# 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. Meta-analyses 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]**

Central 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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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).

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

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

**Table 2.** Categorization of catheter-related bloodstream infection definitions

| Category | Definition | Clinical Signs or Symptoms |
|---|---|---|
| α | Identical molecular fingerprint | S+<br>S− |
| β | Phenotypically indistinguishable, i.e. micro-organisms are considered identical if they are of the same species, morphological appearance, and have the same antibiotic sensitivity pattern | S+<br>S− |
| βX | Phenotypically indistinguishable but blood taken through central venous catheter, not via a peripheral vein | S+<br>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.

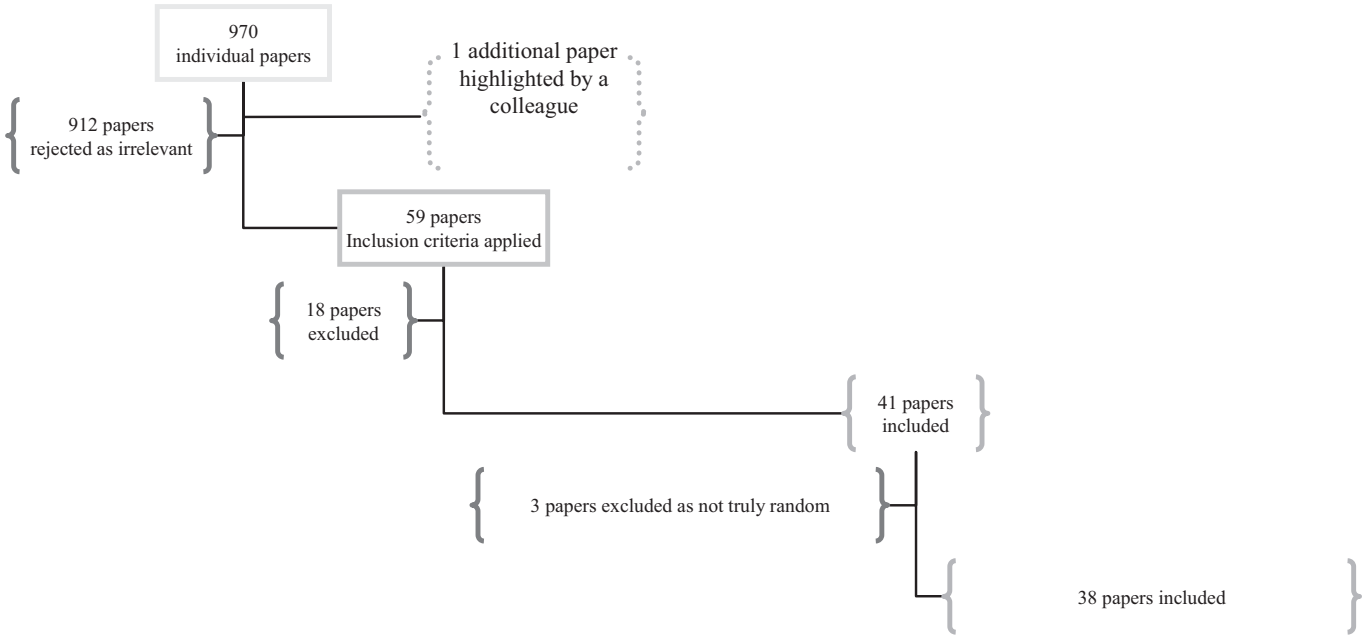


**Figure 1. Flow diagram showing the selection of trials.**



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 meta-analyses 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 silver-sulphadiazine+) 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).

Table 3. Study characteristics

| 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 | 16 | | βS+ | 1 | Mean = 13.3; Range = 3–28 |
| | Silver impregnated cuff | 17 | | | | Mean = 11.76; Range = 3–36 |
| Bach, 1996 (18) | Standard | 117 | | αS− | 1 | NS |
| | CHSS | 116 | | | | |
| Pemberton, 1996 (19) | Standard | 40 | 40 | βS− | >1 Unclear if they were of the same type | Mean = 11; SD = 6 |
| | CHSS | 32 | 32 | | | |
| Van Heerden, 1996 (20) | Standard | 26 | | NR | 1 | Study period, 5–7 days |
| | CHSS | 28 | | | | |
| George, 1997 (21) | Standard | 60 | 35 | NR | >1 Could be different types | NS |
| | CHSS | | 44 | | | |
| Logghe et al, 1997 (22) | Standard | 538 | 342 | βXS+ | >1 Unclear if they were of the same type† | Mean = 20; SD = 12 |
| | CHSS | | 338 | | | Mean = 20; SD = 13 |
| Maki et al, 1997 (23) | Standard | 86 | 195 | αS+ | >1 Could be different types | Mean = 145; SD = 82 hrs |
| | CHSS | 72 | 208 | | | Mean = 143; SD = 67 hrs |
| Raad et al, 1997 (24) | Standard | 251 | 136 | αS+βS+ | >1 Unclear if they were of the same type | Median = 6; Range = 1–21 |
| | Minocycline rifampin | | 130 | | | Median = 6; Range = 1–28 |
| Tennenberg et al, 1997 (25) | Standard | 145 | | βS+ | 1 | Mean = 5.3; SD = 0.2 |
| | CHSS | 137 | | | | Mean = 5.1; SD = 0.2 |
| Trerotola et al, 1998 (26) | Standard | 44 | | NR | 1 | Mean = 125 |
| | Silver | 47 | | | | Mean = 61 |
| Bach et al, 1999 (27) | Standard | 33 | | NR | 1 | Mean = 4.06; SD = 2 |
| | Silver | 34 | | | | Mean = 4.49; SD = 2.3 |
| Boswald et al, 1999 (28) | Standard | 79 | | βS+ | 1 | Median = 8; Range = 5–51 |
| | Silver impregnated | 86 | | | | Median = 9; Range = 5–27 |
| Collin, 1999 (29) | Standard | 61 | 139 | βS+ | >1 Of the same type | Mean = 7.3; SD = 5.0 |
| | CHSS | 50 | 98 | | | Mean = 9.0; SD = 6.1 |
| Darouiche et al, 1999 (30) | CHSS | 370 | 382 | βS+ | >1 Could be different types | Mean = 8.2; Median = 7; Range = 1–36 |
| | Minocycline rifampin | 350 | 356 | | | Mean = 8.4; Median = 6; Range = 1–55 |
| Hannan et al, 1999 (31) | Standard | 228 | 177 | βS− | >1 Unclear if they were of the same type | Mean = 7.6; Range = 1–32 |
| | CHSS | | 174 | | | Mean = 7.5; Range = 1–17 |
| Marik et al, 1999 (32) | Standard | 39 | | βS− | 1 | Mean = 6; SD = 4 |
| | CHSS | 36 | | | | Mean = 6; SD = 3 |
| | Minocycline rifampin | 38 | | | | Mean = 6; SD = 3 |
| Moss et al, 2000 (33) | Standard | 98 | | NR | 1 | Mean = 102 hrs |
| | CHSS | 106 | | | | Mean = 91 hrs |
| Sheng et al, 2000 (34) | Standard | 204 | 122 | βS+ | >1 Could be different types | Mean = 8.2; SD = 4.6 |
| | CHSS | | 113 | | | Mean = 9.1; SD = 5.5 |
| Jaeger et al, 2001 (35) | Standard | 25 | | βS− | 1 | Mean = 19.3; SD = 11.5 |
| | CHSS | 25 | | | | Mean = 14.8; SD = 7.2 |
| Stoiser et al, 2002 (36) | Standard | 47 | | βS+ | 1 | Median = 11; Range = 4–46 |
| | Silver impregnated | 50 | | | | Median = 10.5; Range = 3–39 |
| Theaker et al, 2002 (37) | Standard | 181 | 131 | NR | >1 Unclear if they were of the same type | Mean = 7.2; Median = 6 |
| | CHSS | | 101 | | | Mean = 7.4; Median = 7 |
| Bong et al, 2003 (38) | Standard | | 142 | αS+ | >1 Unclear if they were of the same type | Median = 14 |
| | Silver impregnated | | 128 | | | Median = 10.5 |
| Chatzinikolaou et al, 2003 (39) | Standard | 64 | | βS+ | 1 | Mean = 8; SD = 6; Median = 7; Range = 1–32 |
| | Minocycline rifampin | 66 | | | | Mean = 8; SD = 6; Median = 6; Range = 1–32 |
| Corral et al, 2003 (39) | Standard | 65 | 103 | βS+ | >1 Of the same type | Mean = 14; SD = 7; Range = 4–40 |
| | Silver impregnated | 80 | 103 | | | Mean = 12; SD = 7; Range = 4–38 |
| Ranucci et al, 2003 (40) | Benzalkonium chloride | 277 | | βS+ | 1 | Mean = 9; SD = 6.9; Median = 7; Range = 1–49 |
| | Silver, carbon and platinum | 268 | | | | Mean = 9.1; SD = 6.9; Median = 7 Range = 3–43 |
| Brun-Buisson et al, 2004 (41) | Standard | 175 | NS | βS+ | >1 Of the same type | Mean = 12; SD = 11.7; Median = 9 |
| | CHSS + | 155 | | | | Mean = 10.5; SD = 8.8; Median = 8 |
| Carrasco et al, 2004 (42) | Heparin | 91 | 132 | βS+ | >1 Of the same type | Mean = 13.6 |
| | CHSS | 89 | 128 | | | Mean = 12.7 |
| Hanna et al, 2004 (43) | Standard | 173 | 174 | βXS+ | >1 Of the same type | Mean = 63.01; SD = 30.80 |
| | Minocycline rifampin | 182 | 182 | | | Mean = 66.21; SD = 30.88 |
| Leon et al, 2004 (44) | Standard | 180 | | βS+ | 1 | Mean = 9; SD = 5 |
| | Minocycline rifampin | 187 | | | | Mean = 9; SD = 5 |
| Yücel et al, 2004 (45) | Standard | 105 | | βS+ | 1 | Mean = 6.7; Median = 6; Range = 2–19 |
| | Miconazole and rifampicin | 118 | | | | Mean = 7.5; Median = 6; Range = 2– 36 |

Table 3.—*continued*

| 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; Range = 1–58 |
| | CHSS + | 51 | | | | Mean = 14.3; SD = 8.2; Range = 2–52 |
| Rupp et al, 2005 (47) | Standard | 362 | | βS+ | 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; SD = 4.2 |
| | Silver impregnated | 85 | 160 | | | Mean = 9.3; SD = 4 |
| | CHSS | 70 | 165 | | | Mean = 9.7; SD = 4 |
| Moretti et al, 2005 (49) | Standard | 266 | 266 | βS+ and βS– | 1 | NS |
| | Silver impregnated | 273 | 273 | | | |
| Ostendorf et al, 2005 (50) | Standard | 94 | 94 | αS− | 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 | αS− | NS | Mean = 149.9 hrs; SD = 93.5 hrs; Median = 140 hrs |
| | Minocycline rifampin | — | 319 | | | Mean = 149.4 hrs; SD = 92.5 hrs; Median = 139 hrs |
| Osma et al, 2006 (52) | Standard | 69 | 69 | βS+ | 1 | Mean = 8.9; SD = 4.6; Median = 8; Range = 3–20 |
| | CHSS+ | 64 | 64 | | | Mean = 11.7; SD = 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 | | | 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 infection-control 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

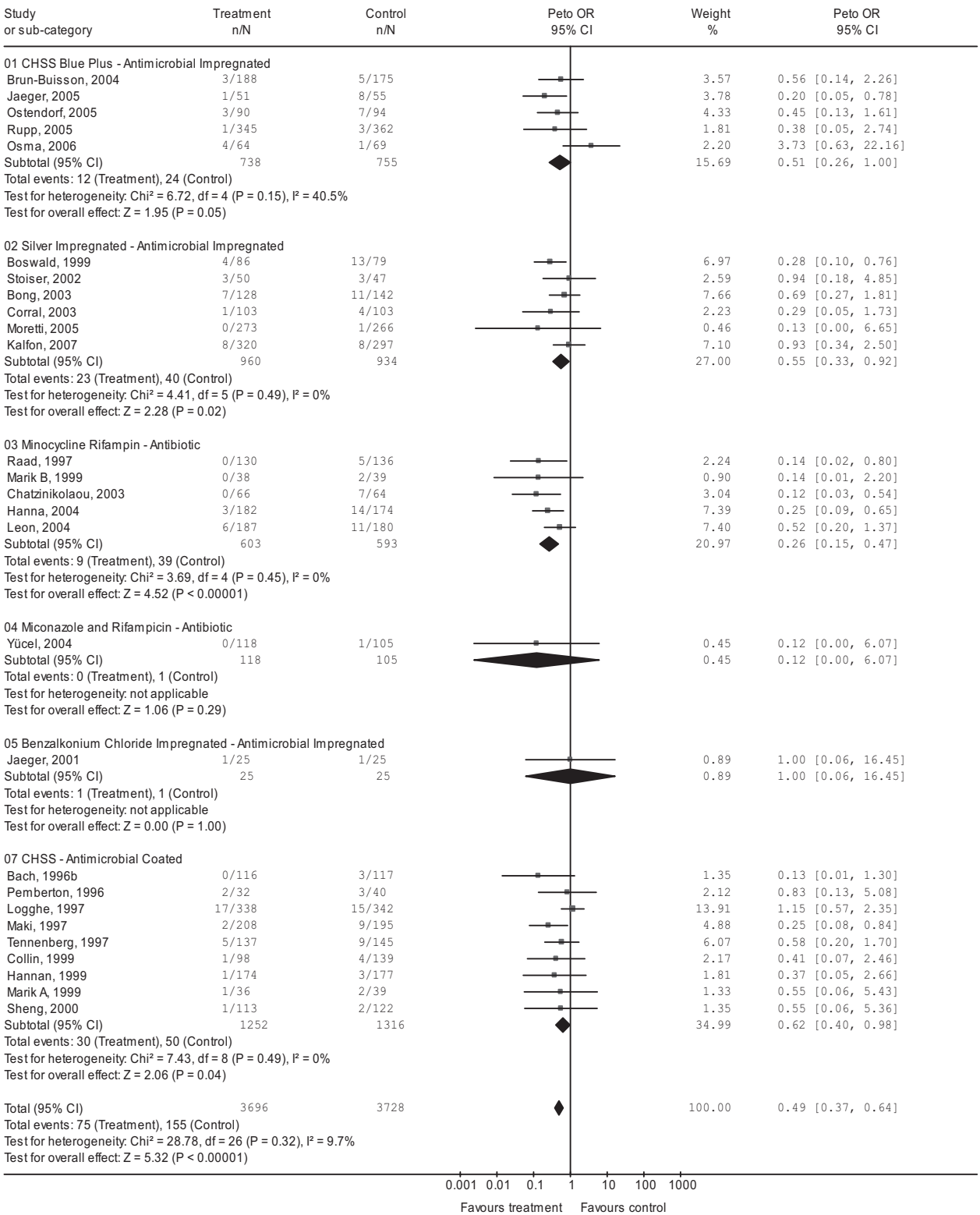


**Figure 2. Catheter-related bloodstream infection rates—subgrouped by different treatment catheters.**

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 infection-control 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-

Table 4. Results of subgroup meta-analyses and sensitivity analyses

| 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 | αS+ | 3 | 25/473 (5.29) | 9/466 (1.93) | 0.39 (0.20, 0.77) |
| | αS− | 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) | 0.42 (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) |
| | 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) | Lower Limit (OR = 0.34) | 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.

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 (cost-effectiveness 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 decision-analytic 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, decision-makers 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.

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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. *Crit Care Med* 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]. *Anaesthesiology* 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. *Intensive Care Med* 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. *J Am Soc Nephrol* 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. *Am Surg* 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. *Peritoneal Dialysis Int* 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. *Infect Control Hosp Epidemiol* 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. *JAMA* 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. *Ann Surg* 1993; 218:206–210 | Cuff vs. 2nd cuff |

**Appendix 1**—*continued*

| 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. *Clin Intensive Care* 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. *Arch Intern Med* 1998; 158:81–87 | Not truly random (randomised by last digit of patients medical records) |
| Kamal GD, Pfaller MA, Rempe LE, et al: Reduced intravascular catheter infection by antibiotic bonding. A prospective, randomized, controlled trial. *JAMA* 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. *Crit Care Med* 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. *Am J Med* 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. *Intensive Care Med* 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. *J Infect Dis* 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. *Crit Care Med* 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. *Gynecol Oncol* 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. *Anaesthesia* 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). *Crit Care Med* 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. *Clin Intensive Care* 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 |

**Appendix 2**—*continued*

| | 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 |