The clinical effectiveness of central venous catheters treated with anti-infective agents in preventing catheter-related bloodstream infections: A systematic review*

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Objectives: To assess the clinical effectiveness of central venous catheters (CVCs) treated with anti-infective agents (AI-CVCs) in preventing catheter-related bloodstream infections (CRBSI).

Data Sources: MEDLINE (OVID), EMBASE, SCI//Web of Science, SCI/ISI Proceedings, and the Cochrane Library.

Study Selection: A systematic review of the literature was conducted using internationally recognized methodology. All included articles were reports of randomized controlled trials comparing the clinical effectiveness of CVCs treated with AI-CVCs with either standard CVCs or another anti-infective treated catheter. Articles requiring in-house preparation of catheters or that only reported interim data were excluded.

Data Extraction: Data extraction was carried out independently and crosschecked by two reviewers using a pretested data extraction form.

Data Synthesis: Meta-analyses were conducted to assess the effectiveness of AI-CVCs in preventing CRBSI, compared with standard CVCs. Results are presented in forest plots with 95% confidence intervals.

Results: Thirty-eight randomized controlled trials met the inclusion criteria. Methodologic quality was generally poor. Metaanalyses of data from 27 trials assessing CRBSI showed a strong treatment effect in favor of AI-CVCs (odds ratio 0.49 (95% confidence interval 0.37–0.64) fixed effects, test for heterogeneity, chi-square = 28.78, df = 26, p = 0.321, $I^2 = 9.7$). Results subgrouped by the different types of anti-infective treatments generally demonstrated treatment effects favoring the treated catheters. Sensitivity analyses investigating the effects of methodologic differences showed no differences to the overall conclusions of the primary analysis.

Conclusion: AI-CVCs appear to be effective in reducing CRBSI compared with standard CVCs. However, it is important to establish whether this effect remains in settings where infection-prevention bundles of care are established as routine practice. This review does not address this question and further research is required. (Crit Care Med 2009; 37:702–712)

KEY WORDS: catheterization; central venous; anti-infective agents; infection; treatment outcome; infection control; review [publication type]

entral venous catheters (CVCs) include a variety of vascular access devices with many clinical applications. However, their use is associated with a range of complications, notably local and systemic infections. Catheter-related bloodstream infections

(CRBSIs) are of particular importance. Such infections may begin in the soft tissues and then spread along the external surface of the CVC into the bloodstream, or may be introduced directly through the lumen of the CVC into the bloodstream. The risk of CRBSI may therefore be reduced by preventing contamination of the CVC both internally and externally. This can be done through aseptic practice, as defined by evidence-based practice in infection control, (1) both at the time of insertion and during ongoing use and maintenance of the line.

Diagnosis of CRBSI is not straightforward. There are several methods of varying certainty. Inconsistent and inter-changeable use of definitions and terms (e.g., catheter-related bacteraemia, catheter-related sepsis, etc.) further confuse the issue (2).

Accurate diagnosis of CRBSI requires that colonization of the CVC be established in the laboratory using standardized methodologies and end points. An identical organism then needs to be isolated from the bloodstream using blood cultures taken from a peripheral vein (1). However, even if this approach is used there remains a variety of diagnostic techniques.

Data related to the use of CVCs and the rates of CRBSI are not routinely col-

*See also p. 789.

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Supported, in part, by 05/38/01 from the NIHR Health Technology Assessment Programme. See the

HTA Programme website for further project information. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

The authors have not disclosed any potential conflicts of interest.

All work on this article was conducted at The University of Liverpool.

Contributors: RD, KD, JH conducted the clinical review, GS provided clinical expertise, and CG provided statistical supervision. JH, RD, and TW drafted the manuscript with help from all authors.

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DOI: 10.1097/CCM.0b013e3181958915

lected in the UK National Health Service (NHS). The last estimate, in 1994, was that across the NHS over 200,000 CVCs were inserted in adult patients annually (3). In the same year, information from the Department of Health indicated that as many as 6,000 patients are affected by CRBSIs annually (4), and that mortality attributable from such infections may have been as high as 10% to 25% (5). Data from NHS logistics indicate that in 2004–2005 the NHS purchased at least 238,500 CVCs. (NHS logistics, personal communication).

Despite awareness of the scale of the problem for over a decade, only relatively recently has there been national guidance on evidence-based clinical standards for preventing healthcare-associated infections (evidence-based practice in infection control 2001 and 2007) (1, 4) and practical guidance on implementing these (Royal College of Nursing) (6).

In the meantime, there have been significant developments in the design of CVCs aimed at reducing the risk of CRBSI. These innovations include some form of anti-infective agent i.e., antiseptic or antibiotic coating the external and/or internal surface of a CVC or impregnated into the full thickness of the CVC.

Previous reviews (5, 7–10) indicated that anti-infective (AI)-CVCs may reduce the incidence of CRBSI. New trial data are available and this review was conducted to integrate these data with that from previous reviews. This article, which is an update of the review conducted for and published by National Coordinating Centre for Health Technology Assessment only reports results for the primary outcome of CRBSI. For details of secondary outcomes please refer to the full review (11).

METHODS

This review was conducted using internationally accepted standards (12). The process included peer review of the protocol and input from clinical and statistical advisors.

Searching

A comprehensive search strategy was developed and used to interrogate electronic databases (Table 1). Search terms included a combination of index terms (e.g., catheter infection) and free text words (e.g., venous or catheter).

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Selection

The identified citations were assessed for inclusion in a two-stage process. Two reviewers (JH, RD) independently scanned all the titles and abstracts for potentially eligible studies. In stage two, full text copies of these papers were assessed independently by at least two reviewers (JH, RD) for inclusion using the criteria outlined in Table 1. Disagreements were resolved by discussion.

Two reviewers independently evaluated the included studies for methodologic quality according to standard internationally accepted methods (13). These included the appropriateness of randomization methods, allocation of concealment, the blinding of assessors, administrators, and patients, and the percentage of patients lost to follow up. Any discrepancies were resolved through discussion.

Data Extraction

Data extraction was carried out independently and crosschecked by two reviewers (JH, KD). Data from each trial relating to trial design and clinical outcomes were extracted using a pretested data extraction form within Microsoft Access. After looking at the data, an outcome categorization system was developed that took into consideration the various diagnostic methods utilized in the trials (Table 2).

Quantitative Data Synthesis

Meta-analyses were conducted to assess the effectiveness of AI-CVCs in preventing CRBSI, compared with standard CVCs. Results are presented in forest plots with 95% confidence intervals (CIs). As CRBSI is a relatively rare event and no heterogeneity was detected, the fixed effects method; Peto's odds ratio (OR) was used for analysis. Heterogeneity was investigated by visually examining the forest plots to see if the CIs overlap. The chi-square test (14) using a 10% level of statistical significance and the I^2 test (15) with a value of 50% used to

Table 1. Databases searched and inclusion and exclusion criteria

Electronic Databases	MEDLINE (OVID)
(1985 to September 2007)	EMBASE
	SCI//Web of Science
	SCI/ISI Proceedings
	The Cochrane Library
Study design	Randomised controlled trial
Population	Patients requiring a central venous catheter
Interventions	 AI-CVCs
Comparator	 Standard CVCs
	 AI-CVCs
Outcomes	 Primary outcome
	 Catheter related bloodstream infection
	 Secondary outcomes
	 Clinical symptoms
	 Colonization
	 Local clinical signs
Exclusion criteria	 Nonrandomized controlled trial
	 AI-CVCs requiring in house preparation
	 Interim data only

AI-CVCs, central venous catheters treated with anti-infective agents. Validity assessment.

Table 2.	Categorization o	catheter-related	bloodstream	infection	definitions
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Category	Definition	Clinical Signs or Symptoms
α	Identical molecular fingerprint	S+
	0 1	S-
β	Phenotypically indistinguishable, i.e. micro-organisms are considered identical if they are of the same	S+
	species, morphological appearance, and have the same antibiotic sensitivity pattern	S-
βX	Phenotypically indistinguishable but blood taken	S+
	through central venous catheter, not via a peripheral vein	S-
θ	Recognized pathogen but no link to line	S+

S+, clinical signs and symptoms of infection reported; S-, no clinical signs or symptoms reported.

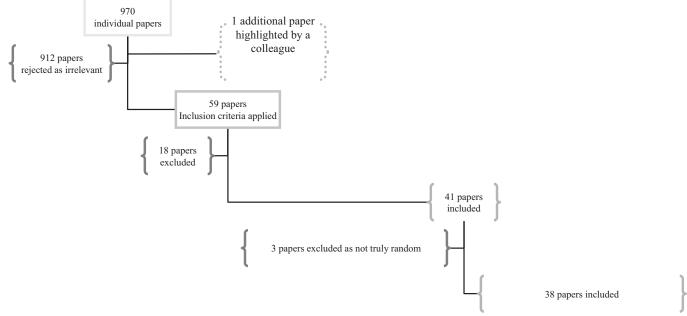


Figure 1. Flow diagram showing the selection of trials.

indicate moderate levels of heterogeneity were also used. To examine heterogeneity subgroup analyses were conducted on the categories of treatment (e.g., antibiotic or anti-septic), types of AI-CVCs (e.g., Silver or minocycline rifampin), outcome categorizations, duration of insertion, and insertion sites, where statistical heterogeneity was detected DerSimmonian and Lairds random effects model (16) was used. Furthermore, sensitivity analyses were conducted to assess the impact of randomization and blinding.

Using the ORs from the CRBSI analysis a range of number needed to treat values were calculated for a selection of control group events found within the meta-analysis. The largest and smallest control group events and several values in between were used.

RESULTS

Trial Flow. Figure 1 depicts the process of trial selection.

Study Characteristics. Overall, methodological quality of included studies was poor, with almost half the studies failing to report relevant methodology, most noticeably the method of randomization, allocation concealment, and blinding procedures.

Twenty-five of the 38 studies reported the method of randomization, with 24 being truly random and two unclear. Allocation of concealment was stated in 19 trials with ten concealing allocation. Blinding of assessors, administrators, and patients were adequately reported in 19 trials with blinding of assessors occurring in 12 trials, administrators in eight trials, and patients in 11 trials.

The 38 included trials consisted of 32 studies comparing an AI-CVC with a standard CVC, four comparing an AI-CVC with another AI-CVC (30, 40, 42, 51), and two three-armed trials that compared a standard CVC with two different AI-CVCs (32, 48) (Table 3).

Seventeen trials allowed more than one CVC per patient. Four trials stated the number of CVCs used rather than the number of patients, and therefore the number of patients included in the analysis cannot be calculated but lies between 8655 and 10,483.

Quantitative Data Synthesis. Of the 38 included studies, 28 compared standard CVCs with AI-CVCs and provided CRBSI rates; on clinical advice a further trial, which assessed an impregnated cuff, (17) was considered a different technology and was excluded from the metaanalyses resulting in 27 trials being included in the meta analyses.

The meta-analysis of all trials reporting CRBSI suggested a statistically significant advantage for treated CVCs in comparison with standard catheters in reducing CRBSI (OR, 0.49 [95% CI 0.37– 0.64], 27 studies, fixed effects) (Fig. 2). There was only a small amount of heterogeneity detected (chi-square 28.78, df =26, [p = 0.32] $I^2 = 9.7\%$).

When trials were grouped by type of AI-CVCS, the direction of the treatment

effect favored the treated catheter in all subgroups except for benzalkonium chloride AI-CVCs where neither treated nor standard catheter was favored (OR 1.00 [95% CI 0.06–16.45], 1 study); however, the study was small and the CI was very wide. Three of the four subgroups containing more than one study achieved statistical significance, with the remaining group (chlorhexidine and silversulphadiazine+) just failing to achieve statistical significance (Fig. 2).

Further subgroup analyses were conducted on different outcome categories of CRBSI diagnosis, different categories of catheter treatment, duration of insertion, and insertion site. These showed advantages with regards to the direction and strength of treatment effect for AI-CVC in most subgroups (Table 4). In addition to subgroup analyses, sensitivity analyses were conducted on methodologically important factors of randomization and blinding (Table 5). The sensitivity analyses were generally consistent with the results of the overall meta-analysis (Fig. 2).

Following clinical advice, a *post hoc* sensitivity analysis to assess the impact of including/excluding two trials (22, 43) that measured CRBSI by taking blood through the CVC (category βX) was conducted. The results of this sensitivity analyses were also consistent with the results of the overall meta-analysis (OR 0.45 [95% CI 0.33–0.60], 25 studies, fixed effects).

ID	Type of CVC	No of Patients	No of CVCs	Catheter-Related Bloodstream Infection Diagnostic Category	No. of CVCs per Patients	Duration of CVC Insertion
Babycos, 1993 (17)	Tunneled standard Silver impregnated cuff	16 17		$\beta S +$	1	Mean = 13.3; Range = 3–28 Mean = 11.76; Range = 3–36
Bach, 1996 (18)	Standard CHSS	117 116		$\alpha S-$	1	NS
Pemberton, 1996 (19)	Standard CHSS	40 32	40 32	βS-	>1 Unclear if they were of the same type	Mean = 11; $s_D = 6$
Van Heerden, 1996 (20)	Standard CHSS	26 28	01	NR	1	Study period, 5–7 days
George, 1997 (21)	Standard CHSS	60	35 44	NR	>1 Could be different types	NS
Logghe et al, 1997 (22)	Standard CHSS	538	342 338	$\beta XS +$	>1 Unclear if they were of the same type†	Mean = 20; sp = 12 Mean = 20; sp = 13
Maki et al, 1997 (23)	Standard CHSS	86 72	195 208	$\alpha S +$	>1 Could be different types	Mean = 145 ; sp = 13 Mean = 145 ; sp = 82 hrs Mean = 143 ; sp = 67 hrs
Raad et al, 1997 (24)	Standard	251	136	$\alpha S + \beta S +$	>1 Unclear if they were of the	Median = 6; Range = $1-21$
Tennenberg et al, 1997 (25)	Minocycline rifampin Standard	145	130	$\beta S+$	same type 1	Median = 6; Range = $1-28$ Mean = 5.3; sp = 0.2
Trerotola et al, 1998 (26)	CHSS Standard	137 44		NR	1	Mean = 5.1 ; sD = 0.2 Mean = 125
Bach et al, 1999 (27)	Silver Standard	47 33		NR	1	Mean = 61 Mean = 4.06 ; sp = 2
Boswald et al, 1999 (28)	Silver Standard	34 79		$\beta S+$	1	Mean = 4.49 ; sp = 2.3 Median = 8; Range = $5-51$
Collin, 1999 (29)	Silver impregnated Standard	86 61	139	$\beta S +$	>1 Of the same type	Median = 9; Range = $5-27$ Mean = 7.3; sp = 5.0
Darouiche et al, 1999 (30)	CHSS CHSS	50 370	98 382	$\beta S +$	>1 Could be different types	Mean = 9.0 ; sp = 6.1 Mean = 8.2 ; Median = 7;
	Minocycline rifampin	350	356			Range = $1-36$ Mean = 8.4 ; Median = 6 ;
Hannan et al, 1999 (31)	Standard	228	177	βS-	>1 Unclear if they were of the	Range = $1-55$ Mean = 7.6; Range = $1-32$
Marik et al, 1999 (32)	CHSS Standard	39	174	βS-	same type 1	Mean = 7.5; Range = $1-17$ Mean = 6; sp = 4
	CHSS Minocycline rifampin	36 38				Mean = 6; $SD = 3$ Mean = 6; $SD = 3$
Moss et al, 2000 (33)	Standard CHSS	98 106		NR	1	Mean $= 102$ hrs Mean $= 91$ hrs
Sheng et al, 2000 (34)	Standard CHSS	204	122 113	$\beta S +$	>1 Could be different types	Mean = 8.2 ; sD = 4.6 Mean = 9.1 ; sD = 5.5
Jaeger et al, 2001 (35)	Standard CHSS	25 25	115	βS-	1	Mean = 19.3 ; sb = 3.5 Mean = 19.3 ; sb = 11.5 Mean = 14.8 ; sb = 7.2
Stoiser et al, 2002 (36)	Standard	47		$\beta S +$	1	Median = 11; Range = $4-46$
Theaker et al, 2002 (37)	Silver impregnated Standard	50 181	131	NR	>1 Unclear if they were of the	Median = 10.5; Range = 3–39 Mean = 7.2; Median = 6
Bong et al, 2003 (38)	CHSS Standard		101 142	$\alpha S +$	same type >1 Unclear if they were of the	Mean = 7.4; Median = 7 Median = 14
Chatzinikolaou et al,	Silver impregnated Standard	64	128	$\beta S+$	same type 1	Median = 10.5 Mean = 8; sp = 6; Median = 7;
2003 (39)	Minocycline rifampin	66				Range = $1-32$ Mean = 8; sp = 6; Median = 6;
Corral et al, 2003 (39)	Standard	65	103	βS+	>1 Of the same type	Range = $1-32$ Mean = 14; sp = 7; Range = 4-
Ranucci et al, 2003 (40)	Silver impregnated Benzalkonium chloride	80 277	103	βS+	1	Mean = 12; s _D = 7; Range = 4- Mean = 9; s _D = 6.9; Median =
	Silver, carbon and	268				Range = $1-49$ Mean = 9.1 ; sp = 6.9 ; Median =
Brun Ruisson at al 2004 (41)	platinum Standard	175	NC	0S+	>1 Of the same time	Range = $3-43$ Mean = 12 ; sp = 11.7 ; Median
Brun-Buisson et al, 2004 (41)	Standard CHSS +	175 155	NS	βS+	>1 Of the same type	Mean = 10.5 ; sp = 8.8 ; Median
Carrasco et al, 2004 (42)	Heparin CHSS	91 89	132 128	$\beta S +$	>1 Of the same type	Mean = 13.6 Mean = 12.7
Hanna et al, 2004 (43)	Standard Minocycline rifampin	173 182	174 182	$\beta XS +$	$>\!\!1$ Of the same type	Mean = 63.01 ; sD = 30.80 Mean = 66.21 ; sD = 30.88
Leon et al, 2004 (44)	Standard Minocycline rifampin	180 187	100	$\beta S +$	1	Mean = 9; sD = 5 Mean = 9; sD = 5
/ücel et al, 2004 (45)	Standard	107		$\beta S +$	1	Mean = 6.7 ; Median = 6 ;
	Miconazole and rifampicin	118				Range = $2-19$ Mean = 7.5; Median = 6; Range = $2-36$

ID	Type of CVC	No of Patients	No of CVCs	Catheter-Related Bloodstream Infection Diagnostic Category	No. of CVCs per Patients	Duration of CVC Insertion
Jaeger et al, 2005 (46)	Standard	55		βS-	1	Mean = 16.6 ; sd = 9.7 ;
	CHSS +	51				Range = 1–58 Mean = 14.3; sp = 8.2; Range = 2–52
Rupp et al, 2005 (47)	Standard	362		$\beta S+$	1	De novo insertion Mean = 142 hrs, Range = 2–790 hrs; Guidewire exchange Mean = 120 hrs; Range = 0.1–719 hrs
	CHSS +	345				De novo insertion Mean = 123 hrs, Range = 0.1–764 hrs; Guidewire exchange Mean = 124 hrs; Range = 0.1–1109 hrs
Dunser et al, 2005 (48)	Standard	120	160	NR	>1 Could be different types	Mean = 10.7 ; sp = 4.2
	Silver impregnated	85	160			$Mean = 9.3; s_D = 4$
	CHSS	70	165			Mean = 9.7 ; sp = 4
Moretti et al, 2005 (49)	Standard	266	266	$\beta S+$ and $\beta S-$	1	NS
	Silver impregnated	273	273			
Ostendorf et al, 2005 (50)	Standard	94	94	$\alpha S-$	1	Mean = 10.81; Median = 10; Range = 1–29
	CHSS+	90	90			Mean = 12.29; Median = 12; Range = 1–74
Fraenkel et al, 2006 (51)	Silver-platinum-carbon impregnated	—	327	$\alpha S-$	NS	Mean = 149.9 hrs; sD = 93.5 hrs; Median = 140 hrs
	Minocycline rifampin	—	319			Mean = 149.4 hrs; sp = 92.5 hrs; Median = 139 hrs
Osma et al, 2006 (52)	Standard	69	69	$\beta S+$	1	Mean = 8.9 ; sD = 4.6 ; Median = 8 Range = $3-20$
	CHSS+	64	64			Mean = 11.7; sp = 5.8; Median = 10; Range = $3-29$
Kalfon et al, 2007 (53)	Standard	256	297	βS+	>1	Median = 10; Range = $1-90$
	Silver impregnated	268	320	F-2 '		Median = 10; Range = $1-117$

CVC, central venous catheter; NR, not reported; NS, not stated; CHSS, chlorhexidine and silver-sulphadiazine molecularly bonded to the outer wall of the CVC body only; CHSS+, chlorhexidine and silver-sulphadiazine molecularly bonded to the outer wall of the CVC body, the inner lumens, the inside and outside of the hub and to the internal and external walls of the extension lines applied to both the internal and external surface of the CVC.

Depending on the value of the control group event the number needed to treat varies between 13 (95% CI 10–19) and 655 (95% CI 530–928).

A meta-analysis of the rates of CRBSI per 1000 days was also conducted. Rates were obtained from either the published papers, calculated from results in the published article or from contact with authors. The results of the meta-analysis were consistent with the main analyses (OR 0.40 [95% CI 0.27–0.58], 18 studies, fixed effects) but showed more heterogeneity ($I^2 = 31.6\%$). This analysis can be interpreted as a reduction of 60% in the rate of CRBSI's per 1000 days in the treatment group compared with the standard.

DISCUSSION

The basic conclusion of the review is that AI-CVCs are clinically effective in reducing CRBSIs. However, the complexity of the issue and the limitations of the trials require that caveats be highlighted; the quality of trials included in the review and the place of AI-CVCs in an infectioncontrol bundle of care.

The quality assessment highlighted the poor methodology of many of these trials with poor reporting or unsatisfactory blinding and randomization. Although these factors need to be considered when assessing the results, (54) sensitivity analyses on blinding and randomization showed no differences in direction of effect, although the strength of the treatment effect decreased for those studies where randomization was unclear and for those studies where there was no blinding.

Furthermore, it is not possible to reach a conclusion regarding the duration of effect of AI-CVCs because of the lack of available studies assessing CRBSI rates in AI-CVCs inserted for longer than 12 days. In this review, only seven of the 24 trials assessing CRBSI had a mean duration of over 12 days. Three of the six studies with mean insertion times of 13–20 days assessed types of AI-CVCs that failed to reach statistical significance in the AI-CVC type subgroup and only one study had an average insertion time of greater than 20 days. Further trials assessing CRBSI rates when AI-CVCs are inserted for longer than 12 days are required, particularly trials assessing AI-CVCs coated both internally and externally, and those using antibiotics.

Although systematic reviews of treatments in complex clinical situations are an established method for assessing the effectiveness of a defined intervention, they are not a panacea for complex interventions (55). This review is an excellent case in point. The review addressed the question of effectiveness of AI-CVCs compared with standard CVCs, but a more important question for clinicians is whether it is possible to reduce the rate of CRBSIs regardless of the CVC used. For this, AI-CVCs need to

Jaeger 2005 1 1/31 4/33 4/32 4/33 4/42 4/31 0.0.54 2.2. Subtail (95% C1) 738 735 5/00 4/64 1/49 5/8 5 5 7 0.28 10.0.5 4/2.3 10.65 2.3 10.65 2.3 10.65 2.3 10.65 2.3 10.65 2.3 10.65 2.4 10.65 2.6 10.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.67 2.5 10.60 0.65 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5 10.60 0.5	Study or sub-category	Treatment n/N	Control n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
Jangape 2005 1/51 0/55 3.78 0.20 0.045 0.20 0.045 0.20 0.045 0.20 0.2	1 CHSS Blue Plus - Antimicrobia	al Impregnated				
Definition 2005 Definition 2005 Defin	Brun-Buisson, 2004	3/188	5/175		3.57	0.56 [0.14, 2.26]
Type, 2005 1/345 3/362 Brana, 2006 4/44 1/69 Brana, 2006 1/64 1/69 Brana, 2006 1/64 1/69 Brana, 2006 1/64 1/69 Brana, 2006 1/64 1/67 Brana, 2006 1/64 1/67 Brana, 2006 1/64 1/67 Brana, 2006 1/64 1/67 Brana, 2006 1/67 1/67 Brana, 2006 1/67 1/77 Brana, 2008 1/123 1/124 Constraint Brance 1/123 1/124 Constraint Brance 1/273 1/65 0.64 10.77 1.51 Brana, 2006 1/723 1/263 1/73 1/145 10.005 0.55 10.33 0.55 Callon, 207 8/220 8/2273 10.01 10.01 1.03 0.55 10.33 0.55 10.33 0.55 10.33 0.55 10.33 0.55 10.33 0.55 10.33 0.55 10.33 0.55 10.33 0.55 10.33 0.55 <t< td=""><td>Jaeger, 2005</td><td>1/51</td><td>8/55</td><td></td><td>3.78</td><td>0.20 [0.05, 0.78]</td></t<>	Jaeger, 2005	1/51	8/55		3.78	0.20 [0.05, 0.78]
Supp. 2005 1/345 3/352 1.8 0.38 [0.5, 2.7, 2.05] Defina, 2006 4/44 1/69 2.20 3.75 15.69 0.51 [0.5, 2.7, 2.05] Defina (2006 7.44 1.60 0.51 [0.5, 2.7, 2.05] 15.69 0.51 [0.5, 2.7, 2.05] Defina (2007 7.6, 1.05) 1.6, 0.77	Ostendorf, 2005	3/90	7/94		4.33	0.45 [0.13, 1.61]
bin a 2006 4/44 1/49 bin a 2006 2.20 3.75 [0.45, 22.2] bin events: 12 (Treatment), 24 (Control) 55 15.69 0.51 [0.26, 1.00] bin events: 12 (Treatment), 24 (Control) 55						
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Jale webs: 12 (Treatment), 24 (Control) stif or hetrogeneity (Ch ⁺ = 6, 2, 1 = 6, 1, 5), F = 40, 5%, stif or overall effect Z = 1, 95 (P = 0, 05) 2. Silve Impegnated -Amin (cobial Impregnated loss) 0.003 1/128 1/128 1/142 0.733 1/128 1/128 1/142 0.733 1/128 1/103 4/103 0.733 1/228 1/133 4/103 0.28 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 0.29 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 0.303 1/128 1/133 4/103 0.241 0.24 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 121 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 7, 66 121 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 2, 24 121 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 2, 24 121 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 2, 24 121 (for hetrogeneity (Ch ⁺ = 4, 1, 4] 2, 24 121 (for hetrogeneity (Ch ⁺ = 4, 2, 6] 121 (for hetrogeneity (Ch ⁺ = 4, 2, 6] 121 (for hetrogeneity (Ch ⁺ = 4, 2, 6] 121 (for hetrogeneity (Ch ⁺ = 4, 2, 6] 121 (for hetrogeneity (Ch ⁺ = 4, 2, 6] <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td></td<>						
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Jorral, 2003 1/103 4/103 2.23 0.29 [0.05, 1, 1, 2] Jorral, 2005 0/173 1/266 0.46 0.13 [0.06, 6, 65 Jation, 2007 8/320 8/297 7.10 0.33 [0.34, 2, 25 Jationski 23 (Treatment), 40 (Control) set for overall effect Z = 2.28 (P = 0.02) 27.00 0.55 [0.33, 0.92 J Macogoline Rifempin - Antibiotic and, 1997 0/138 2/39 0.90 0.14 [0.05, 0, 0.5 Jata events: 9 (Treatment), 40 (Control) set for overall effect Z = 2.28 (P = 0.02) 0.46 7.14 7.39 0.52 [0.37, 0.46 Jata events: 9 (Treatment), 39 (Control) set for overall effect Z = 1.06 (P = 0.45), P = 0% 20.97 0.26 [0.15, 0.47 Set for overall effect Z = 4.52 (P < 0.00001)	Stoiser, 2002	3/50	3/47		2.59	0.94 [0.18, 4.85]
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bareti 2005 0/273 1/266 dinn, 2007 8/320 8/297 abblai (95% C1) 960 934 diale vents: 23 (Treatment), 40 (Control) stor heterogenetity, Chf ≠ 4,41, df = 5 (P = 0.49), F = 0% stor overall effect Z = 2.28 (P = 0.02) Mancycline Fittighn - Antibolic aad, 1997 0/130 5/136 tana, 2004 0/138 2/39 0.30 0/46 7/64 mana, 2004 3/182 14/174 7.39 0.25 (0.3), 0.62 20.97 0.26 (0.15, 0.47) stor heterogenetity, Chf ≠ 3,63 of = 4 (P = 0.45), F = 0% stor overall effect Z = 4.52 (P < 0.0001) H. Conzole and Rifempicin - Antibolic Code, 2004 0/118 1/150 tor overall effect Z = 4.52 (P < 0.0001) H. Conzole and Rifempicin - Antibolic Stor overall effect Z = 0.00 (P = 0.29) stor heterogenetity, not applicable stor overall effect Z = 0.00 (P = 0.29) Senzalkonium Chiorde Impregnated ager, 2001 1/13 1/150 tor overall effect Z = 0.00 (P = 0.29) Stor heterogenetity, not applicable stor overall effect Z = 0.00 (P = 0.29) Stor heterogenetity, not applicable stor overall effect Z = 0.00 (P = 0.29) Chief S C1) 2.5 2.5 Senzalkonium Chiorde Impregnated ager, 1995 0/116 3/117 embeton, 1906 2/12 3/42 4.88 0.25 (10.00, 6.07 0.13 (0.01, 1.3.3 0.55 (0.18, 0.43 0.13 (0.01, 1.3.3 0.55 (0.18, 0.43 0.13 (0.01, 1.3.3 0.55 (0.18, 0.43 0.13 (0.01, 1.3.3 0.55 (0.18, 0.43 0.13 (0.01, 1.3.5 0.13 (0.01, 1.2.2 0.13 (0.01, 1.3.5 0.13 (0.01, 1.3.5 0.13 (0.01, 1.3.5 0.13 (0.01, 1.3.5 0.13 (0.01, 1.3.5 0.13 (0.01, 1.2.2 0.13 (0.01, 1.3.5 0.13 (0.01, 1.2.2 0.13 (0.01, 0.5, 1.6.5						
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Figure 2. Catheter-related bloodstream infection rates—subgrouped by different treatment catheters.

be considered in the wider context of prevention of infection.

Prevention of CRBSIs commences with the prevention of micro-organism colonization of the insertion site or the lumen i.e., an aseptic insertion site and catheter. This is not a function of the type of catheter used, but rather of bundles of care that include infectioncontrol practices.

If good infection-control practices are compromised, then the use of antiseptic

technologies such as AI-CVCs, BioPatch (56), and an antibiotic lock (57) may be a "safety net" to prevent contaminating micro-organisms from developing into a CRBSI. Encouraging results have been obtained from studies with varied infec-

Analysis	Subgroup	No. of Trials	No. of Catheter- Related Bloodstream Infections in Standard Central Venous Catheters (%)	No of Catheter- Related Bloodstream Infections in Treated Central Venous Catheters (%)	Odds Ratio (95% Confidence Interval)
Outcomes	α S+	3	25/473 (5.29)	9/466 (1.93)	0.39 (0.20, 0.77)
outcomes	$\alpha S -$	2	10/211(4.74)	3/206 (1.46)	0.34(0.11, 1.02)
	βS+	14	71/1992 (3.56)	29/1958 (1.48)	0.34(0.11, 1.02) 0.42(0.28, 0.62)
	βS-	7	25/633 (3.95)	14/676 (2.07)	0.36(0.16, 0.84)
	βXS+	2	29/516 (5.62)	20/520 (3.8)	0.67 (0.38, 1.20)
Categories of treatment	Antibiotics	6	40/698 (5.73)	9/721 (1.2)	0.26 (0.15, 0.46)
eurogenee er treutment	Externally treated	9	50/1316 (3.80)	30/1252 (2.40)	$0.62 \ (0.40, \ 0.98)$
	Externally and internally treated	12	65/1714(3.79)	36/1723 (2.09)	0.55(0.37, 0.81)
Duration	5–12 days	20	97/2731 (3.55)	45/2753 (1.63)	$0.46\ (0.33,\ 0.64)$
	13–20 days	5	39/667 (5.85)	27/645 (4.19)	0.71(0.43, 1.17)
	>20 days	1	14/174 (8.05)	3/182 (1.6)	0.25(0.09, 0.65)
Insertion site	>90% femoral	1	7/64 (10.9)	0/66 (0.0)	0.12(0.03, 0.54)
	>90% jugular	3	24/251 (9.56)	5/253 (2.0)	0.23 (0.11, 0.50)
	>90% subclavian	4	31/692 (4.48)	29/628 (4.62)	1.01 (0.60, 1.69)
	Mixed	19	91/2682 (3.39)	41/2749 (1.49)	0.44 (0.31, 0.63)
Randomization	Randomized	16	93/2237 (4.16)	42/2240 (1.88)	0.45(0.32, 0.64)
	Unclear	11	60/1452 (4.13)	33/1456 (2.27)	0.55 (0.36, 0.83)
Blinding	Attempted	13	90/1964 (4.58)	40/1955 (2.05)	0.45(0.32, 0.64)
_	Open	4	19/813 (2.34)	13/848 (1.53)	0.67 (0.33, 1.35)
	Not stated	10	44/912 (4.82)	22/893 (2.46)	0.50 (0.30, 0.81)

Attempted, trials that had attempted blinding of the administrator or the assessor; Open, that did not blind either the administrator or the assessor.

Table 5. Numbers needed to treat to avoid an occurrence of catheter-related bloodstream infections

Study Used	Control Group Event Rate	Number Needed to Treat (OR $= 0.45$)		Upper Limit $(OR = 0.60)$
Moretti et al, 2005 (49)	0.0030	655	530	928
Rupp et al, 2005 (47)	0.0083	237	192	336
Bach et al, 1996 (18)	0.0256	78	63	110
Marik et al, 1999 (32)	0.0500	40	32	57
Pemberton et al, 1996 (19)	0.0750	27	22	39
Chatzinikolaou et al, 2003 (39)	0.1094	19	15	27
Boswald et al, 1999 (28)	0.1646	13	10	19

OR, odds ratio.

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tion controls and training measures. Furthermore, to ensure best practice, some hospitals have developed specialist teams to deal with insertion and maintenance of CVCs (58).

Because of the diverse reporting of clinical practice in the included trials, it was not possible to determine the quality of aseptic procedures. The rates of CRBSI reported in the control arms of the trials ranged from <1% to 16%, with a median of 5%. This median rate is similar to the 3% reported in clinical practice (59), which may infer that aseptic techniques were of a similar standard to the usual clinical practice. Therefore, taking into consideration the studies that have found a decrease in CRBSI rates after the introduction of various strategies that aim to improve clinical practice (1), it is possible that the benefits of AI-CVCs found in this review are not necessarily additive but rather substitutes for the benefits of meticulous aseptic technique. Therefore, it would be of interest to determine whether the strength of benefits of AI-CVCs over standard CVCs identified in this review remain after the introduction of appropriate infection prevention methods.

The economic performance (costeffectiveness and potential cost-savings) of using AI-CVCs to reduce the number of CRBSIs in patients requiring a CVC was also estimated. Results show that the use of AI-CVCs instead of standard CVCs can lead to a reduction in CRBSIs and decreased medical costs. A basic decisionanalytic model was constructed to explore a range of possible scenarios for the NHS in England and Wales. We estimated the incremental cost per patient to be equal to -£138.20 i.e., for every patient who receives an AI-CVC, there is an estimated cost-saving of £138.20. The results of a series of multivariate sensitivity analyses reveal that estimates of potentially large cost-savings, depending on the size of the population, maybe anticipated under a wide range of cost and clinical assumptions. However, when considering the purchase of AI-CVCs, decisionmakers in the NHS should ensure that their patient populations and the important characteristics of local clinical practice are indeed similar to those described in our economic evaluation.

CONCLUSIONS

AI-CVCs appear to be effective in reducing CRBSI compared with standard CVCs. However, it is important to establish whether this effect remains after effective infection-control bundles of care are established as routine practice. This review does not address this question and further research addressing the impact of this is required.

ACKNOWLEDGMENTS

We acknowledge the assistance of Dr. R Hill for providing advice on the assessment process, and all contributors to the project: Prof. A Bagust for conducting the economic evaluation and Dr. Y. Dundar for the development of the search strategies.

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infection with newer chlorhexidine-silver sulfadiazine-coated catheters: A randomized controlled trial. *Intensive Care Med* 2004; 30:837–843

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APPENDICES

Appendix 1—Details of trials excluded from the review

Trial Reference	Reason for Exclusion
Appelgren P, Ransjo U, Bindslev L, et al: Surface heparinization of central venous catheters reduces microbial colonization in vitro and in vivo: Results from a prospective, randomized trial. <i>Crit Care</i> <i>Med</i> 1996; 24:1482–1489	Standard CVC vs. Heparin bonded CVC
Bach A, Bohrer H, Bottiger BW, et al: Reduction of bacterial colonization of triple-lumen catheters with antiseptic bonding in septic patients [abstract]. <i>Anaesthesiology</i> 1994; 81:a261	Interim results
Bach A, Darby D, Bottiger B, et al: Retention of the antibiotic teicoplanin on a hydromer-coated central venous catheter to prevent bacterial colonization in postoperative surgical patients. <i>Intensive Care Med</i> 1996; 22:1066–1069	In house preparation of AI-CVCs
Barbosa D, Pignatari A, Draibe S, et al: A randomized trial evaluating topic mupirocin for the prevention of infections related to central venous catheters for hemodialysis. <i>J Am Soc Nephrol</i> 1997; 8:152a	In house preparation of AI-CVCs
Ciresi DL, Albrecht RM, Volkers PA, et al: Failure of antiseptic bonding to prevent central venous catheter-related infection and sepsis. <i>Am Surg</i> 1996; 62:641–646	Not truly random (randomised by last digit of patients medical records)
Crabtree JH, Burchette RJ, Siddiqi RA, et al: Efficacy of silver-ion implanted catheters in reducing peritoneal dialysis-related infections. <i>Peritoneal Dialysis Int</i> 2003; 23:368–374	Peritoneal catheters
Dahlberg PJ, Agger WA, Singer JR, et al: Subclavian hemodialysis catheter infections: A prospective, randomized trial of an attachable silver-impregnated cuff for prevention of catheter-related infections. <i>Infect Control Hosp Epidemiol</i> 1995; 16:506–511	Silver cuff vs. noncuffed
Flowers RH III, Schwenzer KJ, Kopel RF, et al: Efficacy of an attachable subcutaneous cuff for the prevention of intravascular catheter-related infection. A randomized, controlled trial. <i>JAMA</i> 1989; 261:878–883	Cuff vs. noncuffed
Groeger JS, Lucas AB, Coit D, et al: A prospective, randomized evaluation of the effect of silver impregnated subcutaneous cuffs for preventing tunneled chronic venous access catheter infections in cancer patients. <i>Ann Surg</i> 1993; 218:206–210	Cuff vs. 2nd cuff

Trial Reference	Reason for Exclusion
Hannan M, Juste R, Shankar U, et al: Colonization of triple lumen catheters. A study on antiseptic bonded and standard catheters. <i>Clin Intensive Care</i> 1996;7:56	Full paper published later
Heard SO, Wagle M, Vijayakumar E, et al: Influence of triple-lumen central venous catheters coated with chlorhexidine and silver sulfadiazine on the incidence of catheter-related bacteremia. <i>Arch Intern Med</i> 1998; 158:81–87	Not truly random (randomised by last digit o patients medical records)
Kamal GD, Pfaller MA, Rempe LE, et al: Reduced intravascular catheter infection by antibiotic bonding. A prospective, randomized, controlled trial. <i>JAMA</i> 1991; 265:2364–2368	In house preparation of AI-CVCs
Leon C, Alvarez-Lerma F, Ruiz-Santana S, et al: Antiseptic chamber-containing hub reduces central venous catheter-related infection: A prospective, randomized study. <i>Crit Care Med</i> 2003; 31:1318–1324	Antiseptic chamber containing hub v standard luer lock connector
Maki DG, Cobb L, Garman JK, et al: An attachable silver-impregnated cuff for prevention of infection with central venous catheters—A prospective randomized multicenter trial. <i>Am J Med</i> 1988; 85:307–314	Cuff vs. noncuffed
Pierce CM, Wade A, Mok Q: Heparin-bonded central venous lines reduce thrombotic and infective complications in critically ill children. <i>Intensive Care Med</i> 2000: 26:967–972	Standard CVC V Heparin bonded CVC
Radd I, Costerton W, Sabharwal U, et al: Ultrastructural analysis of indwelling vascular catheters—A quantitative relationship between luminal colonization and duration of placement. <i>J Infect Dis</i> 1993: 168:400–407	Subgroup of a later and included study
Ramsay J, Nolte F, Schwarzmann S: Incidence of catheter colonization and catheter-related infection with an antiseptic-impregnated triple-lumen catheter. <i>Crit Care Med</i> 1994; 22:a115	Interim data
Smith HO, DeVictoria CL, Garfinkel D, et al: A prospective randomized comparison of an attached silver-impregnated cuff to prevent central venous catheter-associated infection. <i>Gynecol Oncol</i> 1995; 58:92–100	Cuff vs. noncuffed
Thornton J, Todd NJ, Webster NR: Central venous line sepsis in the intensive care unit—A study comparing antibiotic coated catheters with plain catheters. <i>Anaesthesia</i> 1996; 51:1018–1020	In house preparation of AI-CVCs
Trazzera S, Stern G, Bhardway R, et al: Examination of antimicrobial-coated central venous catheters in patients at high risk of catheter-related infections in a medical intensive care unit and leukemia/bone marrow transplant unit (abstract). <i>Crit Care Med</i> 1995; 23:A153	Nonrandomized controlled trial
Van Vliet J, Leusink JA, De Jongh BM, et al: A comparison between two types of central venous catheters in the prevention of catheter-related infections: The importance of performing all the relevant cultures. <i>Clin Intensive Care</i> 2001; 12:135–140	Not truly random (randomised by alternate days)

AI-CVCs, anti-infective treated central venous catheters.

Appendix 2

	Describe	Reported	Page
Title	Identify the report as a meta-analysis [or systematic review] of randomized controlled trials	Yes	1
Abstract			
Objectives	The clinical question explicitly	Yes	3
Data sources	The databases (ie, list) and other information sources	Yes	3
Review methods	The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication	Yes	3
Results	Characteristics of the randomized controlled trials included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses	Yes	3
Conclusion	The main results	Yes	3
Introduction	The explicit clinical problem, biological rationale for the intervention, and rationale for review	Yes	4, 5
Methods			
Searching	The information sources, in detail (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)	Yes	5, 6
Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)	Yes	5,6
Validity assessment	The criteria and process used (eg, masked conditions, quality assessment, and their findings)	Yes	6
Data abstraction	The process or processes used (eg, completed independently, in duplicate)	Yes	7

	Describe	Reported	Page
Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, and how clinical heterogeneity was assessed	Yes	7
Quantitative data synthesis	The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias	Yes	7
Results	•		
Trial flow	Provide a meta-analysis profile summarising trial flow	Yes	8
Study characteristics	Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)	Yes	8-12
Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg tables of counts, means and SD s, proportions)	Yes	12–16
Discussion	Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda	Yes	16–18