KEY QUESTIONS FOR PREVENTION OF INTRAVASCULAR CATHETER-RELATED INFECTIONS

A Review from the UPHS Center for Evidence-based Practice

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Keywords: Catheters, catheter-associated infections, bloodstream infections

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METHODS

SPECIFIC AIM:

To evaluate the following questions based on the drafted recommendations:

1. What is the appropriate level of CG required for skin antisepsis prior to CVC placement and maintenance?
2. What type of CG dressing (i.e., sponge, non-sponge) should be used for temporary short-term catheters in patients older than 2 months to reduce the risk of infection?
3. Do split-septum needleless connectors have decreased risk of infection compared to mechanical valve needless connectors?

METHODS:

Study designs: Systematic reviews (SR), meta-analyses (MA), and randomized controlled trials (RCT); controlled trials if SR, MA, RCT unavailable

Databases: Cochrane Database of Systematic Reviews, Medline

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1. WHAT IS THE APPROPRIATE LEVEL OF CG REQUIRED FOR SKIN ANTISEPSIS PRIOR TO CVC PLACEMENT AND MAINTENANCE?

Search Strategy for Systematic Reviews

COCHRANE LIBRARY

Keyword	Reviews	Retrieved	Included
Chlorhexidine and Catheter	1	1	0
Skin antiseptic and Catheter	1	0	0

MEDLINE

Search	Syntax	Results	Retrieved	Included
1	exp Chlorhexidine/		-	-
2	exp Anti-infective agents, Local/ad, ae, tu, th [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy]	4782 32460	-	-
3	exp Catheterization, Central Venous/	9276	-	-
4	1 or 2		-	-
5	3 and 4	34210 189	-	-
6	limit 5 to (English language and humans)	169	-	-
7	Limit 5 to (meta analysis or “review”)	30	1	1

Search Strategy for Primary Studies

MEDLINE

Search	Syntax	Results	Retrieved	Included
1	exp Chlorhexidine/		-	-
2	exp Anti-infective agents, Local/ad, ae, tu, th [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy]	4782 32460	-	-
3	exp Catheterization, Central Venous/	9276	-	-
4	1 or 2		-	-
5	3 and 4	34210 189	-	-
6	limit 5 to (English language and humans)	169	15	6

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2. WHAT TYPE OF CG DRESSING (I.E., SPONGE, NON-SPONGE) SHOULD BE USED FOR TEMPORARY SHORT-TERM CATHETERS IN PATIENTS OLDER THAN 2 MONTHS TO REDUCE THE RISK OF INFECTION?

Search Strategy for Systematic Reviews

COCHRANE LIBRARY

Keyword	Reviews	Retrieved	Included
Chlorhexidine and Catheter	1	1	0
Skin antiseptic and Catheter	1	0	0

MEDLINE

Search	Syntax	Results	Retrieved	Included
1	exp Chlorhexidine/	4803	-	-
2	exp Anti-infective agents, Local/ad, ae, tu, th [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy]	32530	-	-
3	exp Catheterization, Central Venous/	9299	-	-
4	exp Catheters, Indwelling/	13703		
5	1 or 2	34292	-	-
6	3 or 4	20629	-	-
7	5 and 6	318		
8	limit 7 to (english lanuage and humans)	270	-	-
9	limit 8 to (meta analysis or “review”)	43	2	1

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Search Strategy for Primary Studies

MEDLINE

Search	Syntax	Results	Retrieved	Included
1	exp Chlorhexidine/	4803	-	-
2	exp Anti-infective agents, Local/ad, ae, tu, th [Administration & Dosage, Adverse Effects, Therapeutic Use, Therapy]	32530	-	-
3	exp Catheterization, Central Venous/	9299	-	-

4	exp Catheters, Indwelling/	13703		
5	1 or 2	34292	-	-
6	3 or 4	20629	-	-
7	5 and 6	318		
8	limit 7 to (english language and humans)	270	-	-
9	limit 8 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)	104	12	6

3. DO SPLIT-SEPTUM NEEDLELESS CONNECTORS HAVE DECREASED RISK OF INFECTION COMPARED TO MECHANICAL VALVE NEEDLESS CONNECTORS?

Search Strategy for Systematic Reviews

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COCHRANE LIBRARY

Keyword	Reviews	Retrieved	Included
needleless connector	0	0	0
needleless valve	0	0	0
split septum	0	0	0
mechanical valve	0	0	0

MEDLINE

Search	Syntax	Results	Retrieved	Included
1	Needless connector.mp	11	-	-
2	needleless valve.mp.	5	-	
3	split septum.mp	4	-	
4	exp Sepsis/	73405	-	-
5	exp Catheter-Related Infections/	292	-	-
6	exp Bacterial Infections/	613440	-	-
7	exp Cross Infection/	38075	-	-
8	4 or 5 or 6 or 7	676356	-	-
9	exp Equipment Contamination/ae, pc [Adverse Effects, Prevention &	2450	-	-

	Control]			
10	8 and 9	852	-	-
11	1 or 2 or 3 or 10	865	-	-
12	limit 11 to english language	770	-	-
13	limit 12 to (meta analysis or “review”)	160	0	0

Search Strategy for Primary Studies

MEDLINE

Search	Syntax	Results	Retrieved	Included
1	needleless connector.mp.	11	-	-
2	needleless valve.mp.	5	-	
3	split septum.mp	4	-	
4	exp Sepsis/	73405	-	-
5	exp Catheter-Related Infections/	292	-	-
6	exp Bacterial Infections/	613440	-	-
7	exp Cross Infection/	38075	-	-
8	4 or 5 or 6 or 7	676356	-	-
9	exp Equipment Contamination/ae, pc [Adverse Effects, Prevention & Control]	2450	-	-
10	8 and 9	852	-	-
11	1 or 2 or 3 or 10	865	-	-
12	limit 11 to english language	770	-	-
13	limit 12 to (clinical trial, all or clinical trial or comparative study or controlled clinical trial or multicenter study or randomized controlled trial)	160	16	4

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META-ANALYSIS

Where there were multiple RCTs of the same comparison in similar patient populations, we used meta-analytic techniques to try and obtain a summary effect size (risk ratio) and confidence interval. This analysis was done using RevMan 5 software. Heterogeneity of reported results was evaluated with both the chi-square test (critical value of $p < 0.10$ because this statistic lacks power) and the I^2 statistic (critical value of 50%). If significant heterogeneity was observed, summary results were not reported as they may not be valid because they would be combining two different quantities. There was not sufficient evidence for meta-regression or any other analyses to statistically ascertain the causes of heterogeneity.

EVIDENCE REVIEW

1. WHAT IS THE APPROPRIATE LEVEL OF CG REQUIRED FOR SKIN ANTISEPSIS PRIOR TO CVC PLACEMENT AND MAINTENANCE?

TABLE 4. SYSTEMATIC REVIEWS AND META-ANALYSES

Author, Yr	Design	Population	Intervention	Comparison	N	N Test	N Cntrl	Events Test	Events Cntrl	RR (95% CI); p value	Comments
Chaiyakunapruk, 2002[1]	SR/MA	Inpatients with vascular catheters	CG 1 study used CG 0.25%, benzalkonium chloride 0.025%, and benzyl alcohol 4% 4 studies used CG 0.5% alcohol 1 study used CG 1% alcohol 2 studies used CG 2% aqueous	PVP-I PVP-I 10% in all studies except 1 study which used 70% alcohol followed by PVP-I 10%)	8 studies 4143 catheters (1493 central venous, 1361 peripheral venous, 704 peripheral arterial, 395 pulmonary arterial, 75 peripherally inserted central venous, 62 introducer sheaths, 53 HD catheters)	1871	2028	17	43	All catheters RR 0.49 (0.28-0.88) Central vascular catheters* RR 0.51 (0.27-0.97) Noncentral catheters** RR 0.45 (0.05-3.77)	Outcome=CR-BSI (identical species and antibiogram from blood and catheter culture)
						1877	2124	123	287	All catheters RR 0.49 (0.31-0.71) Central vascular catheters* RR 0.52 (0.29-0.95) Noncentral catheters** RR 0.39 (0.21-0.71)	Outcome=Positive catheter culture (colonization)

CG=Chlorhexidine gluconate; CI=Confidence interval; Cntrl=Control; CR-BSI=Catheter-related bloodstream infection; HD=Hemodialysis; MA=Meta-analysis; PVP-I=Povidone-iodine; RR=Risk Ratio; SR=Systematic review

*Central vascular catheters include non-tunneled central venous, pulmonary arterial, and peripherally inserted central venous catheters; **noncentral catheters not specified but may include peripheral venous, peripheral arterial, introducer sheaths, and HD catheters. This SR/MA was not included in GRADE table because various formulations of CG were included together; however data from the studies included in this SR/MA that were pertinent to CVC placement and maintenance were included in Table 5.

TABLE 5. PRIMARY STUDIES

Author, Yr	Design	Power and	Population	Intervention	Comparison	N	N	N	Events	Events	RR/OR	Comments

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	Quality	Sample Size					Test	Cntrl	Test	Cntrl	(95% CI); p value	
Valles, 2008[4]	RCT 1,2,7,9	200 catheters from each group needed for 80% power assuming 65% reduction in catheter colonization with CG	Adult medical-surgical ICU pts in a university affiliated hospital with catheter placement (AC and/or CVC)	CG 0.5% alcoholic	CG 2% aqueous	631 catheters per protocol; 998 catheters ITT	226	211	3.98%	4.26%	NS	Outcome=CR-BSI (per protocol)
									14.2%	16.1%	RR 0.8 (0.5-1.3); p≥0.20	Outcome=Bacterial colonization of catheter (per protocol)
				CG 2% aqueous	PVP-I 10% aqueous		211	194	4.26%	4.63%	NS	Outcome=CR-BSI (per protocol)
									16.1%	24.7%	RR 0.6 (0.4-0.9); p=0.03	Outcome=Bacterial colonization of catheter (per protocol)
							339	329	39.5%	48%	RR 0.8 (0.7-0.9); p=0.03	Outcome=Bacterial colonization of catheter (ITT)
				CG 2% alcoholic	PVP-I 10% aqueous		226	194	3.98%	4.63%	NS	Outcome=CR-BSI (per protocol)
									14.2%	24.7%	RR 0.5 (0.3-0.8); p<0.01	Outcome=Bacterial colonization of catheter (per protocol)
							329	329	35.1%	48%	RR 0.7 (0.6-0.8); p<0.01	Outcome=Bacterial colonization of catheter (ITT)
Mimoz, 2007[5]	RCT 1,2,7,8,9	260 CVC per group for 80% power to detect difference of 50% in colonization rates	Surgical ICU pts of university affiliated hospital with CVC	CG 0.25%, benzalkonium chloride 0.025%, and benzylic alcohol 4%	PVP-I 5% in 70% ethanol	481 CVC	242	239	4 (1.7%)	10 (4.2%)	p=0.09	Outcome=CR-BSI
									28 (11.6%)	53 (22.2%)	p=0.002	Outcome=Bacterial colonization of CVC
Langgartner, 2004[6]	RCT 1,2	--	Adult pts of a university hospital	CG 0.5%/ propanol 70%	PVP-I 10%	119pts; 140 CVC ; 1910 CVC-	45 CVC	52 CVC	11 (24.4%); 18.4/100	16 (30.8%); 21/1000 CVC- days	NS	Outcome=Bacterial colonization of CVC

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			with CVC			days			0 CVC-days			
				CG 0.5%/ propanol 70% followed by PVP-I 10%			43 CVC		2 (4.7%); 3.5/1000 CVC-days		P=0.006	
Humar, 2000[7]	RCT 1,2,7,9	Need 320 and 88 patients for 80% power to see 75% risk reduction with CG	Pts >18 years of age with CVC in MICU or SICU of 3 university affiliated hospitals	CG 0.5% tincture	PVP-I 10%	242 pts	125	117	4 (3.2%) 4.6/1000 CVC-days	4 (3.4%) 4.1/1000 CVC-days	NS	Outcome=CR-BSI
									0 (0%)	4 (3.4%)	P=0.53	Outcome=Exit-site infections
						180 pts had CVC tips cultured	88	92	24 (27%) 34/1000 CVC-days	31 (34%) 46/1000 CVC-days	NS	Outcome=significant CVC-tip colonization
Mimoz, 1996[8]	RCT 1,2	Need 308 catheters for 80% power to detect true difference in response rates between two groups ≥75%	Pts with catheter (CVC or AC) in a university hospital surgical-trauma ICU	CG 0.25%, benzalkonium chloride 0.025%, and benzyl alcohol 4%	PVP-I 10%	315 catheters (158 CVC and 157 AC)	170	145	6 (3.5%)	16 (11.0%)	RR 0.4 (0.1-1.0); p=0.05	Outcome=Catheter related sepsis/1000 catheter-days (all catheters)
									5 (2.9%)	19 (13.1%)	RR 0.3 (0.1-1.0); p=0.02	Outcome=CVC related sepsis/1000 CVC-days
									12 (7.1%)	31 (21.4%)	RR 0.4 (0.1-0.9); p<0.01	Outcome=Catheter colonization/1000 catheter-days (all catheters)
									8 (4.7%)	31 (21.4%)	RR 0.3 (0.1-1.0); p=0.03	Outcome=CVC colonization/1000 CVC-days
Maki, 1991[9]	RCT 1,7,8	--	All patients >18 years of age with catheter (CVC or AC) in a	CG 2% aqueous	PVP-I 10% or 70% alcohol	668 catheters (176 CVC and 492 AC)	214; 67 CVC	454 (227 per group); 109 CVC (77 in	1 (0.5%)	9 (4.0%)	--	Outcome=CR-BSI (all catheters)
									1 (1.5%)	7 (6.4%)	OR 0.23 (0.03-1.80); p=0.18	Outcome=CR-BSI (CVC)

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			university hospital SICU					PVP-I and 32 in 70% alcohol group)	5 (2.3%)	32 (14.1%)	OR 0.32 (0.10-0.86); p=0.02	Outcome=Local catheter related infection/100 catheters
									4 (5.9%)	20 (18.3%)	OR 0.28 (0.08-0.93); p=0.02	Outcome=Local CVC related infection/100 CVC

AC=Arterial catheter; Cfu=Colony forming unit; CG=Chlorhexidine gluconate; CI=Confidence interval; Cntrl=Control; CR-BSI=Catheter-related bloodstream infection; CVC=Central venous catheter; ICU=Intensive care unit; ITT=intention to treat; MICU=Medical intensive care unit; NS=nonsignificant; OR=Odds ratio; pts=Patients; PVC=Peripheral venous catheter; PVP-I=Povidone-iodine; RCT=Randomized controlled trial; RR=Risk ratio; SD=Standard deviation; SICU=Surgical intensive care unit

SUMMARY AND CONCLUSIONS FOR Q1: WHAT IS THE APPROPRIATE LEVEL OF CG REQUIRED FOR SKIN ANTISEPSIS PRIOR TO CVC PLACEMENT AND MAINTENANCE?

There is only 1 study which directly compared two formulations of chlorhexidine. This RCT compared CG 0.5% alcoholic vs. CG 2% aqueous solution prior to CVC and/or AC catheter insertion and assessed for CR-BSI or bacterial colonization of the catheter[4] There was 1 SR/MA which compared different formulations of CG vs. PVP-I for all catheters (central and non-central catheters)[1]; 5 studies included in this SR/MA evaluated central catheters (CVC and/or AC)[5,6,7,8,9].

There is evidence that there is no significant difference in CR-BSI between the use of CG 0.5% alcoholic vs. CG 2% aqueous solution prior to CVC placement.

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2. What type of CG dressing (i.e., sponge, non-sponge) should be used for temporary short-term catheters in patients older than 2 months to reduce the risk of infection?

Table 7. Systematic Reviews and Meta-Analyses

Author, Yr	Design	Population	Intervention	Comparison	N	N Test	N Cntrl	Events Test	Events Cntrl	OR (95% CI); p value	Comments
Ho, 2006[10]	SR/MA	Pts with intravascular or epidural catheters	CG impregnated dressing	Placebo or PVP-I dressing	8 studies of vascular and epidural catheters	1149	1247	26 (2.3%)	46 (3.7%)	OR 0.61 (0.30-1.26); p=0.19	Outcome=CR-BSI
						1174	1272	174 (14.8%)	342 (26.9%)	OR 0.47 (0.34-0.65); p<0.00001	Outcome=Bacterial colonization of catheter or exit-site

CG=Chlorhexidine gluconate; CI=Confidence interval; Cntrl=Control; CR-BSI=Catheter-related bloodstream infection; MA=Meta-analysis; OR=Odds ratio; PVP-I=Povidone-iodine; pts=Patients; SR=Systematic review

*Intravascular catheter includes CVC and AC. This SR/MA was not included in the GRADE table because it did not separate sponge vs. non-sponge dressings and included patients with epidural catheters.

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Table 8. Primary Studies

Author, Yr	Design Quality	Power and Sample Size	Population	Intervention	Comparison	N	N Test	N Cntrl	Events Test	Events Cntrl	RR/OR (95% CI); p value	Comments
Timsit, 2009[11]	RCT 1,2,7,9	1600 pts per group for 80% power	Adult pts (>18 years of age) with catheters (AC or CVC) in ICU of 3 university and 2 general hospitals	CG-impregnated sponge dressing (Biopatch®) with Tegaderm® dressing	Standard semipermeable transparent dressing (Tegaderm®)	1636 pts; 3778 catheters	1953	1825	10 (0.5%) 0.6 per 1000 catheter - days	19 (1.1%) 1.4 per 1000 catheter - days	HR 0.39 (0.17-0.93); p=0.03	Outcome=Major catheter related infections (catheter-related clinical sepsis without BSI or CR-BSI)
									6 0.40 per 1000 catheter-days	17 1.3 per 1000 catheter-days	HR 0.24 (0.09-0.65); p=0.005	Outcome=CR-BSI

Ruschulte, 2008[12]	RCT 1,2	Maximum of 707 pts per group for 80% power	Adult pts with CVC undergoing chemotherapy from two high dependency units at a university hospital	CG Biopatch®	Standard sterile dressing	601 pts; 9731 CVC-days	300	301	19 (6.3%)	34 (11.3%)	RR 0.54 (0.31-0.94); p=0.016	Outcome=CVC-related infection
Chambers, 2005[13]	RCT 1,7,8	--	Adults pts with tunneled catheters undergoing chemotherapy in a hematology unit	CG Biopatch®	No dressing	112 catheters	58	54	5 (9%)	23 (43%)	OR 0.13 (0.04-0.37); p<0.001	Outcome=Exit-site and/or tunnel infection
Levy, 2005[14]	RCT 1,2,7	70 pts per group for 80% power to demonstrate 30% to 10% reduction in colonization	Pts 0-18 year old with CVC in cardiac ICU of a tertiary care pediatric hospital	CG Biopatch® covered with transparent polyurethane	Transparent Polyurethane dressing	145 pts	74	71	4 (5.4%)	3 (4.2%)	p=1.00	Outcome=CR-BSI
									11 (14.8%)	21 (29%)	RR 0.61 (0.37-1.0); p=0.04	Outcome=Bacterial colonization
Hanazaki, 1999[15]	RCT 1,7,8,9	--	Pts with CVC undergoing abdominal surgery	CG Biopatch® covered with Bioclusive® dressing	Transparent film dressing (Bioclusive®)	50 pts; 124 CVC sites cultured	25; 60	25; 64	0 (0%)	7 (10.9%)	p<0.01	Outcome=Bacterial colonization of Biopatch® site
									14 (23.3%)	17 (26.6%)	NS	Outcome=Bacterial colonization of more distant site Bioclusive® dressing site
Roberts, 1998[16]	RCT 1,7	11,000 to demonstrate significant difference	Pts with CVC in the ICU	CG Biopatch® with Opsite IV 3000™	Opsite IV 3000™	33 pts	17	16	6 (35.3%)	4 (25%)	NS	Outcome=Bacterial colonization of CVC tip and exit site

AC=Arterial catheter; BSI=Bloodstream infection; CG=Chlorhexidine gluconate; CI=Confidence interval; Cntrl=Control; CR-BSI=Catheter-related bloodstream infection; CVC=Central venous catheter; HR=Hazard ratio; ICU=Intensive care unit; NS=nonsignificant; OR=Odds ratio; pts=Patients; PVP-I=Povidone-iodine; RCT=Randomized controlled trial; RR=Risk ratio

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SUMMARY AND CONCLUSIONS FOR Q2: WHAT TYPE OF CG DRESSING (I.E., SPONGE, NON-SPONGE) SHOULD BE USED FOR TEMPORARY SHORT-TERM CATHETERS IN PATIENTS OLDER THAN 2 MONTHS TO REDUCE THE RISK OF INFECTION?

There are no studies directly comparing different types of CG dressing (sponge vs. non-sponge). There is 1 SR/MA which compared CG dressing vs. placebo or PVP-I dressing but likely included different types of CG dressings and included patients with epidural catheters[10].

There is evidence that CG sponge dressing results in significantly decreased rates of infection compared to standard or no dressing.

3. DO SPLIT-SEPTUM NEEDLELESS CONNECTORS HAVE DECREASED RISK OF INFECTION COMPARED TO MECHANICAL VALVE NEEDLESS CONNECTORS?

TABLE 16. PRIMARY STUDIES

Author, Yr	Design	Population	Intervention	Comparison	N	N Test	N Cntrl	Events Test	Events Cntrl	OR (95% CI); p value	Comments
Jarvis, 2009[25]	QE	Pts with CVC on wards or ICUs at 5 hospitals	Clearlink (n=2), UltraSite (n=3), or SmartSite (n=2)	Interlink (n=4) or needle (n=1)	16 ICUs	--	--	9.49	6.15	RR 1.54 (1.37-1.74); p<0.001	Outcome=BSI per 1000 CVC-days; Pre-introduction of mechanical valve
					14 ICUs	--	--	9.49	5.77	RR 1.65 (1.38-1.96); p<0.001	Outcome=BSI per 1000 CVC-days; Post-introduction of mechanical valve
Field, 2007[26]	QE	Pts with CVC in hematology-oncology units	CLAVE	Interlink	98 pts	83	62	5.8	2.6	IRR 2.2; p=0.031	Outcome=CR-BSI per 1000 catheter-days
Rupp, 2007[27]	QE	Pts with CVC admitted to multiple patient care units of a hospital	SmartSite Plus	Interlink	--	--			--	RR 2.79 (2.27-3.43)	Outcome=BSI
Salgado, 2007[28]	QE	Pts with CVC at a long-term acute care hospital facility	SmartSite	Split-septum device	--	--	--	5.95	1.79	RR 3.32 (2.88-3.83); p<0.001	Outcome=CR-BSI per 1000 CVC-days

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SUMMARY AND CONCLUSIONS FOR Q3: DO SPLIT-SEPTUM NEEDLELESS CONNECTORS HAVE DECREASED RISK OF INFECTION COMPARED TO MECHANICAL VALVE NEEDLESS CONNECTORS?

There are no RCTs comparing infection rates in split-septum vs. mechanical valve needless connectors. There are 4 quasi-experimental studies that evaluated an effect size after switching from one type of needless connector to another resulted in increased rates of BSI[25,26,27,28].

There is evidence that some mechanical valves are significantly associated with increased rates of BSI.

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APPENDIX A—ABBREVIATIONS

AC	Arterial catheter
BSI	Bloodstream infection
Cfu	Colony forming unit
CG	Chlorhexidine gluconate
CI	Confidence interval
Cntrl	Control
CR-BSI	Catheter-related bloodstream infections
CVC	Central venous catheter
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HCW	Healthcare worker
HD	Hemodialysis
HR	Hazard ratio
hrs	hours
ICU	Intensive care unit
ITT	Intention-to-treat
IV	Intravenous
MA	Meta-analysis
MICU	Medical intensive care unit
MSB	Maximal sterile barrier
NS	Nonsignificant
OR	Odds ratio
Pts	Patients
PVC	Peripheral venous catheter

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PVP-I	Povidone-iodine
RCT	Randomized controlled trial
RR	Risk ratio
SD	Standard deviation
SICU	Surgical intensive care unit
SR	Systematic review
Vs	Versus
Yr	Year

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