Antimicrobial central venous catheters in adults: a systematic review and meta-analysis

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Several antimicrobial central venous catheters (CVCs) are available. We did a meta-analysis to assess their efficacy in reducing microbial colonisation and preventing catheter-related bloodstream infection (CRBSI). An extensive literature search of articles in any language was undertaken. We assessed randomised clinical trials in which available antimicrobial CVCs were compared with either a standard CVC or another antimicrobial CVC. Outcomes assessed were microbial colonisation of CVCs and CRBSI. The first-generation chlorhexidine–silver sulfadiazine (CSS) CVCs reduce colonisation (odds ratio [OR] 0·51 [95% CI 0·42–0·61]) and CRBSI (OR 0·68 [0·47–0·98]), as do the minocycline–rifampicin CVCs (OR 0·39 [0·27–0·55] and OR 0·29 [0·16–0·52], respectively). The minocycline–rifampicin CVCs outperformed the first-generation CSS CVCs in reducing colonisation (OR 0·34 [0·23–0·49]) and CRBSI (OR 0·18 [0·07–0·51]). Many shortcomings in methodological quality limit our interpretation of the study results. However, the available evidence suggests that use of CSS and minocycline–rifampicin CVCs are useful if the incidence of CRBSI is above institutional goals despite full implementation of infection prevention interventions.

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Introduction

Central venous catheters (CVCs) are used primarily to administer drugs, fluids, and to monitor haemodynamic status. Their use is associated with infections, either localised at the site of insertion or systemic with bloodstream infection and metastatic seeding of distant anatomic sites. Indeed, CVCs are also responsible for the highest proportion of hospital-acquired bacteraemias.[1] Not surprisingly, catheter-related infections are the most common cause of nosocomial endocarditis,[2,3] and have also been reported to increase medical costs and extend hospital stay independently of other confounding variables.[4–8] Many predisposing risk factors have been reported to be independently associated with the development of catheter-related bloodstream infections (CRBSIs), such as the duration of catheterisation, anatomical location of CVC placement, and the receipt of total parenteral nutrition via the CVC.[9–12]

Preventive strategies to reduce the risk of CRBSI include the use of a maximum sterile barrier technique during CVC insertion,[13] chlorhexidine-containing cutaneous antiseptics,[14] educational programmes for health-care workers,[15] comprehensive prevention programmes,[16,17] novel technologies such as chlorhexidine gluconate dressings,[18] catheter hubs containing iodinated alcohol,[19] and the modification of catheter materials.[20–22]

The surfaces of intravascular catheters are ideal for microbial colonisation. After insertion, the catheter surface is conditioned by a film that may include fibrin, fibronectin, fibrinogen, collagen, elastin, thrombospondin, laminin, vitronectin, and von Willibrand's factor.[23] The proteins facilitate the adherence of microorganisms (ie, staphylococcal species) in the biofilm. This biofilm, combined with exopolysaccharide material produced by colonising microorganisms, protects them from chemotherapeutic agents and opsonophagocytosis.[24] Fragments of biofilm may detach and seed the blood with microorganisms.[25]

Antimicrobial agents, such as antiseptics or antibiotics coated onto or incorporated into the catheter polymer, have more recently been used in an attempt to prevent

	Surface activity	Name (manufacturers or distributors)	Availability	
			UK	USA
Silver with platinum and carbon (iontophoretic)	External and internal	Vantex CVC kits (Edwards Life Sciences, Irvine, CA, USA)	Yes	Yes
Silver in a ceramic zeolite matrix (impregnated)	External and internal	Multicath Expert range (Vygon Ltd, Ecouen, France)	Yes	No
First-generation chlorhexidine and silver sulfadiazine	External	ARROWg+ard Blue (Arrow International, Inc, Reading, PA, USA)	Yes	Yes
Second-generation chlorhexidine and silver sulfadiazine	External (plus internal chlorhexidine coating)	ARROWg+ard Blue PLUS (Arrow International, Inc)	Yes	Yes
Benzalkonium chloride	External and internal	Hydrocath Assure (BD Ltd, Franklin Lakes, NJ, USA)	Yes	Yes
Benzalkonium chloride–heparin bonded	External and internal	AMC Thromboshield treatment (Edwards Life Sciences)	Yes	Yes
Minocycline and rifampicin	External and internal	Cook Spectrum (Cook Medical, Inc, Bloomington, IN, USA)	Yes	Yes
Miconazole and rifampicin	External and internal	Multistar (Vygon Ltd)	Yes	No

Table 1: **Types of adult antimicrobial CVC commercially available in the UK and USA**

For the **Cochrane Collaboration handbook** see http://www.cochrane-handbook.org

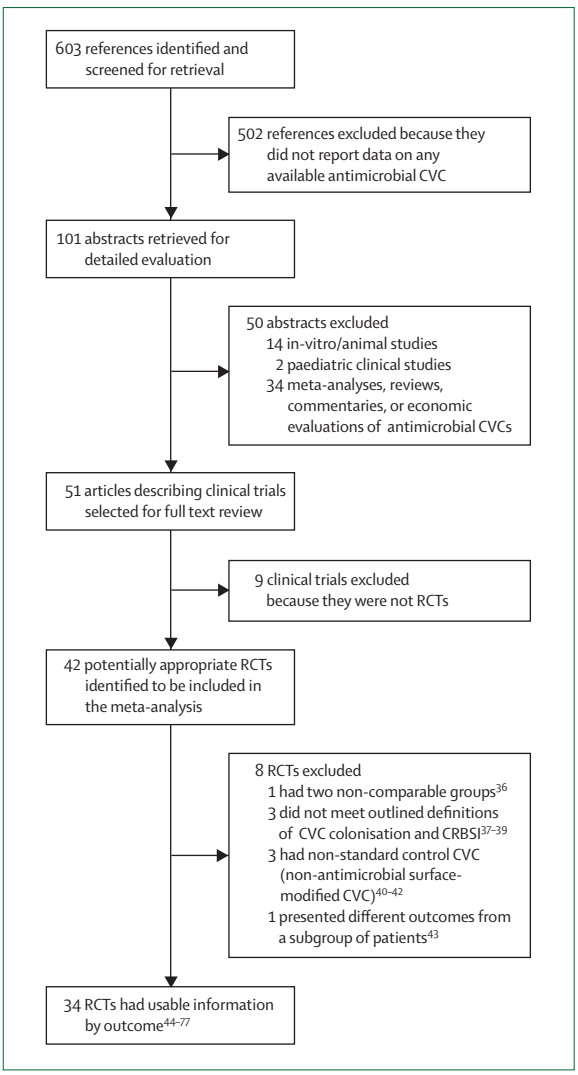

***Figure 1*: Flow chart of RCT identification, inclusion, and exclusion**
CVC=central venous catheter. CRBSI=catheter-related bloodstream infection. RCT=randomised controlled trial.

colonisation and the development of CRBSI. Several antimicrobial CVCs are currently commercially available within the UK and USA (table 1). 238 500 CVCs were issued in England by UK National Health Service Logistics during the 2004–05 financial year. Of these, 10 077 (4·2%) were antimicrobial, 3452 (34%) of which were silver-impregnated CVCs and the remaining 6625 (66%) were coated with chlorhexidine–silver sulfadiazine (CSS). Thus, current use of antimicrobial CVCs in the UK is relatively low. Data on use in the USA are currently unavailable.

The purpose of this meta-analysis was to determine the efficacy of antimicrobial CVCs on the basis of the available data. All adult populations were included in the analysis and potential reductions in CRBSI were determined. As CVC colonisation can be a precursor to CRBSI,[26–28] this endpoint was also considered.

Methods

The QUORUM (quality of reporting of meta-analyses) statement and Cochrane Collaboration handbook were used as guidance for the completion of this meta-analysis.[29,30]

Search strategy

An extensive, unrestricted computerised Medline (1950 to April 12, 2008), Embase (1982 to April 12, 2008), CINAHL (1982 to April 12, 2008), and Cochrane Library literature search of articles in any language was done independently by two reviewers (ALC and TSJE). The following terms were used in various combinations: "central venous catheter", "colonisation", "bacteraemia", "bloodstream infection", "silver", "silver-sulfadiazine", "chlorhexidine", "benzalkonium chloride", "rifampicin", "minocycline", and "miconazole". No special search features were used. The reference lists of the retrieved articles were reviewed for additional studies. Data from abstracts, conference proceedings, and correspondence were included as long as the data were not subsequently duplicated in published articles. Studies lacking data were included if an investigator subsequently provided the required information. Additionally, contact was made with the manufacturers of antimicrobial CVCs to acquire any data not published at the time of the search.

Selection criteria

The inclusion criteria for the meta-analyses consisted of randomised controlled trials (RCTs) in adults of commercially available antimicrobial CVCs (treatment groups) and standard non-surface modified polyurethane or silicone CVCs (control groups). Additionally, trials that compared various commercially available antimicrobial CVCs were included in separate analyses. Data from animal studies were not included.

Catheter colonisation or CRBSI, or both, were the analysis endpoints. Catheter colonisation was defined as microbial growth from a catheter tip or other segment of either at least 15 colony-forming units (CFU) after semi-quantitative culture,[31] or at least 1000 CFU after quantitative vortex culture method,[32] or at least 100 CFU after quantitative sonication and vortex culture method.[33] The Centers for Disease Control and Prevention (CDC) definition of CRBSI was used for this meta-analysis: bacteraemia or fungaemia in a patient with an intravascular catheter with at least one positive blood culture obtained from a peripheral vein and no apparent source for bloodstream infection except for the catheter.[34] Because most studies reported no defined requirements for the presence of clinical symptoms of bloodstream infection, we included studies with or without specification of clinical symptoms. One of the following was also present: a semiquantitative or quantitative culture of the catheter tip with significant growth as noted above, with the same microorganism isolated from the catheter segment and peripheral blood; simultaneous

quantitative blood cultures with at least a five to one ratio of growth from blood drawn from a CVC and peripheral vein, respectively; differential time to blood-culture positivity with growth in the catheter-drawn blood culture detected at least 2 h before growth of the same microorganism in a simultaneously drawn blood culture from a peripheral vein.

Data abstraction

For the analysis, the following data was independently abstracted (by ALC and TSJE): (1) author identification, (2) year of publication, (3) patient groups and study setting, (4) the type of antimicrobial CVCs under investigation, (5) number of CVC lumens, (6) sample size (number of CVCs studied), (7) duration of catheterisation, (8) incidence of colonisation, (9) incidence of CRBSI, (10) whether more than one study CVC per patient was allowed, (11) whether guidewire exchange was allowed, and (12) whether the definition of CRBSI expressly stated the requirement of clinical symptoms. Any disagreements were resolved by discussion.

Quality assessment

After concealment of information about the authors, affiliations, and date and source of manuscript, two authors (ALC and TSJE) independently assessed the methodological quality of the studies under investigation. This included assessment of allocation concealment, blinding, percentage of withdrawals and dropouts, and use of intention-to-treat analysis. Any disagreements were resolved by discussion.

Quantitative data synthesis

All statistical analyses were done with MetAnalysis 1.0 software.[35] Peto odds ratios (ORs) with 95% CIs were calculated for each study that met the entry criteria. The

	Patient group	CVC type	CVC lumen (n)	Mean CVC indwell, per CVC type (days)	More than one study CVC per patient permitted?	Guidewire exchange permitted?	Clinical symptoms of CRBSI required?	Concealment of allocation used?	Study double blind?	Proportion of withdrawals or dropouts	Intention-to-treat analysis reported?
Bach et al (1996)[44]	Cardiac surgery	CSS-1 *vs* standard	2 or 3	7·8 *vs* 7·8	No	No	No	..	..	..	No
Bach et al (1999)[45]	Cardiac surgery	Silver alloy coated *vs* standard	2	4·5 *vs* 2·3	No	Yes	No	..	..	13%	No
Brun-Buisson et al (2004)[46]	ICU	CSS-2 *vs* standard	1 or 2	10·5 *vs* 12·0	Yes	Yes	Yes	..	Yes	8·6%	No
Ciresi et al (1996)[47]	Parenteral nutrition	CSS-1 *vs* standard	3	12·9 *vs* 11·5	Yes	Yes	Yes	..	..	5·4%	No
Chatzinikolaou et al (2003)[48]	Haemodialysis	Minocycline–rifampicin *vs* standard	2	8 *vs* 8	No	No	Yes	Unclear	No	7·1%	No
Collin (1999)[49]	Various	CSS-1 *vs* standard	1, 2, or 3	9·0 *vs* 7·3	Yes	Yes	No	..	..	2·1%	No
Corral et al (2003)[50]	ICU	Silver iontophoretic *vs* standard	3	12 *vs* 14	Yes	Yes	Yes	..	No	19·8%	No
Darouiche et al (1999)[51]	Various	CSS-1 *vs* minocycline–rifampicin	3	8·4 *vs* 8·2	Yes	No	Yes	Yes	No	14·7%	No
Dunser et al (2005)[52]	General and surgical ICU	Silver alloy-coated *vs* CSS-1 *vs* standard	3 or 4	9·3 *vs* 9·7 *vs* 10·7	No	No	NA	..	No	..	No
Fraenkel et al (2006)[53]	ICU	Silver iontophoretic *vs* minocycline–rifampicin	3	6·2 *vs* 6·2	No	No	No	Yes	No	11·1%	No
Goldschmidt et al (1995)[54]	Oncology	Silver alloy-coated *vs* standard	1	13·3 *vs* 12·7	Yes	No	Yes	..	..	12·4%	No
Hanna et al (2004)[55]	Oncology	Minocycline–rifampicin *vs* standard	1 or 2	66·2 *vs* 63·0	Yes	No	Yes	Yes	No	4·0%	No
Hannan et al (1999)[56]	ICU	CSS-1 *vs* standard	3	7·5 *vs* 7·6	Yes	No	No	..	No	..	No
Harter et al (2002)[57]	Haematological malignancy	Silver alloy-coated *vs* standard	1	12·8 *vs* 13·3	Yes	No	Yes	..	..	12·4%	No
Heard et al (1998)[58]	Surgical ICU	CSS-1 *vs* standard	3	8·5 *vs* 9·0	Yes	Yes	Yes	..	..	15·6%	No
Jaeger et al (2001)[59]	Oncology	Benzalkonium chloride *vs* standard	3	14·8 *vs* 19·3	No	No	No	..	No	..	No
Jaeger et al (2005)[60]	Haematological malignancy	CSS-1 *vs* standard	3	14·3 *vs* 16·6	No	No	No	..	No	..	No
Kalfon et al (2007)[61]	Medical, surgical, and polyvalent ICU	Silver impregnated *vs* standard	2 or 3	13·1 *vs* 12·9	Yes	No	No	Unclear	No	19·2%	No

(Continues on next page)

	Patient group	CVC type	CVC lumen (n)	Mean CVC indwell, per CVC type (days)	More than one study CVC per patient permitted?	Guidewire exchange permitted?	Clinical symptoms of CRBSI required?	Concealment of allocation used?	Study double blind?	Proportion of withdrawals or dropouts	Intention-to-treat analysis reported?
(Continued from previous page)											
Leon et al (2004)[62]	ICU	Minocycline–rifampicin *vs* standard	3	10·3 *vs* 10·4	No	No	Yes	Yes	No	21·1%	Yes
Logghe et al (1997)[63]	Haematological malignancy	CSS-1 *vs* standard	..	20 *vs* 20	Yes	No	No	..	..	..	No
Maki et al (1997)[64]	Medical and surgical ICU	CSS-1 *vs* standard	3	6 *vs* 6	Yes	Yes	Yes	Yes	Yes	8·8%	No
Marik et al (1999)[65]	Medical ICU	CSS-1 *vs* minocycline–rifampicin *vs* standard	3	6 *vs* 6 *vs* 6	No	No	Yes	..	No	5·8%	No
Moretti et al (2005)[66]	Variety	Silver iontophoretic *vs* standard	3	6·2 *vs* 6·2	No	No	Yes	..	No	26·5%	No
Osma et al (2006)[67]	Medical and surgical ICU	CSS-1 *vs* standard	3	11·7 *vs* 8·9	No	No	Yes	..	..	0	Yes
Ostendorf et al (2005)[68]	Haematological malignancy	CSS-2 *vs* standard	2	12·2 *vs* 10·8	No	No	No	..	Yes	24·9%	No
Pemberton et al (1996)[69]	Parenteral nutrition	CSS-1 *vs* standard	3	10 *vs* 11	No	No	Yes	..	..	18%	No
Raad et al (1997)[70]	Various	Minocycline–rifampicin *vs* standard	3	6 *vs* 6	Yes	No	Yes	Yes	No	10·7%	No
Ranucci et al (2003)[71]	Medical and surgical	Silver iontophoretic *vs* benzalkonium chloride	2	9·1 *vs* 9·0	No	No	Yes	..	..	10·2%	No
Rupp et al (2005)[72]	ICU	CSS-2 *vs* standard	3	6·9 *vs* 6·7	No	Yes	Yes	Yes	Yes	9·4%	Yes
Sheng et al (2000)[73]	Surgical ICU	CSS-1 *vs* standard	3	9·1 *vs* 8·2	Yes	No	Yes	..	Yes	..	No
Stoiser et al (2002)[74]	Haematology-oncology	Silver impregnated *vs* standard	3	10·5 *vs* 11	No	No	NA	..	..	37%	No
Tennenberg et al (1997)[75]	Medical, surgical, ICU	CSS-1 *vs* standard	2 or 3	5·1 *vs* 5·3	No	No	Yes	..	No	19%	No
van Heerden et al (1996)[76]	ICU	CSS-1 *vs* standard	3	6·6 *vs* 6·8	No	No	NA	..	..	11·5%	No
Yucel et al (2004)[77]	Various	Miconazole–rifampicin *vs* standard	3	7·5 *vs* 6·7	No	No	Yes	Yes	No	29·4%	No

CSS-1=first-generation CVC, coated with chlorhexidine and silver sulfadiazine on the external surface only. CSS-2=second-generation CVC, coated with chlorhexidine and silver sulfadiazine on the external surface and chlorhexidine on the internal surface. ICU=intensive care unit. NA=not applicable. ..=not reported.

Table 2: **Characteristics and quality of RCTs comparing antimicrobial CVC with standard non-antimicrobial catheters or alternative antimicrobial CVC**

rate of CVC colonisation and CRBSI were analysed separately and various pooled ORs were calculated by both the Peto fixed-effects models (FEMs) and the DerSimonian-Laird random-effects models (REMs).[35] The Peto calculation is based on a modification of the Mantel-Haenszel method; the presence of a zero value does not affect the calculation, and no approximation is therefore required.[35] The ORs were plotted in order of increasing test CVC dwell time to observe the effect of duration of catheterisation. The Cochran *Q* statistic and I^2 test were used to assess heterogeneity. I^2 values of 0% indicate no observed heterogeneity whereas larger values indicate increasing heterogeneity. Results of the Peto FEM are quoted unless substantial heterogeneity is present, in which case the results of the DerSimonian-Laird REM are stated.

For clinical relevance, the number needed to treat (NNT) was calculated for each study that assessed the effect of antimicrobial CVC on rates of CRBSI (versus standard CVC) with an estimated OR value of less than 1·0. NNT is calculated as the reverse of the pooled risk difference and in this case indicates the expected number of patients who need to receive the antimicrobial CVC rather than the standard CVC or comparator CVC for one additional patient to avoid CRBSI. The value given is relevant for the characteristics of the studies on which it is calculated (for that particular CVC indwell period and baseline rate of CRBSI). For each antimicrobial CVC type assessed in a minimum of four eligible trials, publication bias was assessed by the generation of funnel plots and associated testing for asymmetry. Additionally, in CVC groups in which ten or more studies were included, Spearman correlation was used to assess whether an association existed between the mean antimicrobial CVC indwell duration and the estimated effect size for CVC colonisation or CRBSI (differences in study sizes were not taken into account).

	Number of CVC studied (per protocol)	Colonisation (per protocol)		Catheter-related bloodstream infection (per protocol)	
		n (%)	Rate (per 1000 CVC days)	n (%)	Rate (per 1000 CVC days)
CSS-1 *vs* standard					
Bach et al (1996)[44]	116 *vs* 117	21 (18·1%) *vs* 36 (30·8%)	23·2 *vs* 39·4	0 *vs* 3 (2·6%)	0 *vs* 3·3
Ciresi et al (1996)[47]	124 *vs* 127	10 (10·9%) *vs* 12 (12·1%)	6·3 *vs* 8·2	8 (8·7%) *vs* 8 (8·1%)	5·0 *vs* 5·5
Collin (1999)[49]	98 *vs* 139	2 (2·0%) *vs* 25 (16·5%)	2·3 *vs* 24·6	1 (1·0%) *vs* 4 (2·9%)	1·1 *vs* 3·9
Hannan et al (1999)[56]	174 *vs* 177	47 (27·2%) *vs* 71 (40·2%)	36·0 *vs* 52·8	1 (0·6%) *vs* 3 (1·7%)	0·8 *vs* 2·2
Heard et al (1998)[58]	151 *vs* 157	60 (39·7%) *vs* 81 (51·6%)	46·7 *vs* 57·3	5 (3·3%) *vs* 6 (3·8%)	3·9 *vs* 4·2
Logghe et al (1997)[63]	338 *vs* 342	..	..	17 (5·0%) *vs* 15 (4·4%)	2·5 *vs* 2·2
Maki et al (1997)[64]	208 *vs* 195	28 (13·5%) *vs* 47 (24·1%)	22·4 *vs* 40·2	2 (1·0%) *vs* 9 (4·6%)	1·6 *vs* 7·7
Osma et al (2006)[67]	64 *vs* 69	14 (21·9%) *vs* 14 (20·3%)	18·7 *vs* 22·8	4 (6·3%) *vs* 1 (1·4%)	5·3 *vs* 1·6
Pemberton et al (1996)[69]	32 *vs* 40	..	..	2 (6·3%) *vs* 3 (7·5%)	6·3 *vs* 6·8
Jaeger et al (2005)[60]	51 *vs* 55	5 (9·8%) *vs* 9 (16·4%)	6·9 *vs* 9·9	1 (2·0%) *vs* 8 (14·5%)	1·4 *vs* 8·8
Sheng et al (2000)[73]	113 *vs* 122	9 (7·1%) *vs* 25 (20·5%)	8·8 *vs* 25	1 (0·8%) *vs* 2 (1·6%)	1·0 *vs* 2·0
Tennenberg et al (1997)[75]	137 *vs* 145	8 (5·8%) *vs* 32 (22·1%)	11·4 *vs* 41·6	5 (3·6%) *vs* 9 (6·2%)	7·2 *vs* 11·7
van Heerden et al (1996)[76]	28 *vs* 26	4 (14·3%) *vs* 10 (38·5%)	21·6 *vs* 56·6	..	..
CSS-1 *vs* minocycline–rifampicin *vs* standard					
Marik et al (1999)[65]	36 *vs* 38 *vs* 39	7 (19·4%) *vs* 4 (10·5%) *vs* 11 (28·2%)	32·4 *vs* 17·5 *vs* 47·0	1 (2·8%) *vs* 0 *vs* 2 (5·1%)	4·6 *vs* 0 *vs* 8·5
Silver alloy coated *vs* CSS-1 *vs* standard					
Dunser et al (2005)[52]	160 *vs* 165 *vs* 160	27 (16·9%) *vs* 12 (7·3%) *vs* 19 (11·9%)	18·1 *vs* 7·5 *vs* 11·9	..	..
CSS-1 *vs* minocycline–rifampicin					
Darouiche et al (1999)[51]	382 *vs* 356	87 (22·8%) *vs* 28 (7·9%)	27·1 *vs* 9·6	13 (3·4%) *vs* 1 (0·3%)	4·1 *vs* 0·3
CSS-2 *vs* standard					
Brun-Buisson et al (2004)[46]	188 *vs* 175	7 (3·7%) *vs* 23 (13·1%)	3·6 *vs* 11·0	3 (1·6%) *vs* 5 (2·9%)	1·5 *vs* 2·4
Ostendorf et al (2005)[68]	90 *vs* 94	11 (12·2%) *vs* 31 (33·0%)	10·0 *vs* 30·5	3 (3·3%) *vs* 7 (7·4%)	2·7 *vs* 6·9
Rupp et al (2005)[72]	384 *vs* 393	32 (9·3%) *vs* 59 (16·3%)	12·1 *vs* 22·4	1 (0·3%) *vs* 3 (0·8%)	0·4 *vs* 1·1
Silver alloy coated *vs* standard					
Bach et al (1999)[45]	34 *vs* 33	9 (26·5%) *vs* 7 (21·2%)	58·8 *vs* 92·2	2 (5·9%) *vs* 2 (6·1%)	13·1 *vs* 26·4
Goldschmidt et al (1995)[54]	120 *vs* 113	54 (45·1%) *vs* 50 (44·2%)	33·8 *vs* 34·8	6 (5·0%) *vs* 10 (8·8%)	3·8 *vs* 7·0
Harter et al (2002)[57]	107 *vs* 93	..*	..	4·7 (5%) *vs* 8 (8·8%)	3·7 *vs* 6·5
Silver iontophoretic *vs* standard					
Corral et al (2003)[50]	103 *vs* 103	29 (28·2%) *vs* 41 (39·8%)	23·5 *vs* 27·7	3·9 (4%) *vs* 1 (1·0%)	3·2 *vs* 0·7
Moretti et al (2005)[66]	252 *vs* 262	61 (24·4%) *vs* 64 (24·5%)	39·0 *vs* 39·4	0 *vs* 1 (0·4%)	0 *vs* 0·6
Silver iontophoretic *vs* benzalkonium chloride					
Ranucci et al (2003)[71]	268 *vs* 277	50 (18·6%) *vs* 82 (29·6%)	20·5 *vs* 32·9	9 (3·3%) *vs* 12 (4·3%)	3·7 *vs* 4·8
Silver iontophoretic *vs* minocycline–rifampicin					
Fraenkel et al (2006)[53]	294 *vs* 280	43 (14·6%) *vs* 25 (8·9%)	23·6 *vs* 14·4	5 (1·7%) *vs* 4 (1·4%)	2·7 *vs* 2·3
Silver impregnated *vs* standard					
Kalfon et al (2007)[61]	320 *vs* 297	47 (14·7%) *vs* 36 (12·1%)	11·2 *vs* 9·4	8 (2·5%) *vs* 8 (2·7%)	1·9 *vs* 2·1
Stoiser et al (2002)[74]	50 *vs* 47	10 (20·0%) *vs* 14 (29·8%)	19·0 *vs* 27·1	..†	..
Minocycline–rifampicin *vs* standard					
Chatzinikolaou et al (2003)[48]	66 *vs* 64	13 (19·7%) *vs* 16 (25·0%)	24·6 *vs* 31·3	0 *vs* 1 (4·7%)	0 *vs* 2·0
Hanna et al (2004)[55]	182 *vs* 174	..	..	3 (1·6%) *vs* 14 (8·0%)	0·2 *vs* 1·3
Leon et al (2004)[62]	187 *vs* 180	20 (10·7%) *vs* 45 (25·0%)	10·4 *vs* 24·0	6 (3·2%) *vs* 11 (6·1%)	3·1 *vs* 5·9
Raad et al (1997)[70]	130 *vs* 136	11 (8·5%) *vs* 36 (26·5%)	14·1 *vs* 44·1	0 *vs* 7 (5·1%)	0 *vs* 8·6
Benzalkonium chloride *vs* standard					
Jaeger et al (2001)[59]	25 *vs* 25	4 (16·0%) *vs* 4 (16·0%)	10·8 *vs* 8·3	1 (4·0%) *vs* 1 (4·0%)	2·7 *vs* 2·1
Miconazole–rifampicin *vs* standard					
Yucel et al (2004)[77]	118 *vs* 105	6 (5·1%) *vs* 38 (36·2%)	6·8 *vs* 54·0	0 *vs* 0	0 *vs* 0

CSS-1=first-generation CVC, coated with chlorhexidine and silver sulfadiazine on the external surface only. CSS-2=second-generation CVC, coated with chlorhexidine and silver sulfadiazine on the external surface and chlorhexidine on the internal surface. ..=no data. *Data between two study groups were unclear. †Meta-analysis definition for CRBSI not used in study.

Table 3: **Incidence of colonisation and CRBSI in studies comparing antimicrobial CVCs with standard non-antimicrobial and other antimicrobial CVCs**

Results

603 potentially relevant references were initially identified by our search (figure 1). Most of these references were excluded because they did not report on RCTs that assessed colonisation or CRBSI rates associated with the use of any available antimicrobial CVC in adults. Of 42 RCTs identified, eight were excluded from the analysis,[36–43] leaving 34 studies eligible for inclusion (table 2).[44–77] Of these studies, two compared three types of CVC.[52,65] This resulted in 29 comparisons of antimicrobial CVCs and standard CVCs for colonisation,[44–50,52,54,56,58–62,64–68,70,72–77] and CRBSI outcomes.[44–50,54–70,72,73,75] Additionally, colonisation was assessed in five direct comparisons of antimicrobial CVC,[51–53,65,71] four of which also analysed CRBSI.[51,53,65,71]

There was substantial clinical heterogeneity between the studies in setting and patient group, numbers of lumen in experimental CVC, and mean CVC indwell period. Indeed, studies included oncology, haemato-oncology, surgical, medical, and haemodialysis patients, those receiving parenteral nutrition, and those located in intensive care units. The types of CVC used in each study varied from single to triple lumen, with some studies including up to three types. The mean duration of antimicrobial CVC placement ranged from 4·5 days to 66·2 days. More than one study CVC per patient was allowed in 15 studies, and guidewire exchange was allowed in eight RCTs (table 2). Of 31 RCTs assessing CRBSI, ten did not report the requirement of clinical symptoms for the diagnosis to be made (table 2). The sample sizes and rates of colonisation and CRBSI in each study are summarised in table 3. There was substantial variation in sample size (range 50–777 CVCs), and baseline incidence of colonisation and CRBSI on a per-protocol basis ranged from 11% to 52% and 0% to 14·5%, respectively.

The quality of the 34 RCTs included in the analysis is summarised in table 2. Appropriate allocation concealment was described in only eight RCTs (table 2). In the 26 remaining studies, allocation concealment was either not clear or not reported. Only five studies were double blinded.[46,64,68,72,73] In the remaining 29 studies, blinding was either not reported or inadequate for various reasons, such as differences in CVC appearance. Data on the percentage of withdrawals and dropouts was not reported in seven studies (table 2). In the remaining 27 RCTs, reported dropouts ranged between zero and 37%. Of the 34 included trials, only three provided an intention-to-treat analysis.[62,67,72]

Because so few studies provided intention-to-treat analysis, and details of withdrawals and dropouts were absent in some studies, the pooled data was analysed on a per-protocol basis. Estimated OR (95% CI) for each trial that compared antimicrobial CVCs with standard CVCs with regard to colonisation and CRBSI are shown in figure 2 and figure 3. Pooling of all trials indicated a reduction in colonisation with the use of antimicrobial CVCs (REM OR 0·54 [95% CI 0·43–0·67]). Possible publication bias was detected by funnel plot and associated asymmetry test (p=0·04). The pooled data also showed a reduction in CRBSI with the use of antimicrobial CVCs (FEM OR 0·58 [0·45–0·75]; NNT=77). No significant publication bias was detected during this analysis (p=0·06).

Minor increases in estimates of effectiveness for CRBSI were noted if the following studies were excluded (table 4): those allowing the use of more than one study CVC per patient, those allowing guidewire exchange, those not reporting the requirement of clinical symptoms for the diagnosis of CRBSI, and those whereby withdrawals and dropouts were more than 15% or not reported. Additionally, minor decreased estimates of effectiveness for CRBSI were noted when studies that reported the use of concealment of allocation or double blinding were excluded (table 4). The different types of antimicrobial CVC may vary widely in their target for preventing infection and their efficacy. Therefore, each antimicrobial CVC is considered separately.

Silver has broad-spectrum antimicrobial activity with few toxic effects.[78] However, it has greater antimicrobial activity against Gram-negative than against Gram-positive microorganisms.[79] Silver ions inhibit replication by binding to microbial DNA, and also deactivate metabolic enzymes after binding to their sulfhydryl groups.[80] Several types of silver CVC are available (table 1). In our pooled analyses, neither silver-alloy-coated, silver-iontophoretic, nor silver-impregnated CVCs showed any significant reduction in colonisation or CRBSI by comparison with standard CVCs (figures 2 and 3).

The most extensively studied antimicrobial CVCs are those coated with CSS. These antiseptics act synergistically against microorganisms. Chlorhexidine disrupts the microbial cytoplasmic membrane, thus facilitating the uptake of silver ions, which subsequently bind to the DNA and prevent replication.[21] These CVCs were originally marketed with both antimicrobial agents on the external surface only, remaining effective for up to 15 days.[81] Substantial cost savings have been associated with their use in high-risk patients.[82] With longer CVC duration, intraluminal microbial colonisation and migration may be of greater relevance, thereby limiting the efficacy of these first-generation CSS CVCs in such circumstances.[81] A second-generation CSS CVC is now available, which has a three times higher concentration of chlorhexidine, with silver sulfadiazine on the external surface and chlorhexidine on the intraluminal surface of the CVC, extension sets, and hubs.[72]

13 eligible trials that assessed CVC colonisation associated with the first-generation CSS CVC contributed 1465 first-generation CSS CVCs and 1528 standard CVCs for estimation of pooled effects (figure 2). A reduction in colonisation was shown with these antimicrobial CVCs (FEM OR 0·51 [0·42–0·61]). Possible publication bias was not detected by the funnel plot and associated asymmetry test (p=0·24).

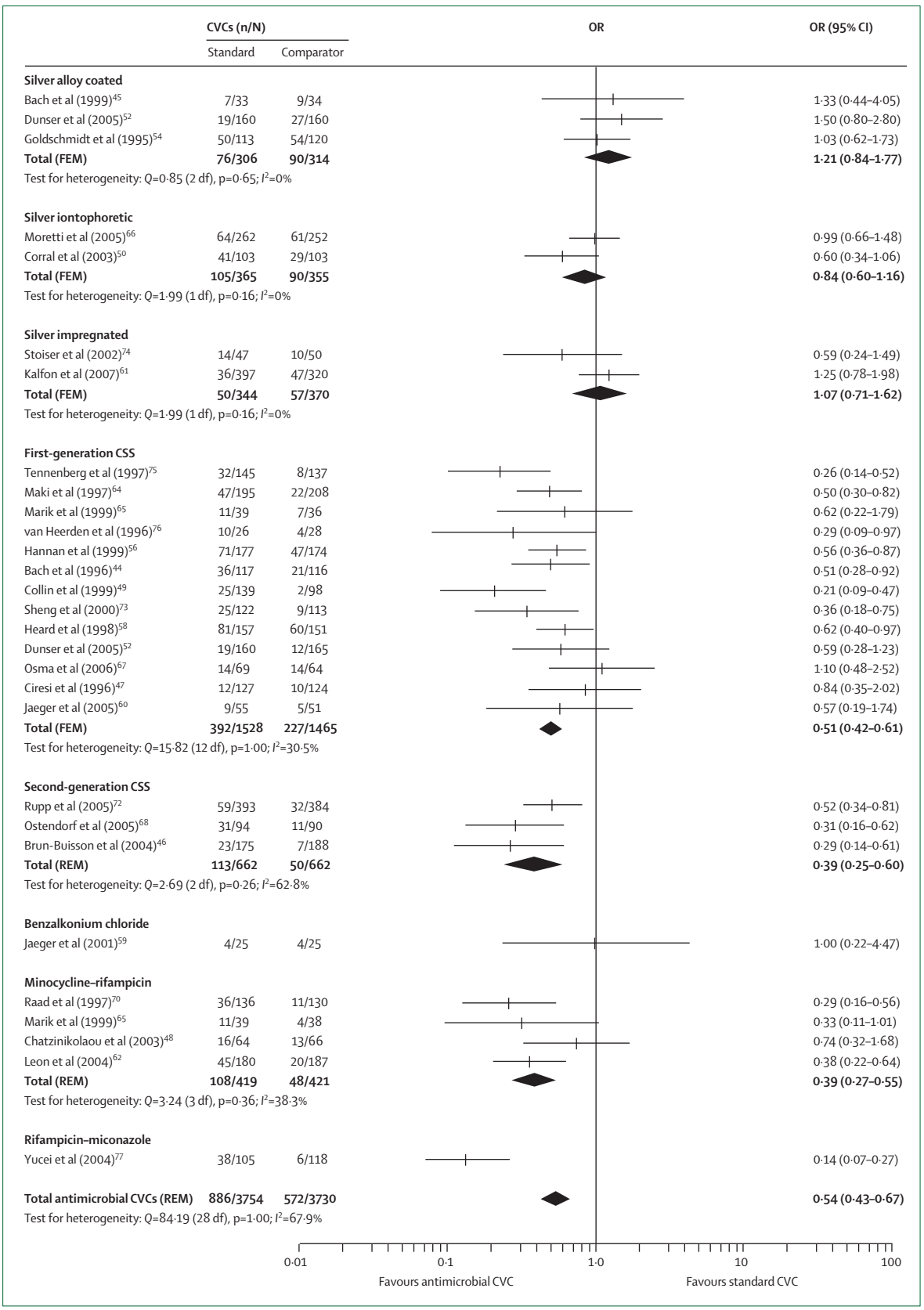

***Figure 2*: CVC colonisation in trials comparing antimicrobial CVCs with standard CVCs**
Within each subgroup, the studies are ordered by increasing mean catheter indwell duration. The vertical line represents the null hypothesis of no difference between test and control groups. Odds ratios (ORs) and 95% CIs are shown. Black diamonds indicate the pooled ORs (95% CIs). Results of the Peto fixed-effects model (FEM) are quoted unless substantial heterogeneity is present, in which case results of the DerSimonian-Laird random-effects model (REM) are stated.

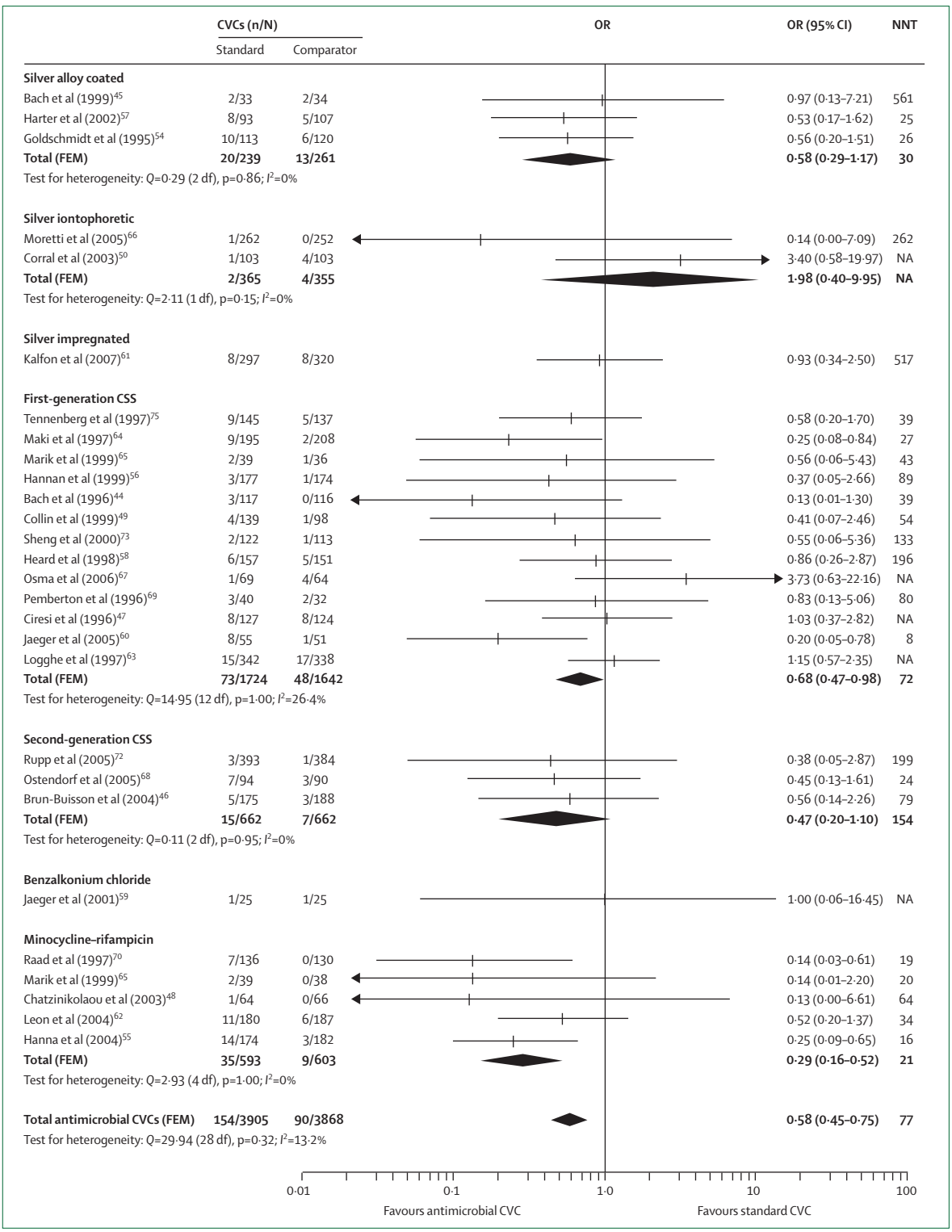

***Figure 3*: CRBSI in trials comparing antimicrobial CVCs with standard CVCs**
Within each subgroup, the studies are ordered by increasing mean catheter indwell duration. The vertical line represents the null hypothesis of no difference between test and control groups. Odds ratios (ORs) and 95% CIs are shown. Black diamonds indicate the pooled ORs (95% CIs). Results of the Peto fixed-effects model (FEM) are quoted unless substantial heterogeneity is present, in which case the results of the DerSimonian-Laird random-effects model (REM) are stated. NNT=number needed to treat (the expected number of people who need to receive the antimicrobial rather than the standard CVC for one additional person to avoid CRBSI). NA=not applicable (if the estimated OR is ≥1·0).

Additionally, a reduction in the incidence of CRBSI was shown after pooling of data of 1642 first-generation CSS CVCs and 1724 standard CVCs from 13 studies that assessed this outcome (FEM OR 0·68 [0·47–0·98]; NNT=72; figure 3). Possible publication bias was not detected by the funnel plot and associated asymmetry test (p=0·06). The observed reduction in colonisation decreased with extended duration of catheterisation (Spearman r_s=–0·52; p=0·07), as did the observed reduction in the CRBSI rate (Spearman r_s=–0·43; p=0·14), although neither correlation was significant.

Three trials assessed the rates of colonisation and CRBSI associated with the use of the second-generation CSS CVCs.[46,68,72] 662 CVCs were available in each group for analysis of both outcomes. A significant reduction in CVC colonisation was seen (REM OR 0·39 [0·25–0·60]; figure 2). However, the reduction in CRBSI was not significant (FEM OR 0·47 [0·20–1·10]; NNT=154).

Benzalkonium chloride is a quaternary ammonium compound that inhibits membrane function and DNA replication,[21] and has a more pronounced antimicrobial activity against Gram-positive than Gram-negative bacteria.[83] This antiseptic has been bound to negatively charged heparin in anti-thrombogenic catheters.[20] Catheters have also been coated with benzalkonium chloride suspended in Hydromer gel (Hydromer, Inc, Branchburg, NJ, USA). Only one study on benzalkonium chloride CVCs met the selection criteria.[59] 25 patients were included in each group. This CVC failed to show a decrease in the occurrence of colonisation or CRBSI (figure 2 and figure 3).

Four eligible trials assessed colonisation associated with minocycline–rifampicin CVCs (figure 2). A reduction in colonisation was shown with such antimicrobial CVCs (FEM OR 0·39 [0·27–0·55]). Possible publication bias for colonisation data was not detected by the funnel plot and associated asymmetry test (p=0·84). Additionally, a reduction in the incidence of CRBSI was shown after pooling of data from five studies that assessed this outcome (FEM OR 0·29 [0·16–0·52]; NNT=21; figure 3). Possible publication bias for CRBSI data was not detected by the funnel plot and associated asymmetry test (p=0·2).

In one clinical trial, minocycline–rifampicin CVCs left in situ for a mean of 66 days were associated with a significant reduction in CRBSI.[55] The antimicrobial durability of minocycline–rifampicin silicone CVCs may therefore extend beyond 4 weeks.[84] These CVCs have also been shown to be cost effective for patients catheterised for more than 1 week.[85]

Rifampicin–miconazole CVCs have been shown to be more efficacious than CSS CVCs in vitro, and the half-life of inhibitory activity of the former exceeded 3 weeks.[77,86,87] Serum concentrations of rifampicin and miconazole during clinical use are low.[87] In the only trial that assessed the efficacy of this CVC, reduced colonisation was seen (OR 0·14 [0·07–0·27]).[77] No patients developed CRBSI.

	Model	Pooled OR (95% CI)	Heterogeneity (I^2)	Studies excluded (references)
No studies excluded	FEM	0·58 (0·45–0·75)	13·2%	..
More than one study CVC per patient	FEM	0·50 (0·32–0·78)	0%	46,47,49,50, 54–58,61,63,64, 70,73
Guidewire exchange allowed	FEM	0·54 (0·40–0·73)	17·7%	45–47,49,50,58, 64,72
Did not report requirement of clinical symptoms for the diagnosis of CRBSI	FEM	0·53 (0·39–0·73)	16·7%	44,45,49,56, 59–61,63,68
Withdrawals and dropouts >15% or not reported	FEM	0·47 (0·32–0·68)	19·0%	44,50,56,58–63, 66,68,69,73,75,77
Reported use of allocation concealment	FEM	0·71 (0·53–0·95)	0%	55,62,64,70,72,77
Reported double blinding	FEM	0·62 (0·47–0·82)	23·7%	46,64,68,72,73

FEM=fixed-effects model.

Table 4: **Comparison of CRBSI when certain studies are excluded from the meta-analysis**

Table 5 shows the comparisons between non-standard CVCs. One trial found that the use of first-generation CSS CVCs resulted in a lower incidence of colonisation than silver-alloy-coated CVCs, although this trial did not assess CRBSI.[52] However, first-generation CSS CVCs were found to be substantially less effective than minocycline–rifampicin CVCs in two studies.[51,65] Silver-iontophoretic CVCs were compared with minocycline–rifampicin CVCs in one study.[53] A reduction in colonisation was seen with the use of minocycline–rifampicin CVCs, although no reduction in CRBSI was shown. Silver-iontophoretic CVCs were associated with a lower rate of colonisation compared with benzalkonium-chloride-coated CVCs in one study.[71] However, no significant difference in CRBSI was shown.[71]

Discussion

The pooled results from all trials that assessed the effect of antimicrobial CVCs versus standard CVCs showed a reduction in colonisation and CRBSI. However, results varied between different antimicrobial CVCs. The meta-analysis indicated that silver-alloy-coated CVCs did not reduce colonisation nor CRBSI. Additionally, no reduction in colonisation or CRBSI was shown with either silver-impregnated or silver-iontophoretic CVCs. Silver-alloy-coated and iontophoretic CVCs were also inferior to first-generation CSS CVCs and minocycline–rifampicin CVCs, but not to benzalkonium chloride CVCs. On the basis of these results, the overall efficacy of silver-based CVCs has not been proven.

However, the use of first-generation and second-generation CSS CVCs significantly reduces catheter colonisation. Use of first-generation CSS CVCs significantly reduced the incidence of CRBSI. Use of second-generation CSS CVCs also resulted in a reduction in the incidence of CRBSI, although this did not reach significance. One possible explanation for this finding is

	Number of CVCs in each group	OR (95% CI)		NNT (for CRBSI)	References
		Colonisation	CRBSI		
CSS-1 *vs* silver alloy coated	165 *vs* 160	0·40 (0·21–0·79)	..	..	52
Minocycline–rifampicin *vs* CSS-1*	394 *vs* 418	0·34 (0·23–0·49)	0·18 (0·07–0·51)	32	51,65
Minocycline–rifampicin *vs* silver iontophoretic	280 *vs* 294	0·58 (0·35–0·96)	0·84 (0·22–3·13)	367	53
Silver iontophoretic *vs* benzalkonium chloride	268 *vs* 277	0·55 (0·37–0·82)	0·77 (0·32–1·84)	103	71

CSS-1=first-generation CVC, coated with chlorhexidine and silver sulfadiazine on the external surface only. NNT=number needed to treat to prevent one patient with CRBSI.
*Meta-analysis of both studies by fixed-effects model (no significant heterogeneity: I^2=0% for both comparisons).

***Table 5*: Comparisons between different non-standard CVCs**

that analyses of second-generation CSS were underpowered because they were done more recently than studies of the original CVC, and during this time the overall incidence of CRBSI has decreased because of other infection prevention strategies.[16,88]

Two factors need to be considered before CSS CVCs are selected for use. First, hypersensitivity reactions associated with chlorhexidine-containing CVCs, albeit infrequent, have been reported in the UK and Japan, and may be associated with genetic predisposition or previous exposure to chlorhexidine-containing products.[21] Second, limited antimicrobial activity of CSS CVCs against *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and *Enterobacter cloacae* has been shown in vitro.[65,89,90] However, in-vivo resistance to chlorhexidine or silver sulfadiazine associated with the use of CSS CVCs has not been reported.[64,72,82]

The benzalkonium chloride CVC was assessed in one study in which no significant reduction in the rate of colonisation nor CRBSI were observed. Limited antimicrobial activity of benzalkonium chloride CVCs against *Candida albicans*, *Escherichia coli*, and *Klebsiella pneumoniae*, and complete inactivity against *Pseudomonas aeruginosa* has been shown in vitro.[20] Further clinical trials of these devices are needed because the only study was underpowered.

Minocycline–rifampicin CVCs reduce the risk of both colonisation and CRBSI. The combination of minocycline and rifampicin is active against many Gram-positive and Gram-negative bacteria. However, this combination of antibiotics has limited activity against *P aeruginosa* in vitro. In two studies, this antimicrobial CVC was associated with a significant increase in *Candida* spp colonisation.[62,91] Again, these findings need to be taken into consideration when selecting an antimicrobial CVC for use in patients at particular risk of candida infection. With regard to the possibility of the emergence of resistance to minocycline and rifampicin, one study showed that staphylococcal isolates recovered over 4 years from the blood and CVC tip cultures of pre-engraftment bone-marrow-transplant patients with the minocycline–rifampicin CVC remained highly susceptible to both antibiotics.[92] Conversely, another study reported increased rifampicin resistance in coagulase-negative staphylococci in an intensive care unit associated with the use of these catheters.[93] In-vitro resistance of Gram-positive cocci to the combination of minocycline and rifampicin has also been reported.[91,92,94] If these CVCs are used, close monitoring for the development of resistance is required.

Minocycline–rifampicin CVCs outperformed first-generation CSS CVCs. The reason for the superior activity of the minocycline–rifampicin CVCs in these studies might relate to the fact that the minocycline–rifampicin CVC is active intraluminally and extraluminally, whereas the first-generation CSS CVCs are only active externally. However, the superior efficacy of the intraluminally and extraluminally coated second-generation CSS CVCs over the first-generation CSS CVCs has yet to be shown. This might suggest that the superior efficacy of the minocycline–rifampicin CVC is more dependent on the type of antimicrobial agents used.

Rifampicin–miconazole CVCs significantly reduced catheter colonisation. Similar to the minocycline–rifampicin CVCs, the reduced antimicrobial activity of rifampicin–miconazole CVCs against *C albicans*, *P aeruginosa*, *Enterobacter* spp, and *E coli* has been shown in vitro.[86] However, the only clinical assessment of this CVC to date did not show any evidence of reduced activity against these microorganisms.[77] Further clinical assessments are required to address this issue and the role of this CVC in prevention of CRBSI.

One concern about the validity of results from clinical trials on the prevention of CRBSI is the criteria used to make the diagnosis. The CDC's guideline of "no apparent source for bloodstream infection except for the catheter" may mean that some investigators will search more vigorously for a source than will others.[34] This could account in part for the wide variation between studies in the incidence of baseline CRBSI in similar patient populations. For this reason, future RCTs should determine total bloodstream infection rates per 1000 days in addition to CRBSI. Total bloodstream infection rates were only assessed in three studies included in our meta-analysis.[63,64,72]

Additionally, steps to exclude the possibility of contamination with skin microflora and to confirm that

any bloodstream infection was truly catheter related were rarely undertaken. This investigation may be aided by the use of molecular typing of microorganisms recovered, again not done in most of these studies. Furthermore, the high risk of contamination with microorganisms such as coagulase-negative staphylococci suggests that the presence of clinical symptoms of CRBSI is crucial for diagnosis. Some studies did not report the presence of clinical symptoms to support the diagnosis. A minor increased estimate of effectiveness for CRBSI was seen when such studies were excluded. However, we could not determine whether this omission was simply an oversight during manuscript preparation. Indeed, in clinical practice, most blood cultures would only normally be ordered for patients with clinical symptoms. The CDC guidelines for the diagnosis of CRBSI are by no means definitive, although they are used widely, providing the most suitable outcome measure currently for such studies.

We noted substantial variation in methodological quality in the studies included in this meta-analysis. Indeed, allocation concealment, double blinding, intention-to-treat analysis, and low rates of withdrawals and dropouts were infrequently reported. We found that a lack of allocation concealment and lack of double-blinding resulted in minor reductions in the estimate of effectiveness. Exclusion of studies with high rates of withdrawals and dropouts resulted in an increased estimate of effectiveness. Additionally, many studies were confounded by the inclusion of more than one CVC per patient and the use of guidewire exchange. This latter scenario might result in differing effect sizes because subsequent CVC insertions may put the patient at higher risk of infection. When we excluded studies that allowed the use of more than one test CVC per patient or guidewire exchange, we noted a minor increase in estimate of effect size. In a study that investigated the relation between methodological trial quality and the effects of antimicrobial CVCs, the quality of the studies seemed to have no effect on the outcome.[95] Indeed, whereas the exclusion of studies of lower quality in our meta-analysis resulted in minor differences in the estimates of effectiveness, the trends associated with the use of antimicrobial CVCs were still evident. Whether variation in definitions of CRBSI, a lack of reporting on comorbidities and associated interventions, and general study quality are sufficient reasons to question the evidence has long been debated.[96–99] Indeed, the inclusion of patients who have more than one intravascular device in situ or have undergone guidewire exchange has been suggested to bias study results more toward the null hypothesis rather than toward the alternative hypothesis.[99] One further potential quality issue about the assessment of colonisation of antimicrobial CVCs and CRBSI is the general lack of reporting of whether a neutraliser was used to mitigate carry-over of the antimicrobial agent into the culture medium. This should be considered in further trials.

The sub-optimum quality of many studies that assessed antimicrobial CVCs constrains our interpretation of the data in ways that cannot be overcome by meta-analysis. Additionally, quality indicators are often not reported. We acknowledge these serious shortcomings; however, this should not circumvent the establishment of recommendations on the use of such devices in defined circumstances. The driver for such an approach is the importance of intravascular catheters as a major cause of sepsis. As such, the use of either the CSS or minocycline–rifampicin CVCs may be considered when baseline incidence of CRBSI is above institutional goals despite adherence to basic infection prevention measures. The minocycline–rifampicin CVC is preferred when long periods of catheterisation are expected. In such scenarios, robust monitoring of microbial sensitivity to the agents used in these CVCs and the incidence of any adverse events should be undertaken. The use of other antimicrobial CVCs cannot be recommended until further large, high quality studies are undertaken.

The English epic (evidence-based practice in infection control) guidelines recommend the use of an antimicrobial CVC for adult patients at increased risk of CRBSI who require central venous access for 1–3 weeks.[100] By comparison, the CDC's Hospital Infection Control Practices Advisory Committee recommend the use of antimicrobial CVC in adults whose catheter is expected to remain in situ for greater than 5 days and who are being cared for in a hospital unit in which the CRBSI rate is above the goal set by the individual institution despite implementing a comprehensive strategy to reduce infection rates.[34] The use of CSS and minocycline–rifampicin CVCs might also be cost effective if used for patients in intensive care units in whom the incidence of CRBSI is above the tenth percentile according to published data and only after other interventions have been undertaken to reduce the risk of infection.[34]

Despite the quality of many of the studies assessed in this meta-analysis, the results substantiate the approach taken by the epic and CDC guidelines, and recently by a compendium.[101]

Search strategy and selection criteria

These are described in detail in the Methods section.

For more on the **epic initiative** see http://www.epic.tvu.ac.uk

Conflicts of interest

LAM has received research support from Angiotech and served as a Consultant for CorMedix, Cadence Pharmaceuticals, and Ash Access Technology Inc. TSJE has received research support from Enturia Inc and Baxter Healthcare Ltd. ALC and PN have no conflicts of interest to declare.

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