using PubMed, EMBASE, Cochrane library, and CINAHL. Primary aim was to compare CLABSI rates in patients using ABCs versus standard care. Secondary aims included efficacy of ABCs in relevant subgroups (age, ABC brand, clinical setting), safety, compliance, and costs. Fifteen studies were included in the meta-analysis.

Results: In total, 391 CLABSIs in 273,993 catheter days occurred in the intervention group versus 620 CLABSIs in 284,912 days in the standard care group, resulting in a risk ratio of 0.65 (95%CI 0.55-0.76; P<0.00001). Subgroup analyses showed similar effects, except for non-intensive care unit. In general, ABCs were safe, highly appreciated by patients and caregivers, and cost-effective, while compliance was easy to monitor. In most studies, a substantial risk of bias was observed.

Conclusion: In conclusion, while available evidence suggests that ABCs are effective, safe, easy in use, and cost-effective. However, due to the poor methodological quality of most available studies, more robust data should justify their use at this point.

Keywords

Antiseptic barrier cap; catheter-related bloodstream infection; central line-associated bloodstream infection; central venous catheter; infection control; passive disinfection; port protector

Introduction

A reliable and safe vascular access by means of central venous catheters (CVCs) is crucial for the care of patients in numerous clinical settings, ranging from infusion of parenteral nutrition and medication to haemodialysis.[1, 2] Despite their vital importance, these CVCs may cause potentially life-threatening complications, mostly central line-associated bloodstream infections (CLABSIs). [3, 4]

In case of a CLABSI, pathogens may enter the circulation via an extraluminal or the intraluminal route (Figure 1). Contamination via the extraluminal route is most common for short-term (non-tunneled) CVCs when micro-organisms migrate from the skin at the insertion site directly into the vein. To prevent extraluminal contamination, the skin is disinfected prior to catheter insertion.[5] Contamination via the intraluminal route is the most frequent complication seen in long-term subcutaneously tunneled CVCs and frequently occurs due to inadequate antiseptic catheter-handling procedures.[6, 7] The intraluminal route starts at the catheter hub or (if present) needleless connector, from which micro-organisms can adhere, migrate, and colonize the internal lumen of a CVC. These micro-organisms may form a biofilm and subsequently spread into the bloodstream.[7-9] To prevent intraluminal contamination, catheter hubs are disinfected according to standard manual procedures, called "scrub-the-hub". The hub is scrubbed with a dis-infectant wipe and subsequently dried before using the catheter. Since scrubbing duration is generally not described in protocols and compliance differs among healthcare professionals, inadequate disinfection results in an increased risk of CLABSIs.[5, 10-12]

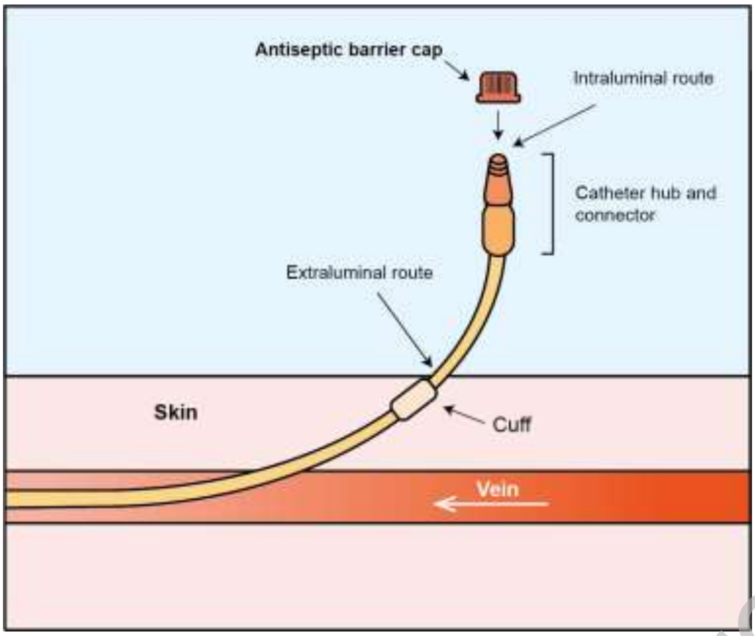

Figure 1. Central venous catheter with antiseptic barrier cap

Antiseptic barrier caps (ABCs) have been developed to decrease CLABSIs by reducing the effect of variations in scrubbing duration and techniques. These plastic caps contain a disinfectant, mostly 70% isopropyl alcohol (IPA) or chlorhexidine gluconate. The cap is screwed directly onto the needle-less connector and continuously bathes the access point in an antimicrobial agent and can be left in place between infusions, providing improved disinfection and preventing touch or airborne pathogens from invading the hub (Figure 1).[11-14] As long as the cap is not removed from the access point, the needle-less connector remains inaccessible, disinfected and protected for up to seven days.[15-18] Most protocols recommend ABCs to be replaced each time the CVC is accessed, or at least once weekly. Hence, ABCs seem a less error-prone approach to prevent CLABSIs as a result of their single-use. The time-saving feature is highly appreciated by healthcare professionals, resulting in high compliance with cap use.[19] Implementation of these caps could provide a considerable help to prevent CLABSIs in clinical practice, as was described in a relative recent meta-analysis.[19]

As several studies with the highest level of evidence on ABCs have been published even more recently, an updated review and meta-analysis seems appropriate. Primary aim of this study was to assess the efficacy and safety of ABCs to prevent CLABSIs. Secondary aims were to evaluate efficacy in different clinical settings, safety, compliance, and costs.

Methods

This study was registered in PROSPERO (registration number: CRD42021288689) and reports according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

A first literature search was conducted on the 24th of November 2021, using MedLine, EMBASE, Cochrane library and CINAHL. The search was updated on 1 June 2022 to avoid missing recently published trials. The following search terms (and their synonyms) were combined: "barrier cap" and "central venous catheter". The full search strategy is presented in the Table S1. An experienced medical librarian of the Radboud University assisted with the literature search.

Study selection

We included studies reporting prospective data on ABCs for CVCs, with CLABSI rates as primary or secondary outcome. Patients from any age group, in any clinical setting were eligible. Publications were only included in the meta-analysis if they reported at least two of the following variables: total catheter days, number of CLABSIs, and/or CLABSIs per 1,000 catheter days. Studies implementing a set of interventions to reduce CLABSI rates were only included if the implementation of ABCs was the sole intervention in a certain time period.

Studies exclusively focusing on catheter connectors or lock solutions were excluded from this review, as well as articles that could not be retrieved, reviews, conference abstracts, letters to editors, case reports, corrigenda and product audits. ABC brands that are currently not commercially available (anymore) were excluded as well.

Data extraction

All identified studies were checked for duplicates, and title and abstract were screened. Included studies were subsequently screened for full text. Literature screening and data collection was independently performed by two authors (MvE and VG) and discrepancies were discussed with YW and GW. The following data was extracted from each article: publication date, study design, country, department, population (children and/or adults), study period, number of patients, number of CVC days, type of CVC, type of brand cap, CLABSI or catheter-related bloodstream infection (CRBSI) rates. In case of missing data, the corresponding or final author of a study was requested via email for additional information.

Outcomes and definitions

Primary outcome of this study was the rate of CLABSIs per 1,000 catheter days in patients using ABCs compared to standard (non-ABC) care, which includes chlorhexidine and IPA wipes. Secondary outcomes were the efficacy of ABCs in various settings, such as adults and children, type of cap brands, and (non-)intensive care unit (ICU) setting. Furthermore, we explored safety, compliance, and costs of the ABCs. Publications with the outcome CLABSI or CRBSI were both included and for readability purposes in this article referred to as CLABSI.

Quality assessment of bias

All randomized and non-randomized studies were assessed using the Risk-of-Bias for randomized trials tool (RoB 2) and the Risk Of Bias In Non-randomized Studies- of Interventions tool (ROBINS-I), respectively. Non-randomized studies were scored as low, moderate, serious, or critical risk of bias, and randomized studies as low, some concerns, and high risk of bias.[20-22] Both assessment were reviewed by two independent reviewers (VG and MvE)

Statistical analysis

The data of included studies in the meta-analyses were pooled and analyzed using the Mantel-Haenszel method with a random effect model. The main outcome of the meta-analysis was expressed in risk ratio (RR), based on catheter days and number of CLABSIs. Heterogenicity between studies was established with Higgins' I2 statistics. A score between 0-40%, 30-60%, 50-90% and 75-100% was defined as might not be important, moderate, substantial and considerable, respectively.[23] A funnel plot was used to determine publication bias, and sensitivity analyses were performed to establish potential factors influencing outcomes, such as type or quality of a study. In addition, subgroup analyses were performed for age (children versus adults), type of brand (Curos™ 3M, St. Paul, MN versus SwabCap™ Excelsior Medical, Neptune City, NJ), and patient population (ICU versus non-ICU), and tested for different effects between subgroups.[24] All analyses were conducted using Review manager version 5.3.5.

Results

Search strategy

Our search yielded 3,599 articles. After removing duplicates, 2,713 potentially relevant articles were screened for title and abstract. Subsequently, 42 articles were assessed for full text, of which 26 studies were excluded for various reasons (Figure 2). Of the remaining 16 studies, corresponding authors of ten articles were approached for additional data on outcomes or for the baseline table, of which two responded.[15, 25] In addition, we approached authors of a previous meta-analysis, of Voor in 't Holt et al, and retrieved missing information from five studies.[11, 16, 18, 26-28] We were unable to retrieve outcome data from one remaining study.[13] Finally, 16 articles were reviewed systematically, of which 15 were included in the meta-analysis (Table 1 and Figure 2).[5, 11, 14-18, 25, 27-33]

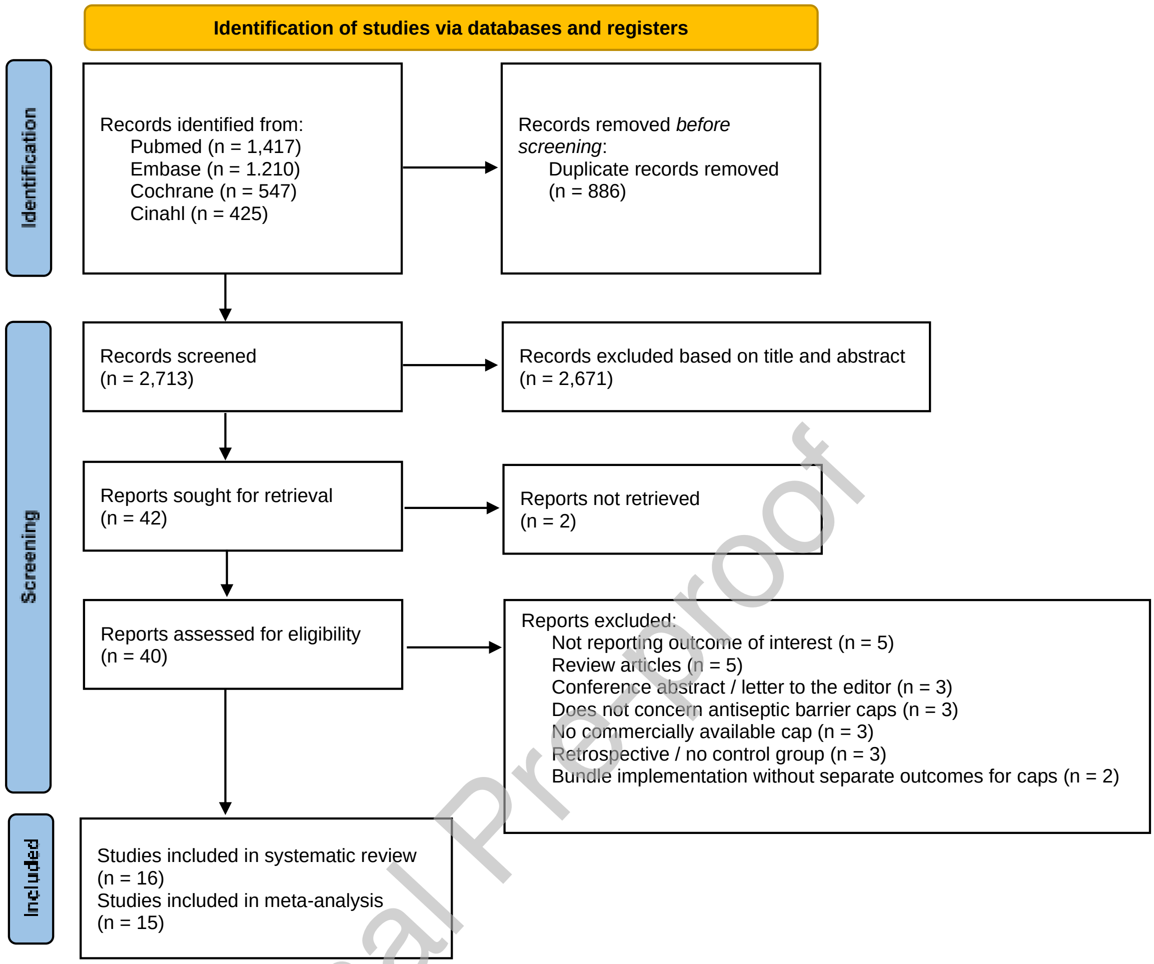

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart [34]

Study characteristics

Study characteristics are shown in Table 1. Ten studies evaluated the Curos cap, and six the SwabCap. Eleven studies included only adults, four exclusively children, and one study included both. Five studies exclusively focused on ICU patients, five on non-ICU, and six had a mixed population. All studies were conducted in the hospital, excluding Millstone et al. these authors conducted a RCT in pediatric hematology-oncology patients in the ambulatory setting.[32] We included three randomized controlled trials (RCTs) and twelve non-RCTs.

Table 1. Characteristics of 16 included studies

Study	Study design	Department (country)	Population	Study period	Number of patients	Number of line days	Type of catheters	Type of intervention	Outcome	BSI rate[1]	Risk of bias[2]
Cameron-Watson *et al.* (2016) [29]	Pre -post intervention design	ICU and non-ICU (United Kingdom)	Adults	SC: 6 months I: 6 months	SC: - I: -	SC: 6,046 I: 5,333	CVC, PICC and arterial VAD, PIV	Curos cap	CRBSI	SC: 4.3 I: 1.5	Critical
Castello et al. (2011) [30]	Pre -post intervention design	Non-ICU (United states)	Children	SC: ≈17 months I: ≈17 months	SC: 5 I: 10	SC: 416 I: 392	CVC	SwabCap	CLABSI	SC: 4.8 I: 0.0	Serious
Cruz (2021) [31]	Pre -post intervention design	ICU and non-ICU (Germany)	Adults	SC: 12 months I: 12 months	SC: 443 I: 431	SC: 4,189 I: 4,818	CVC	Curos cap	CLABSI	SC: 15.28 I: 10.38	Moderate
Helder *et al.* (2020) [5]	Pre -post intervention design	ICU (Netherlands)	Children	SC: 24 months I: 12 months	SC: 1,482 I: 766	SC: 15,225 I: 7,366	CVC	Curos cap	CLABSI	SC: 3.2 I: 2.4	Moderate
Inchingolo *et al.* (2019) [15]	Pre -post intervention design	ICU (Italie)	Adults	SC: 9 months I: 9 months	SC: 86 I: 21	SC: 1,041 I: 326	CVC	Curos cap	CLABSI	SC: 8.6 I: 0.0	Moderate
Kamboj *et al.* (2015) [16]	Pre -post intervention design	ICU and non-ICU (United states)	Adults	SC: 16 months I: 16 months	SC: - I: -	SC: 84,427 I: 83,659	CVC	SwabCap	CLABSI	SC: 2.65 I: 2.02	Serious
Martino *et al.* (2017) [17]	Pre -post intervention design	ICU (United states)	Adults	SC: 6 months I: 24 months	SC: 107 I: 153	SC: 673 I: 1,272	CVC	Curos cap	CLABSI	SC: 7.4 I: 2.36	Serious
Merrill *et al.* (2014) [18]	Pre -post intervention design	ICU and non-ICU (United states)	Adults and children	SC: 12 months I: 12 months	SC: - I: -	SC: 27,866 I: 26,489	CVC, PICC	Curos cap	CLABSI	SC: 1.5 I: 0.88	Serious

Milstone et al. (2021) [32]	RCT	Non-ICU (United states)	Children	SC: 12 months I: 12 months	SC: - I: -	SC: 88,976 I: 88,421	CVC, PICC	Curos cap	CLABSI	SC: 1.27 I: 0.95	Some concerns
Pavia and Mazza (2016) [13]	Pre -post intervention design	Non-ICU (United states)	Children	SC: 15 months I: 6 months	SC: - I: 20-25	SC: - I: -	CVC	SwabCap	CLABSI	SC: 8.59 I: 3.89	Critical
Ramirez *et al.* (2012) [14]	Pre -post intervention design	ICU (United states)	Adults	SC: 12 months I: 12 months	SC: - I: -	SC: 2,105 I: 2,000	CVC, PICC, ports	Curos cap	CLABSI	SC: 1.9 I: 0.5	Critical
Rickard et al. (2021) [33]	RCT	Non-ICU (Australia)	Adults	SC: 20 months I: 20 months	SC: 61 I: 60	SC: 725 I: 588	CVC	SwabCap	CLABSI	SC: 1.38 I: 1.7	Some concerns
Stango *et al.* (2014) [11]	Pre -post intervention design	ICU and non-ICU (United states)	Adults	SC: 21 months I: 21 months	SC: - I: -	SC: 25,000 I: 22,892	CVC	SwabCap	CLABSI	SC: 1.52 I: 0.83	Critical
Sweet *et al.* 2012 [27]	Pre -post intervention design	Non-ICU (United states)	Adults	SC: 12 months I: 6 months	SC: 472 I: 282	SC: 6,851 I: 3,005	CVC, PICC, implanted port	Curos cap	CLABSI	SC: 2.3 I: 0.3	Moderate
Taşdelen Öğülmen et al. 2020 [25]	RCT	ICU (Turkey)	Adults	SC: 5 months I: 5 months	SC: 48 I: 47	SC: 10.218 I: 8,460	CVC	Curos cap	CLABSI	SC: 1.37 I: 0.1	Moderate
Wright *et al.* (2013) [28]	Pre -post intervention design	ICU and non-ICU (United states)	Adults	SC: 9 months I: 18 months	SC: 1,977 I: 2,860	SC: 11,154 I: 18,972	PICC	SwabCap	CLABSI	SC: 1.43 I: 0.69	Serious

Abbreviations: '-' = not mentioned; BSI= bloodstream infection; CLABSI = central line-associated bloodstream infection; CRBSI = catheter-related bloodstream infection; CVC = central venous catheter; ICU = intensive care unit; SC = standard care; PICC: peripherally inserted central catheter; PIV = peripheral intravenous catheter; RCT: randomised controlled trial; VAD: vascular access device; I= intervention (antiseptic barrier caps).

[1] CLABSI or CRBSI [2] ROB2 or ROBINS-II

Meta-analysis

Figure 3 shows the individual and pooled data of all included studies. In total, 391 CLABSIs in 273,993 catheter days occurred in the intervention group with an incidence rate of 1.43/1,000 catheter days. In the standard care group, 620 CLABSIs in 284.912 catheter days occurred, with an incidence rate of 2.18/1,000 catheter days, resulting in a risk ratio of 0.65 (95%CI 0.55-0.76; $P < 0.00001$). Subgroup analyses are presented in Figures 4, 5, and 6. In eleven studies with adult patients, the risk for CLABSIs was reduced by 0.55 (95%CI 0.42-0.73; $P < 0.0001$) and in three studies with children a risk ratio of 0.75 (95%CI 0.58-0.96; P= 0.02) was found (Figure 4). Both type of brands (Curos and SwabCap) showed a decrease in CLABSI risk in favor of the ABCs of 0.59 (95%CI 0.46-0.77; $P < 0.0001$) and 0.71 (95%CI 0.59-0.85; P = 0.0002), respectively (Figure 5). Studies exclusively focusing on ICU populations showed a risk ratio of 0.36 (95%CI 0.15-0.88; P= 0.02). In the non-ICU population, a similar risk reduction was found, although non-significant (0.63, 95%CI 0.33-1.18; P=0.15) (Figure 6).

Heterogenicity between studies for the main outcome and almost all subgroup analyses were low, with an I2 of 0-40%. Only the ICU group showed a heterogenicity of 41%, which was considered substantial.

Study or Subgroup	ABCs Events	ABCs Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
Cameron	8	5333	26	6046	3.9%	0.35 [0.16, 0.77]
Castello	0	392	2	416	0.3%	0.21 [0.01, 4.41]
Cruz	50	4818	64	4189	14.2%	0.68 [0.47, 0.98]
Helder	18	7366	48	15225	7.7%	0.78 [0.45, 1.33]
Inchingolo	0	326	9	1041	0.3%	0.17 [0.01, 2.87]
Kamboj	169	83659	224	84427	29.5%	0.76 [0.62, 0.93]
Martino	3	1272	5	673	1.3%	0.32 [0.08, 1.32]
Merill	23	26489	40	27866	8.4%	0.60 [0.36, 1.01]
Milstone	84	88421	113	88976	20.4%	0.75 [0.56, 0.99]
Raminez	1	2000	4	2105	0.5%	0.26 [0.03, 2.35]
Rickard	1	588	1	725	0.3%	1.23 [0.08, 19.67]
Strango	19	22892	38	25000	7.4%	0.55 [0.31, 0.95]
Sweet	1	3005	16	6851	0.6%	0.14 [0.02, 1.07]
Taşdelen Öğülmen	1	8460	14	10218	0.6%	0.09 [0.01, 0.66]
Wright	13	18972	16	11154	4.5%	0.48 [0.23, 0.99]
Total (95% CI)		**273993**		**284912**	**100.0%**	**0.65 [0.55, 0.76]**
Total events	391		620			

Heterogeneity: Tau² = 0.01; Chi² = 16.26, df = 14 (P = 0.30); I² = 14%
Test for overall effect: Z = 5.26 (P < 0.00001)

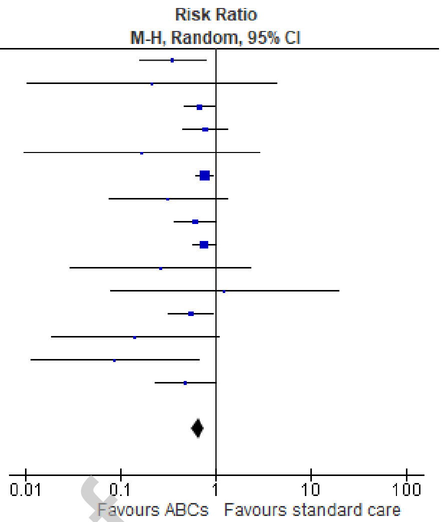

Figure 3. Forrest plot all included studies - results are presented in two groups: antiseptic barrier caps (ABCs) versus standard care, with a risk ratio and 95% confidence intervals (95% CI).

Study or Subgroup	ABCs Events	ABCs Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Adults						
Cameron	8	5333	26	6046	4.7%	0.35 [0.16, 0.77]
Cruz	50	4818	64	4189	15.9%	0.68 [0.47, 0.98]
Inchingolo	0	326	9	1041	0.4%	0.17 [0.01, 2.87]
Kamboj	169	83659	224	84427	29.3%	0.76 [0.62, 0.93]
Martino	3	1272	5	673	1.6%	0.32 [0.08, 1.32]
Raminez	1	2000	4	2105	0.7%	0.26 [0.03, 2.35]
Rickard	1	588	1	725	0.4%	1.23 [0.08, 19.67]
Strango	19	22892	38	25000	8.8%	0.55 [0.31, 0.95]
Sweet	1	3005	16	6851	0.8%	0.14 [0.02, 1.07]
Taşdelen Öğülmen	1	8460	14	10218	0.8%	0.09 [0.01, 0.66]
Wright	13	18972	16	11154	5.5%	0.48 [0.23, 0.99]
Subtotal (95% CI)		**151325**		**152429**	**68.9%**	**0.55 [0.42, 0.73]**
Total events	266		417			
Heterogeneity: Tau² = 0.05; Chi² = 14.75, df = 10 (P = 0.14); I² = 32%						
Test for overall effect: Z = 4.20 (P < 0.0001)						
2.1.2 Children						
Castello	0	392	2	416	0.4%	0.21 [0.01, 4.41]
Helder	18	7366	48	15225	9.1%	0.78 [0.45, 1.33]
Milstone	84	88421	113	88976	21.7%	0.75 [0.56, 0.99]
Subtotal (95% CI)		**96179**		**104617**	**31.1%**	**0.75 [0.58, 0.96]**
Total events	102		163			
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Total (95% CI)		**247504**		**257046**	**100.0%**	**0.64 [0.53, 0.77]**
Total events	368		580			

Heterogeneity: Tau² = 0.02; Chi² = 16.06, df = 13 (P = 0.25); I² = 19%
Test for overall effect: Z = 4.79 (P < 0.00001)
Test for subgroup differences: Chi² = 2.55, df = 1 (P = 0.11), I² = 60.8%

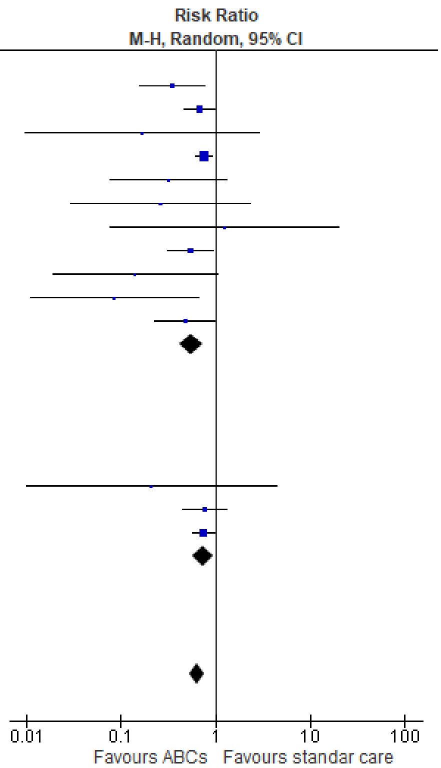

Figure 4. Forrest plot of subgroups (adults and children) - results are presented in two groups: antiseptic barrier caps (ABCs) versus standard care, with a risk ratio and 95% CI. Articles without separate outcomes on children and adults are not included.

Study or Subgroup	ABCs Events	ABCs Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Curos cap						
Cameron	8	5333	26	6046	3.9%	0.35 [0.16, 0.77]
Cruz	50	4818	64	4189	14.2%	0.68 [0.47, 0.98]
Helder	18	7366	48	15225	7.7%	0.78 [0.45, 1.33]
Inchingolo	0	326	9	1041	0.3%	0.17 [0.01, 2.87]
Martino	3	1272	5	673	1.3%	0.32 [0.08, 1.32]
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Sweet	1	3005	16	6851	0.6%	0.14 [0.02, 1.07]
Taşdelen Öğülmen	1	8460	14	10218	0.6%	0.09 [0.01, 0.66]
Subtotal (95% CI)		**147490**		**163190**	**57.9%**	**0.59 [0.46, 0.77]**
Total events	189		339			
Heterogeneity: Tau² = 0.04; Chi² = 12.58, df = 9 (P = 0.18); I² = 28%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
2.3.2 SwabCap						
Castello	0	392	2	416	0.3%	0.21 [0.01, 4.41]
Kamboj	169	83659	224	84427	29.5%	0.76 [0.62, 0.93]
Rickard	1	588	1	725	0.3%	1.23 [0.08, 19.67]
Strango	19	22892	38	25000	7.4%	0.55 [0.31, 0.95]
Wright	13	18972	16	11154	4.5%	0.48 [0.23, 0.99]
Subtotal (95% CI)		**126503**		**121722**	**42.1%**	**0.71 [0.59, 0.85]**
Total events	202		281			
Heterogeneity: Tau² = 0.00; Chi² = 3.23, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Total (95% CI)		**273993**		**284912**	**100.0%**	**0.65 [0.55, 0.76]**
Total events	391		620			
Heterogeneity: Tau² = 0.01; Chi² = 16.26, df = 14 (P = 0.30); I² = 14%						
Test for overall effect: Z = 5.26 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.28, df = 1 (P = 0.26), I² = 21.7%						

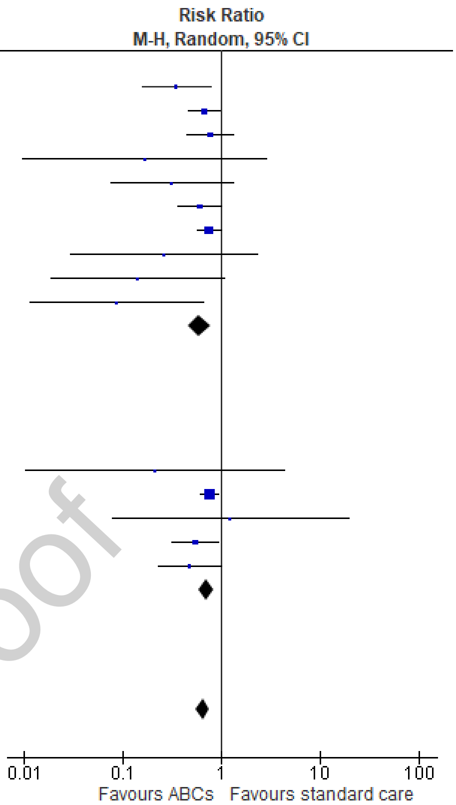

Figure 5. Forrest plot of subgroups (Curos cap and SwabCap) - results are presented in two groups: antiseptic barrier caps (ABCs) versus standard care, with a risk ratio and 95% CI.

Study or Subgroup	ABCs Events	ABCs Total	Standard care Events	Standard care Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 ICU						
Helder	18	7366	48	15225	29.4%	0.78 [0.45, 1.33]
Inchingolo	0	326	9	1041	2.3%	0.17 [0.01, 2.87]
Martino	3	1272	5	673	8.0%	0.32 [0.08, 1.32]
Raminez	1	2000	4	2105	3.7%	0.26 [0.03, 2.35]
Taşdelen Öğülmen	1	8460	14	10218	4.3%	0.09 [0.01, 0.66]
Subtotal (95% CI)		**19424**		**29262**	**47.6%**	**0.36 [0.15, 0.88]**
Total events	23		80			
Heterogeneity: Tau² = 0.40; Chi² = 6.73, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 2.25 (P = 0.02)						
2.5.2 Non-ICU						
Castello	0	392	2	416	2.0%	0.21 [0.01, 4.41]
Milstone	84	88421	113	88976	43.7%	0.75 [0.56, 0.99]
Rickard	1	588	1	725	2.4%	1.23 [0.08, 19.67]
Sweet	1	3005	16	6851	4.3%	0.14 [0.02, 1.07]
Subtotal (95% CI)		**92406**		**96968**	**52.4%**	**0.63 [0.33, 1.18]**
Total events	86		132			
Heterogeneity: Tau² = 0.11; Chi² = 3.38, df = 3 (P = 0.34); I² = 11%						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**111830**		**126230**	**100.0%**	**0.55 [0.36, 0.85]**
Total events	109		212			
Heterogeneity: Tau² = 0.09; Chi² = 10.79, df = 8 (P = 0.21); I² = 26%						
Test for overall effect: Z = 2.68 (P = 0.007)						
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%						

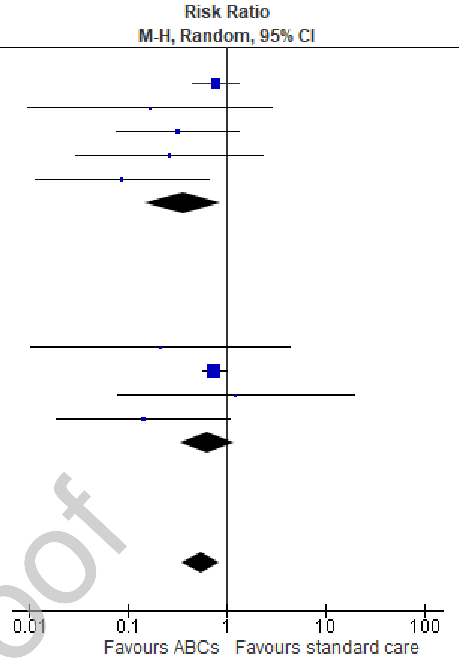

Figure 6. Forrest plot of subgroups (ICU and non-ICU) - results are presented in two groups: antiseptic barrier caps (ABCs) versus standard care, with a risk ratio and 95% CI. Articles without separate outcomes on intensive care unit (ICU) and non-ICU patients are not included.

Secondary outcomes

Safety

Only three studies reported safety data.[5, 32, 33] Two studies reported the use of Curos caps and did not observe damage to the access valves nor any other device-related adverse events.[5, 32] One study investigating SwabCap reported that two needleless connectors became opaque and additionally observed 70% IPA seeping between the rubber inner and outer plastic. However, this did not have any impact on the patient.[33]

Costs

Six studies evaluated costs of ABCs and reported significant annual cost savings.[11, 14, 16, 18, 28, 29] Calculated costs per 1,000 catheter days range from $10,000 to $39,000, with one outlier of $130,144 per 1,000 catheter days (Table 2). The average cost saving per 1,000 catheter days is $41,000.

Table 2. Calculated costs per 1,000 catheter days

	Annual costs savings	Number of catheter days	Costs savings per 1,000 catheter days
Cameron-Watson et al. (2016) [29]	$740,518	5,690	$130,144
Kamboj et al. (2015) [16]	$3,268,990	84,043	$38,897
Merrill et al. (2014) [18]	$282,840	84,043	$10,407
Ramirez et al. (2012) [14]	$39,050	2,053	$19,021
Stango et al. (2014) [11]	$464,440	23,346	$19,395
Wright et al. (2013) [28]	$390,617	15,063	$25,932

Cost savings per 1,000 catheter day are calculated from annual costs and number of catheter days. Annual costs were retrieved from the reported studies. The number of catheter days include mean catheter days of the standard care and ABC groups.

Compliance and satisfaction

Nine studies evaluated compliance when using ABCs [5, 11, 14, 17, 18, 27-29, 33] , and three evaluated satisfaction.[5, 29, 33] ABCs were highly appreciated by health care workers due to time-savings and ease of use.[27, 28] The ease of use and simple monitoring due to the green color of the ABCs increased compliance.[17] All available studies reported a high satisfaction rate. A mean satisfaction of 9, on a scale of 0-10, was scored by 22 registered nurses.[33] In the PICU and the NICU, 28 nurses rated an overall mean of 9.2 and 8.6, respectively.[5] Only one study evaluated ABC satisfaction in patients: 92% of the 1094 patients gave positive feedback and felt empowered by the ABCs.[29]

Quality assessment and publication bias

Overall risk of bias assessment is shown in Table 1. A complete assessment of each study is presented in Figure A1 and A2. In most studies, a substantial risk of bias was observed, mainly because of missing information, lack of correction for confounders, or simultaneous implementation of another intervention. A sensitivity analysis based on the degree of risk of bias (low to moderate, or high to critical) showed in both groups the same significant reduction in CLABSI risk in favor of ABCs, 0.66 (95%CI 0.49-0.90; $P = 0.009$) and 0.62 (95%CI 0.49-0.77; $P < 0.00001$), respectively (Figure A3). Sensitivity analyses based on the study design (RCT or non-RCT) showed in the non-RCT group a significant reduction in CLABSI risk 0.65 (95%CI 0.56-0.77; $P < 0.00001$), but not in the RCT group 0.46 (95%CI 0.11-1.91; $P = 0.29$) (Figure A4). Based on the asymmetric funnel plot presented in Figure 7, publication bias may be present.

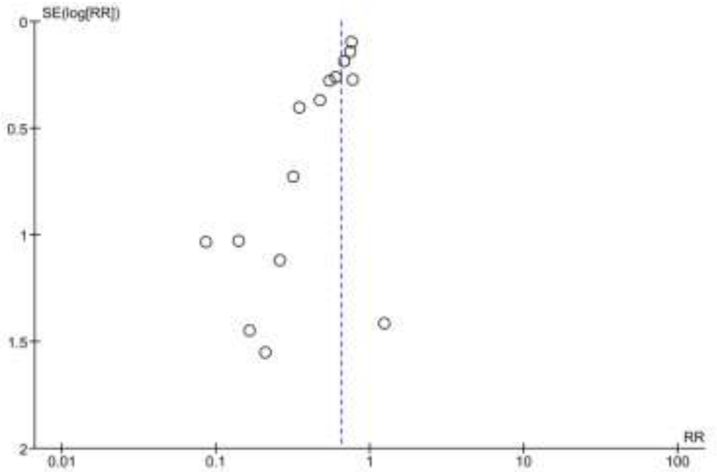

Figure 7. Funnel plot for assessing publication bias

Discussion

A safe and reliable central venous access is the cornerstone of treatments in numerous clinical settings. Despite various preventive measures, the presence of CVCs still poses a serious risk for developing septic complications. It should be emphasized that adequate CVC care with strict adherence to aseptic protocols when handling CVCs remains key to prevent CLABSIs. It is, however, widely recognized that strict compliance with these standard manual catheter care procedures remains difficult for many patients and even healthcare workers. Despite concerns with respect to the quality of the available studies, it seems that use of ABCs holds promise as a secondary measure to prevent CLABSIs, as overall analyses showed a protective effect of ABCs compared to standard care.

Our analysis is a comprehensive update of previous meta-analyses, which showed a CLABSI rate reduction of 0.43-0.60, which is in line with the rate ratio of 0.65 currently found in this study.[19, 26, 35] To date, only one small pilot study showed an increased infection rate with the use of ABCs, but, this concerned a non-significant trend most probably resulted from underpowering.[33] Taken together, the overall trend is in favor of the ABCs, despite the low quality of the majority of the articles.

In this study we performed several subgroup analyses. Almost all groups showed a clear decrease in CLABSI rates with the use of ABCs. Even in younger patients, who tend to be less compliant when managing CVADs due distractions or a more active lifestyle, fewer CLABSIs were seen when using ABCs (Figure 4). This protective effect of ABCs even applied to the ICU population, where CVCs are more often daily accessed, normally resulting in increased risks for CLABSIs.[36] These results show that a simple intervention, screwing an ABC on a CVC connector, prevents various risk full moments during catheter care and illustrates a strong universal effect within different patient populations. That such an effect was not seen in the non-ICU population is probably related due to the relatively small number of studies included, as the (non-significant) trend towards a protective effect for ABCs was similar as in the other subgroups. As head-to-head comparisons between ABC brands (Curos caps en SwabCaps) are currently lacking, it is difficult to establish which brand performs better. Subgroup analyses suggest similar reductions in CLABSI rates for Curos caps and SwabCaps, which may be explained by the close resemblance of both caps: both contain a 70% IPA impregnated sponge that passively disinfects the outside surface of the needle-less connectors. There are only minor differences in cap design, for example in the flexibility of the IPA impregnated sponge.[26] The sensitivity analysis of the groups ‘low to moderate risk of bias’, ‘high to critical risk of bias’ and ‘non-RCT’ all showed a significant decrease in CLABSI in favor of the caps, in contrast to the RCT group which showed a non-significant decrease in CLABSIs. This can partially be explained by the (underpowered) pilot study of Rickard et al.[33] Furthermore, one of the three RCTs was the only conducted study in the ambulatory setting and focused on the pediatric population.[32] Therefore, more research should show the effect of the ABC in the ambulatory setting.

Remarkedly, only a few studies report safety aspects concerning the use of ABCs. Sauron et al. raised concerns about the safety of 70% IPA impregnated ABCs as several access valves malfunctioned shortly after using SwabCaps in their neonatal ICU. The authors investigated IPA concentrations in the bloodstream after infusate passed through the catheter. They found that IPA leaked from the SwabCap through the access valve into the bloodstream, which resulted in IPA concentrations exceeding critical limits for premature neonates. However, the risk for IPA intoxication should be minimized if the needleless connector is dried in open air before drugs infusion.[37] Sauron et al. also assessed whether SwabCaps affected the function and appearance of catheter access valves. While structural macroscopic changes were noted in more than half of the tested valves, none of them malfunctioned.[37]

The importance of compliance to use ABCs was stressed by Merrill et al., who found a strong association between the use of Curos caps and a decrease in CLABSI rate: a 10% increase in compliance resulted in a 7% drop in CLABSI rate (incidence rate ratio 0.93).[18] This is in line with other studies stating that manual disinfection alone is not sufficient to prevent CLABSIs and compliance is an important factor to improve CLABSI prevention.[12, 13, 17, 18, 38] All studies evaluating compliance of ABCs emphasize the ease of use and time-saving aspect of ABCs over standard rubbing methods.[5, 11, 14, 17, 18] In addition, the bright color of ABCs was a valued by caregivers as it highlights the catheter access point and makes compliance easy to monitor.[5, 17] When ABCs are placed on a CVC, unlike with a manual procedure, disinfection of the needleless connector is visualized for all caregivers. Despite the advantages of ABCs over standard manual disinfection procedures alone, compliance is not always guaranteed. Stango et al. found that healthcare workers needed time to adjust to the implementation of SwabCaps and that compliance increased when the use of ABCs was monitored (when observed in place on the connector) and the caps were easily available.[11, 14, 18] The latter was exemplified by a study of Ramirez et al., who noted a broad range in compliance (25-100%), but in particular a low compliance related to poor cap availability in the patient's room. After cap strips were hung on intravenous poles at the bedside, compliance increased and resulted in an average compliance of 73% throughout their trial.[14] It is therefore important to note that education of staff members, monitoring of ABC use, and availability of caps is key to improve and maintain compliance.[11, 14, 15]

CLABSIs have a high impact on patient's experienced quality of life, hospital admission length, and subsequently costs. The Centers for Disease Control and Prevention estimate that for every CLABSI, hospital stay increases by two to five days.[39] Cost-effectiveness is an important issue when implementing any device. Although costs of a single cap are low (around $0.25-0.50), each use of the CVC requires a new cap, and in some patients, this implies the use of several caps per day. Cost effectiveness is also related to CLABSI rates, which differ significantly between patient populations (e.g., pediatric versus adults). All included studies in this review concluded that implementation of ABCs not only decreased CLABSI rates, but also associated healthcare costs. However, interpretation remains difficult since all authors reported absolute costs, which vary per study population. In addition, most studies only calculated product- and CLABSI costs but did not perform an extensive cost-effect analysis. Therefore, these results should be interpreted with caution.

Strengths and limitations

This study has several strengths. First, we performed a comprehensive literature search to identify all available latest prospective studies. If studies lacked outcome data, we actively contacted corresponding authors for more information. Eventually, this resulted in an inclusion of 6 extra (both old and new) studies, including two new RCTs, which were not reported in the latest meta-analysis.[14, 18, 29-32] Second, previous meta-analyses were hampered by inclusion of only one single pediatric study, which precluded subgroup analyses of these patients, whereas we were able to track two additional studies. Finally, the data that we obtained allowed analyses on catheter level instead of patient level, which, in addition to the sensitivity analyses, results in more precise and reliable outcomes.

As with all reviews, the quality of the present study mainly builds on the individual quality of included studies. Heterogenicity between studies and their (mostly) high risk of bias remains a limitation that may have impacted our meta-analyses. The majority of studies concerned pre- and post-intervention designs, and only three RCTs were available. In addition, the variety of (sometimes mixed) patients populations precluded several subgroup analyses, such as those for oncology or hematology patients. On the other hand, while the heterogenicity is substantial (which is inherently associated with the broad range in clinical patient populations that require a CVC), the overall message is that all studies provided support for the use of ABCs. Last, relevant information on infection prevention, such as the use of antimicrobial locks, is missing in some manuscripts and therefore it is not always clear whether the effect of ABCs is on top of other antiseptic measures.

In conclusion, the most recent clinical evidence keeps providing support for the use of ABCs for passive and continuous disinfection of needle-less connectors, without a need for the more cumbersome manual needleless connector disinfection. Despite the limited methodological quality of most available studies, the overall verdict at this point seems to be that ABCs establish an effective strategy to reduce CLABSI rates in patient populations that depend on a CVC. These caps are safe, highly appreciated by health care workers for their ease of use, are timesaving in clinical practice and there are no disadvantages with their use. High-quality and controlled trials in various patient populations with a different infection risk remain necessary to unequivocally establish that ABCs are cost-effective.

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Graphical abstract