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[Intervention Review]

Antimicrobial lock solutions for preventing catheter-related infections in haemodialysis

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ABSTRACT

Background

Patients undergoing haemodialysis (HD) through a central venous catheter (CVC) are exposed to several risks, being a catheter-related infection (CRI) and a CVC lumen thrombosis among the most serious. Standard of care regarding CVCs includes their sealing with heparin lock solutions to prevent catheter lumen thrombosis. Other lock solutions to prevent CRI, such as antimicrobial lock solutions, have proven useful with antibiotics solutions, but not as yet for non–antibiotic antimicrobial solutions. Furthermore, it is uncertain if these solutions have a negative effect on thrombosis incidence.

Objectives

To assess the efficacy and safety of antimicrobial (antibiotic, non-antibiotic, or both) catheter lock solutions for preventing CRI in participants undergoing HD with a CVC.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register up to 18 December 2017 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal, and ClinicalTrials.gov.

Selection criteria

We included all randomised or quasi-randomised control trials (RCTs) comparing antimicrobial (antibiotic and non-antibiotic) lock solutions to standard lock solutions, in participants using a CVC for HD, without language restriction.

Data collection and analysis

Two authors independently assessed studies for eligibility, and two additional authors assessed for risk of bias and extracted data. We expressed results as rate ratios (RR) per 1000 catheter-days or 1000 dialysis sessions with 95% confidence intervals (CI). Statistical analyses were performed using the random-effects model.

Main results

Thirty-nine studies, enrolling 4216 participants, were included in this review, however only 30 studies, involving 3392 participants, contained enough data to be meta-analysed. Risk of bias was low or unclear for most domains in the majority of the included studies.

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Studies compared antimicrobial lock solutions (antibiotic and non-antibiotic) to standard sealing solutions (usually heparin) of the CVC for HD. Fifteen studies used antibiotic lock solutions, 21 used non-antibiotic antimicrobial lock solutions, and 4 used both (antibiotic and non-antibiotic) lock solutions. Studies reported the incidence of CRI, catheter thrombosis, or both.

Antimicrobial lock solutions probably reduces CRI per 1000 catheter-days (27 studies: RR 0.38, 95% CI 0.27 to 0.53; I^2 = 54%; low certainty evidence), however antimicrobial lock solutions probably makes little or no difference to the risk of thrombosis per 1000 catheter days (14 studies: RR 0.79, 95% CI 0.52 to 1.22; I^2 = 83%; very low certainty evidence). Subgroup analysis of antibiotic and the combination of both lock solutions showed that both probably reduced CRI per 1000 catheter-days (13 studies: RR 0.30, 95% CI: 0.22 to 0.42; I^2 = 47%) and risk of thrombosis per 1000 catheter-days (4 studies: RR 0.26, 95% CI: 0.14 to 0.49; I^2 = 0%), respectively. Non-antibiotic antimicrobial lock solutions probably reduced CRI per 1000 catheter-days for tunnelled CVC (9 studies: RR 0.60, 95% CI 0.40 to 0.91) but probably made little or no difference with non-tunnelled CVC (4 studies: RR 0.93, 95% CI 0.48 to 1.81). Subgroup analyses showed that antibiotic (5 studies: RR 0.76, 95% CI 0.42 to 1.38), non-antibiotic (8 studies: RR 0.85, 95% CI 0.44 to 1.66), and the combination of both lock solutions (3 studies: RR 0.63, 95% CI 0.22 to 1.81) made little or no difference to thrombosis per 1000 catheter-days compared to control lock solutions.

Authors' conclusions

Antibiotic antimicrobial and combined (antibiotic-non antibiotic) lock solutions decreased the incidence of CRI compared to control lock solutions, whereas non-antibiotic lock solutions reduce CRI only for tunnelled CVC. The effect on thrombosis incidence is uncertain for all antimicrobial lock solutions. Our confidence in the evidence is low and very low; therefore, better-designed studies are needed to confirm the efficacy and safety of antimicrobial lock solutions.

PLAIN LANGUAGE SUMMARY

Antimicrobial lock solutions for preventing infections in patients using a catheter for haemodialysis

What is the issue?

Most of the people presenting end-stage kidney disease use haemodialysis (HD) to replace kidney function. Frequently, a central venous catheter (CVC) is needed to begin HD. In between HD sessions, the CVC needs a sealing solution to avoid catheter thrombosis (an obstruction due to clots), and this is frequently heparin.

In addition to catheter thrombosis, another frequent complication is catheter-related infection (CRI). CRI originates in the catheter and then spreads to the blood or other organs.

Heparin prevents clot formation but does not prevent infections. Therefore, instead of heparin, the use of sealing solutions that can reduce CRIs has been proposed. These antimicrobial lock solutions could be divided into antibiotic (e.g. vancomycin) and non-antibiotic (e.g. citrate) solutions. Antimicrobial lock solutions should fill the catheter lumen and then be locked in the catheter during in-between HD sessions with or without heparin.

What did we do?

We did a systematic review to assess the question whether antimicrobial (antibiotic or non-antibiotic) lock solutions were better than heparin to prevent CRIs in patients undergoing HD through a CVC and thrombosis compared to heparin. We searched the literature up until 18 December 2017 and identified 39 studies enrolling 4216 patients that met our inclusion criteria.

What did we find?

We included 39 studies, including 3,945 participants undergoing HD through a CVC. The studies compared CVC sealing solutions with heparin to antimicrobial lock solutions. Fifteen studies used only antibiotic lock solutions, 21 used non-antibiotic lock solutions, and 4 used both (antibiotic and non-antibiotic) lock solutions. Studies measured the incidence of CRIs and catheter thrombosis, or both. Overall quality of the studies was low for CRIs and very low for thrombosis. There was no information on funding sources for most of the studies.

In general antimicrobial lock solutions are likely superior to standard solutions in preventing CRIs among patients undergoing HD through a CVC, but non-antibiotic solutions did not prove to reduce CRI. They are no worse than heparin at preventing thrombosis. Other adverse effects were not reported in most studies. Our confidence in these results is low due to the quality of the studies.

Conclusion

Some antimicrobial (antibiotic and the combination of antibiotic-non antibiotic) lock solutions decrease the incidence of CRIs compared to heparin. Their effect on CVC permeability remains unclear. The quality of the studies is low and very low, respectively; therefore, more studies are needed to confirm the benefits and harms of antimicrobial lock solutions.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antimicrobial lock solutions vs control for preventing catheter-related infections in patient undergoing haemodialysis

Antimicrobial lock solutions vs control for preventing catheter-related infections in patient undergoing haemodialysis

Patient or population: CVC-related infection
Setting: haemodialysis therapy
Intervention: antimicrobial lock solutions
Comparison: heparin and other lock solutions

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with heparin and other lock solutions	Risk with antimicrobial lock solutions				
CVC - related infections assessed with: per 1000 days/catheter	Low		RR 0.38 (0.27 to 0.53)	2994 (27 RCTs)	⊕⊕⊖⊖ LOW [1 2 3 4 5]	
	43 per 1.000	16 per 1.000 (12 to 23)				
	High					
	260 per 1.000	99 per 1.000 (70 to 138)				
Thrombosis assessed with: per 1000 days/catheter	Low		RR 0.79 (0.52 to 1.22)	2080 (14 RCTs)	⊕⊖⊖⊖ VERY LOW [6 7 8 9 10]	
	6 per 1.000	5 per 1.000 (3 to 7)				
	High					
	330 per 1.000	261 per 1.000 (172 to 403)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

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Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[1] This judgment is based on the lack of information regarding the following criteria: random sequence generation, allocation concealment and blinding of outcome assesment
[2] the statistics do not show serious heterogeneity and confidence intervals overlap.
[3] the evidence is direct because the studies are in hemodialysis patients and the same sealing solutions the question of this review are used.
[4] no imprecision is observed; because the decision regarding the use of antimicrobial lock solution is sealed better than heparin along the confidence interval
[5] It is suspected a degree of publication bias
[6] 30% of the studies presented insufficient information to assess citerios of:random sequence generation, allocation concealment and blinding of outcome assesment
[7] the statistical test showed a high heterogeneity and the confidence intervals do not overlap
[8] the evidence is not indirect because the studies are in hemodialysis patients and the same sealing solutions the question of this review are used.
[9] The 95% confidence interval of the pooled estimate ranges from 0.41 to 1.39, which is not narrow enough for a confident judgment of the effect size.
[10] Publication bias is suspected as the funnel plot for this outcome shows asymmetry

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BACKGROUND

Description of the condition

Currently, arteriovenous fistulas (AVF) are the preferred access for haemodialysis (HD) patients; nevertheless, when AVFs are not available, a central venous catheter (CVC) has to be installed to start HD. The use of CVC for HD varies among different countries and changes over time in the same country (Ethier 2008). In the United States, the use of CVC has decreased from 27% in 1997 to 15% in 2013 (Pisoni 2015). Using a CVC for HD exposes participants to events such as infections and thrombosis. The use of CVC also increases the risk of mortality and treatment costs (Beathard 2008; Bradbury 2007; Foley 2009; Little 2001; Napalkov 2013). Catheters have a high likelihood of providing an adequate environment for bacterial growth, and leucocytes are unable to surround or phagocytise bacteria. Furthermore, proteins and glycocalyx biofilm coatings of catheters may protect bacteria from antibiotics and leucocytes (Ash 2000). A common complication among participants who undergo HD through CVCs is catheter-related infection (CRI). The incidence of CRI varies according to different settings and different definitions of CRI, but they are reported at rates of 2.5 to 5.5 cases/1000 catheter-days, or 0.9 to 2 episodes/patient/year (Katneni 2007; Napalkov 2013). CRI increase treatment costs and adversely affect participants' quality of life, since they often require hospitalisation to remove the CVC and to initiate intravenous antibiotic therapy according to blood cultures (Klevens 2008; NKF 2006). Several interventions to prevent CRI have been described, being the most important the decrease in the number of patients using a HD catheter and the use of strict aseptic protocols, if it is impossible to remove the catheter. Other interventions are the different types of medicated or impregnated dressings (Ullman 2015), catheter impregnation or coating (Lai 2016), application of mupirocin ointment (McCann 2010), and the use of an anti-infective solution in each CVC lumen while not being used (lock solutions) in order to help prevent colonisation of the intraluminal surface by micro-organisms that can form a biofilm on the inner wall of the CVC (Labriola 2008; Weijmer 2002).

Description of the intervention

Current standard of care for maintenance of HD CVC is to use lock solutions containing high concentrations of heparin to help prevent thrombosis (Ash 2000). However, the use of heparin may cause complications due to its systemic anticoagulant effect. Heparin can also antagonise bactericidal properties of some antibiotics and may promote biofilm formation (Moran 2008; Vanholder 2010). Locking catheter lumens using anti-infective solutions – either antibiotic lock solutions (e.g. gentamicin, vancomycin, minocycline, cefazolin, cefotaxime) or non-antibiotic lock solutions (e.g. sodium citrate, taurolidine) – can help prevent CRI (Betjes 2011; Labriola 2008; Yahav 2008). Antimicrobial (either antibiotic or on-antibiotic) lock solutions may be administered in combination with an anticoagulant (usually heparin) and sometimes with another antibiotic. Citrate is often administered in combination with taurolidine and heparin (Grudzinski 2015; Labriola 2008; Yahav 2008).

How the intervention might work

It has been demonstrated that, compared to standard care, antibiotic lock solutions can reduce the risk of CRI (Yahav 2008). However, antibiotic lock solutions can increase the likelihood of adverse effects such as ototoxicity (associated with gentamicin). Antibiotic lock solutions can also cause potential antimicrobial resistance, which is the main reason this intervention has not been adopted widely (Venditto 2010). In contrast, non-antibiotic antimicrobial lock solutions do not present these specific side effects and they are cheaper than heparin, however, their capacity to reduce CRI is uncertain (Grudzinski 2015; Yahav 2008). In vitro studies have indicated that high concentrations of trisodium citrate for locking catheters reduce antimicrobial activity (Weijmer 2005).

Why it is important to do this review

Although the effects of antimicrobial lock solutions for CVC used in HD have been assessed for the last decades, results and recommendations are controversial. A systematic review including eight randomised controlled trials (RCTs) (Labriola 2008) concluded that, compared to heparin, antimicrobial lock solutions reduced the risk of infection (RR 0.32, 95% CI 0.10 to 0.42), but the results did not differentiate between antibiotic lock solutions and non-antibiotic antimicrobial lock solutions or evaluate the safety of the intervention.

Another systematic review (Yahav 2008) including 16 studies concluded that, compared to heparin, antibiotic lock solutions reduced the risk of CRI (RR 0.39, 95% CI 0.31 to 0.50), whereas the results for non-antibiotic antimicrobial lock solutions were heterogeneous and effective only when associated with other measures to prevent CRI, such as nasal mupirocin or exit site topical iodine/chlorhexidine (RR 0.37, 95% CI 0.30 to 0.47). A more recent systematic review including five RCTs compared citrate to heparin and found no significant difference for bacteraemia, CVC permeability, and bleeding (Grudzinski 2015).

Although evidence for antibiotic lock solutions looks promising, this is not yet a standard of care due to uncertainty on safety issues. Furthermore, current evidence on non-antibiotic antimicrobial lock solutions is conflicting and insufficient to recommend their use. Therefore, a new systematic review should assess the safety and efficacy of these interventions in order to help prevent CRIs.

OBJECTIVES

To assess the efficacy and safety of antimicrobial (antibiotic, non-antibiotic, or both) catheter lock solutions for preventing CRI in participants undergoing HD with a CVC.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs and quasi-RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods, looking at antimicrobial (antibiotic, non-antibiotic, or both) catheter lock solutions for preventing CRI and thrombosis in people undergoing HD through a CVC.

Types of participants

Inclusion criteria

Adults or children with acute kidney injury or end-stage kidney disease undergoing HD using a CVC.

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Exclusion criteria

We excluded studies of participants using a CVC for anything other than HD.

Types of interventions

- All antimicrobial lock solutions: antibiotic (e.g. gentamicin, vancomycin, cefotaxime, and minocycline), non-antibiotic (e.g. citrate, taurolidine, and ethanol) or both compared to heparin, tissue plasminogen activator, and other lock solutions with unknown antimicrobial properties
- Studies investigating non-lock solution interventions were excluded.
- Studies investigating the treatment of CRI with antimicrobial-lock solutions were excluded.

Types of outcome measures

Primary outcomes

- CRI: defined as the presence of symptoms and signs suggesting systemic infection, such as fever (temperature ≥ 38°C) or hypotension, accompanied by positive blood cultures drawn from the catheter and a peripheral vein. Growth of the same micro-organism in blood cultures drawn through both the catheter and a peripheral vein, without other bacteraemia sources of infection than the CVC.

Secondary outcomes

- CVC-related thrombosis, defined as a persistent inability to maintain a blood flow of > 250 mL/min or the need of thrombolytic therapy, or CVC removal due to occlusion.
- CVC colonisation, defined as a positive culture by any methods in participants with or without signs of infection.
- Bacteraemia from any sources.
- Survival of CVC without thrombosis or infection, defined as the number of days the catheter is permeable and free of infection or thrombosis.
- All-cause mortality.
- Adverse effects such as bacterial antibiotic resistance, bleeding episodes, or pulmonary embolism.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 18 December 2017 through contact with the Information Specialist using search terms relevant to this review. The Specialised Register contains studies identified from the following sources:

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of included studies and previous relevant systematic reviews.
2. Abstracts from major conferences and meetings for the past seven years between 2010 and 2017.

Data collection and analysis

Selection of studies

The search strategy was used to obtain titles and abstracts of studies that might be relevant to the review. Retrieved titles and abstracts were reviewed by two authors, and studies considered by any of the reviewers as potentially relevant were initially selected. Full text articles of these studies were further reviewed for eligibility by both authors, who had to both agree for including them in the review. Disagreements not resolved by discussion between authors were referred to a third author.

Data extraction and management

Studies reported in languages other than English or Spanish were translated before assessment. When more than one publication of the same study was found, reports were analysed to select the publication with the most complete data to be included in the analyses. Only when relevant outcomes were published in an earlier version, this version was used.

Two authors carried out data extraction, independently using a data extraction form, devised to record details of participant characteristics, interventions and outcome measures for each included study.

Assessment of risk of bias in included studies

Included studies were independently assessed for methodological quality by two authors. We assessed the following items using the risk of bias assessment tool (Higgins 2011) (Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Were reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk for bias?

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Measures of treatment effect

Studies expressed the main outcomes either as rates of events per catheter-days or per dialysis sessions, we used the generic inverse-variance method to pool the results, reporting the rate ratio (RR) with 95% confidence intervals (95% CI) for each comparison (Higgins 2011).

Unit of analysis issues

We used catheter-days or dialysis-sessions for data reporting and analysis.

Dealing with missing data

Missing data was requested from the authors of included studies, by up to three e-mails to the corresponding author; all relevant information obtained was included in the review.

Assessment of heterogeneity

We explored evidence of statistical heterogeneity across studies was explored using the I^2 and the Chi^2 test for heterogeneity, P-value for statistical significance of chi-square was set at 0.05. I^2 of 0% to 25%, 26% to 50% and over 51%; corresponded to low, medium and high levels of heterogeneity respectively (Higgins 2011).

Assessment of reporting biases

Our search strategy aimed to minimize publication bias. We used funnel plots to assess publication bias for CVC-related infection.

Data synthesis

We pooled data using random-effects model.

Subgroup analysis and investigation of heterogeneity

Planned *a priori* subgroup analyses were used to explore possible sources of heterogeneity. Heterogeneity was explored according to the type of lock solutions and the type of catheters (tunnelled or non-tunnelled).

Sensitivity analysis

Sensitivity analyses were performed on the main outcomes and comparisons excluding studies with high risk of bias and separating randomised from quasi-randomised studies.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b)). We presented the outcomes 1) CVC-related infections per 1000 catheter-days, and 2) thrombosis per 1000 catheter-days Summary of findings for the main comparison.

RESULTS

Description of studies

Results of the search

After searching the Register we identified 196 records. Titles and abstracts were screened and we retrieved 88 full-text articles for further assessment. Of these, 39 studies (58 records) were included and 22 studies (29 records) were excluded. One study was completed prior to publication of this review (CLOCK 2017) and will be assessed in a future update (Figure 1).

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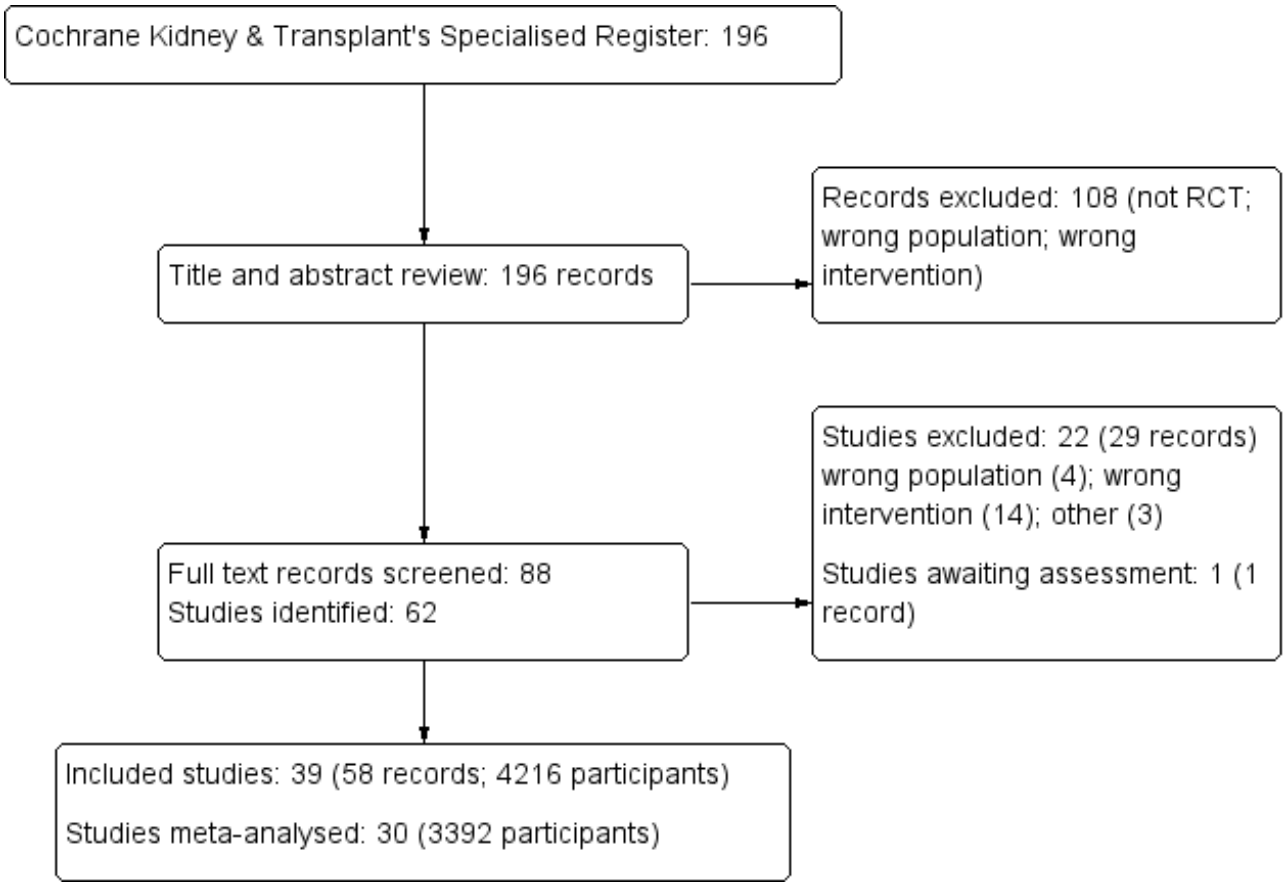
Figure 1. Study selection flow diagram



Included studies

We included 39 studies (4216 participants) in this review (Al-Hwiesh 2007; AZEPTIC 2011; Betjes 2004; Bleyer 2005; Buturovic 1998; Campos 2011; CHARTS 2008; CITRIM 2017; Corbett 2013; Cooper 1999; Davanipur 2011; D'Avella 2007; Dogra 2002; Geron 2008; Hendrickx 2001; Hermite 2012; Kanaa 2015; Kim 2006a; Kokenge 2010; Lange 2007; Lustig 2011; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Plamandon 2005a; Power 2009; Saxena 2006; Saxena 2012; Shirzad 2013; Sofroniadou 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005; Zhang 2009c; Zwiech 2016a).

Of these, nine studies either did not provide enough data, or the relevant data could not be extracted, and therefore were not meta-analysed (Corbett 2013; Kanaa 2015; Kokenge 2010; Lange 2007; Lustig 2011; Plamandon 2005a; Power 2009; Shirzad 2013; Zwiech 2016a).

Study design

Thirty-seven studies were parallel RCTs and two were quasi-randomised (CHARTS 2008; Power 2009).

Setting

Twenty-five studies were undertaken in an outpatient setting, eight in an inpatient setting (Al-Hwiesh 2007; Betjes 2004; Bleyer 2005; CITRIM 2017; Hermite 2012; Kim 2006a; Moghaddas 2015; Sofroniadou 2012), and six did not describe a specific setting (D'Avella 2007; Geron 2008; Kokenge 2010; Lange 2007; Lustig 2011; Plamandon 2005a).

Participants

All studies included adults with ESKD undergoing HD through a CVC; none of the studies included children. Twenty-four studies used tunnelled catheters (Al-Hwiesh 2007; AZEPTIC 2011; CHARTS 2008; Cooper 1999; Corbett 2013; Dogra 2002; Geron 2008; Hendrickx 2001; Kanaa 2015; Kokenge 2010; McIntyre 2004; Moghaddas 2015; Mortazavi 2011; Moran 2012; Nori 2006; Oguzhan 2012; Pervez 2002; Plamandon 2005a; Power 2009; Saxena 2006; Saxena 2012; Solomon 2010; Vercaigne 2016a; Zhang 2009c), six studies used non-tunnelled catheters (Buturovic 1998; CITRIM 2017; Davanipur 2011; Hermite 2012; Kim 2006a; Sofroniadou 2012), six studies used both types of catheters (Betjes 2004; Bleyer 2005; Campos 2011; Lange 2007; Weijmer 2005; Zwiech 2016a), and three studies did not describe the type of catheter (D'Avella 2007; Lustig 2011; Shirzad 2013).

Interventions

Antibiotic lock solutions versus heparin

Fifteen studies used antibiotic lock solutions.

- Minocycline/EDTA and heparin (Nori 2006)
- Vancomycin hydrochloride, gentamicin sulphate, and heparin (Al-Hwiesh 2007)
- Minocycline and EDTA (Bleyer 2005; Campos 2011)

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- Cloxacillin and heparin (Davanipur 2011)
- Cefazolin, gentamicin, and heparin (Kim 2006a)
- Cefotaxime and heparin (Mortazavi 2011; Saxena 2006; Saxena 2012)
- Gentamicin and heparin (McIntyre 2004; Zhang 2009c)
- Cefazolin and heparin (Shirzad 2013)
- Cotrimoxazole (Moghaddas 2015)
- Linezolid and vancomycin (Sofroniadou 2012)
- Gentamicin (Cooper 1999).

Non-antibiotic antimicrobial lock solutions versus heparin and other solutions

Twenty-one studies used non-antibiotic antimicrobial lock solutions. Twenty studies compared non-antibiotic antimicrobial lock solutions versus heparin.

- Hypertonic saline solution (≥ 12%) (D'Avella 2007; Oguzhan 2012)
- Tauloridine (Geron 2008)
- Citrate plus taurolidine (Betjes 2004; Corbett 2013; Solomon 2010; Zwiech 2016a)
- Ethanol plus citrate (Vercaigne 2016a)
- Trisodium citrate (4%) (Buturovic 1998; CHARTS 2008; Plamandon 2005a)
- Trisodium citrate (5%) (Hendrickx 2001)
- Citrate solution (30%) (CITRIM 2017; Weijmer 2005)
- Citrate solution (46.7%) (Power 2009)
- Sodium citrate (7%), methylene blue (0.05%), methylparaben (0.15%), and propylparaben (0.015%) (AZEPTIC 2011)
- Sodium citrate (3.13%) (Lange 2007; Kokenge 2010)
- Trisodium citrate-ethanol-methylene blue (Lustig 2011)
- Cathasept (Kanaa 2015).

One study compared 46.7% citrate solution to 0.9% saline solution (Hermite 2012).

Antibiotic lock solutions plus non-antibiotic antimicrobial lock solutions versus heparin

Four studies used antibiotic lock solutions plus non-antibiotic antimicrobial lock solutions.

- Gentamicin (320 µg/mL) in sodium citrate (4%) (Moran 2012)
- Gentamicin (40 mg/mL) and 1 mL citrate (3.13%) (Dogra 2002)
- Gentamicin (40 mg/mL) plus tricitrasol (46.7%) (Pervez 2002)
- Gentamicin (4 mg/mL) in citrate (3.13%) (Nori 2006).

Outcomes

All included studies reported at least one of our outcomes. Seventeen studies reported only CRI (Al-Hwiesh 2007; CHARTS 2008; Cooper 1999; Davanipur 2011; D'Avella 2007; Dogra 2002; Geron 2008; Hendrickx 2001; Kim 2006a; Lustig 2011; McIntyre 2004; Mortazavi 2011; Saxena 2012; Shirzad 2013; Sofroniadou 2012; Vercaigne 2016a; Zwiech 2016a); four studies reported only thrombosis (Buturovic 1998; Kokenge 2010; Lange 2007; Plamandon 2005a); 15 studies reported CRI and thrombosis (AZEPTIC 2011; Campos 2011; CITRIM 2017; Corbett 2013; Hermite 2012; Moghaddas 2015; Moran 2012; Nori 2006; Oguzhan 2012; Pervez 2002; Power 2009; Saxena 2006; Solomon 2010; Weijmer 2005; Zhang 2009c); two studies reported CRI and colonisation (Betjes 2004; Bleyer 2005); and one study reported CRI, thrombosis, and colonisation (Kanaa 2015).

The 39 studies included were further divided into three groups according to the type of antimicrobial lock solutions: antibiotic, non-antibiotic, and the combination of both. One study with three arms (gentamicin/citrate, minocycline/EDTA and heparin), was included in the two comparisons (antibiotic lock solutions plus non-antibiotic antimicrobial lock solutions and antibiotic lock solutions) (Nori 2006).

See Characteristics of included studies.

Excluded studies

We excluded 22 studies after reviewing the full-text reports (see Characteristics of excluded studies). Four studies had different populations (Beigi 2010; Khosroshahi 2006b; Khosroshahi 2015; Onder 2008); 13 studies used different interventions (Chen 2014b; Chu 2016, Coli 2010; HEALTHY-CATH 2009; Hryszko 2013; Hu 2011; Malo 2010; Mohammad 2016; Oran 2008; PreCLOT 2006; Ray 1999; Sishir 2014; Thomson 2011); one study used a different comparison (Meeus 2005); one study reported different outcomes (Bosma 2010); one study was terminated early (NCT01989091); one study has not been verified since 2009 and no results have been published (NCT00862966); and one study protocol could not be located (ISRCTN27307877).

Risk of bias in included studies

Risk of bias was low or unclear for most domains in the majority of studies. Most authors were contacted for additional or missing information regarding their included studies; however, we only obtained response from one author (Hermite 2012).

Allocation

Sequence generation

Two studies were considered at high risk of bias due to the method used for sequence generation (CHARTS 2008; Power 2009). Seventeen studies reported an appropriate method of sequence generation and were judged to be at low risk of bias (AZEPTIC 2011; Betjes 2004; CITRIM 2017; Dogra 2002; Kanaa 2015; Kim 2006a; Moran 2012; Mortazavi 2011; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Sofroniadou 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005; Zwiech 2016a). Twenty studies reported insufficient information to estimate this risk of bias (Al-Hwiesh 2007; Bleyer 2005; Buturovic 1998; Campos 2011; Cooper 1999; Corbett 2013; D'Avella 2007; Davanipur 2011; Geron 2008; Hendrickx 2001; Hermite 2012; Kokenge 2010; Lange 2007; Lustig 2011; McIntyre 2004; Moghaddas 2015; Nori 2006; Plamandon 2005a; Shirzad 2013; Zhang 2009c).

Allocation concealment

Seven studies reported adequate allocation concealment, representing a low risk of bias (Betjes 2004; CITRIM 2017; Kanaa 2015; Saxena 2006; Saxena 2012; Vercaigne 2016a; Weijmer 2005). One study was at high risk of bias as they did not use allocation concealment (CHARTS 2008). The remaining 31 studies had insufficient details of the method of allocation concealment and were judged to be at unclear risk of bias (Al-Hwiesh 2007; AZEPTIC 2011; Betjes 2004; Buturovic 1998; Campos 2011; Cooper

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1999; Corbett 2013; D'Avella 2007; Davanipur 2011; Dogra 2002; Geron 2008; Hendrickx 2001; Hermite 2012; Kim 2006a; Kokenge 2010; Lange 2007; Lustig 2011; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Plamandon 2005a; Power 2009; Shirzad 2013; Sofroniadou 2012; Solomon 2010; Zhang 2009c; Zwiech 2016a).

Blinding

Participants and personnel

Nine studies were at low risk of bias (Bleyer 2005; CITRIM 2017; Dogra 2002; Hermite 2012; Saxena 2006; Saxena 2012; Solomon 2010; Weijmer 2005; Zhang 2009c). Seven studies showed a high risk of bias because either study participants or personnel were unblinded (Al-Hwiesh 2007; AZEPTIC 2011; CHARTS 2008; Kanaa 2015; McIntyre 2004; Moghaddas 2015; Nori 2006). In the remaining 23 studies insufficient information was provided to determine who were blind and therefore were judged unclear risk of bias (Betjes 2004; Buturovic 1998; Campos 2011; Cooper 1999; Corbett 2013; D'Avella 2007; Davanipur 2011; Geron 2008; Hendrickx 2001; Kim 2006a; Kokenge 2010; Lange 2007; Lustig 2011; Moran 2012; Mortazavi 2011; Oguzhan 2012; Pervez 2002; Plamandon 2005a; Power 2009; Shirzad 2013; Sofroniadou 2012; Vercaigne 2016a; Zwiech 2016a).

Outcome assessment

In seven studies the outcome assessment was blinded (AZEPTIC 2011; Dogra 2002; Hermite 2012; Kanaa 2015; Saxena 2006; Saxena 2012; Solomon 2010). In four studies the outcome assessment was not blinded and was judged to be at high risk of bias (CHARTS 2008; Kim 2006a; Moghaddas 2015; Zhang 2009c). Twenty-eight studies did not provide enough information to be judged, therefore this risk of bias was uncertain (Al-Hwiesh 2007; Betjes 2004; Bleyer 2005; Buturovic 1998; Campos 2011; CITRIM 2017; Cooper 1999; Corbett 2013; D'Avella 2007; Davanipur 2011; Geron 2008; Hendrickx 2001; Kokenge 2010; Lange 2007; Lustig 2011; McIntyre 2004; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Plamandon 2005a; Power 2009; Shirzad 2013; Sofroniadou 2012; Vercaigne 2016a; Weijmer 2005; Zwiech 2016a).

Incomplete outcome data

Twenty-two studies had a low risk of bias, reporting complete data charts (AZEPTIC 2011; Betjes 2004; Campos 2011; CHARTS 2008; Dogra 2002; Hendrickx 2001; Kim 2006a; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Sofroniadou 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005; Zhang 2009c; Zwiech 2016a). One study was rated high risk of bias due to incomplete outcome data (Bleyer 2005). Sixteen studies did not provide sufficient information to determine whether incomplete outcome data were adequately addressed (Al-Hwiesh 2007; Buturovic 1998; CITRIM 2017; Cooper 1999; Corbett 2013; D'Avella 2007; Davanipur 2011; Geron 2008; Hermite 2012; Kanaa 2015; Kokenge 2010; Lange 2007; Lustig 2011; Plamandon 2005a; Power 2009; Shirzad 2013).

Selective reporting

Twenty-eight studies were judged to be at low risk of reporting bias (Al-Hwiesh 2007; AZEPTIC 2011; Betjes 2004; Bleyer 2005; Campos 2011; CHARTS 2008; CITRIM 2017; Davanipur 2011; Dogra 2002; Hendrickx 2001; Hermite 2012; Kanaa 2015; Kim 2006a; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Sofroniadou 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005; Zhang 2009c; Zwiech 2016a). One study was judged to be at high risk of bias (Power 2009) and 10 studies were judged to have unclear risk of bias (Buturovic 1998; Cooper 1999; Corbett 2013; D'Avella 2007; Geron 2008; Kokenge 2010; Lange 2007; Lustig 2011; Plamandon 2005a; Shirzad 2013).

Other potential sources of bias

One study was judged as high risk of bias because researchers declared conflict of interest related to research funding (Moran 2012). Three studies were judged as low risk of bias (Al-Hwiesh 2007; AZEPTIC 2011; Hermite 2012), and the remaining 35 studies reported insufficient information and they were judged to have unclear risk of bias (Betjes 2004; Bleyer 2005; Buturovic 1998; Campos 2011; CHARTS 2008; CITRIM 2017; Cooper 1999; Corbett 2013; D'Avella 2007; Davanipur 2011; Dogra 2002; Geron 2008; Hendrickx 2001; Kanaa 2015; Kim 2006a; Kokenge 2010; Lange 2007; Lustig 2011; McIntyre 2004; Moghaddas 2015; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Plamandon 2005a; Power 2009; Saxena 2006; Saxena 2012; Shirzad 2013; Sofroniadou 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005; Zhang 2009c; Zwiech 2016a).

Effects of interventions

See: **Summary of findings for the main comparison** Antimicrobial lock solutions vs control for preventing catheter-related infections in patient undergoing haemodialysis

See Summary of findings for the main comparison.

Although 39 studies met the inclusion criteria, only 30 could be incorporated into the meta-analyses, as the other nine studies did not present enough data to be included in the meta-analysed (Corbett 2013; Kanaa 2015; Kokenge 2010; Lange 2007; Lustig 2011; Plamandon 2005a; Power 2009; Shirzad 2013; Zwiech 2016a) so all further descriptions refer to the 30 meta-analysed studies.

Antimicrobial lock solutions (antibiotic, non-antibiotic or both) versus control

Catheter-related infection

Twenty seven studies reported the incidence of CRI per 1000 catheter-days (AZEPTIC 2011; Betjes 2004; Bleyer 2005; Campos 2011; CHARTS 2008; CITRIM 2017; Cooper 1999; D'Avella 2007; Davanipur 2011; Dogra 2002; Geron 2008; Hermite 2012; Kim 2006a; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Sofroniadou 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005; Zhang 2009c). Antimicrobial lock solutions probably reduces the incidence of CRI per 1000 catheter days compared to control (Analysis 1.1: RR 0.38, 95% CI 0.27 to 0.53; I^2 = 54%; moderate certainty evidence).

Two studies measured the incidence of CRI per 1000 dialysis sessions (Al-Hwiesh 2007; Hendrickx 2001). Antimicrobial lock solutions may make little or no difference to the reduction of CRI compared with heparin lock solutions (Analysis 1.2: RR 0.47, 95% CI 0.07 to 3.13; I^2 = 81%; low certainty evidence). Heterogeneity was high for this analysis.

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Thrombosis

Fourteen studies reported the incidence of thrombosis, per 1000 catheter-days (AZEPTIC 2011; Buturovic 1998; Campos 2011; CITRIM 2017; Hermite 2012; Moghaddas 2015; Moran 2012; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Solomon 2010; Weijmer 2005; Zhang 2009c). Antimicrobial lock solutions probably make little or no difference to the risk of thrombosis compared to control (Analysis 1.3: RR 0.79, 95% CI 0.52 to 1.22; I^2 = 83%; moderate certainty evidence). Heterogeneity was high for this analysis.

Colonisation

Two studies reported the incidence of colonisation (Betjes 2004; Bleyer 2005). Antimicrobial lock solutions may make little or no difference to the reduction in colonisation compared to control (Analysis 1.4: RR 0.37 95% CI 0.04 to 3.36; I^2 = 70%; low certainty evidence), with high heterogeneity.

Subgroup analyses

To explore sources of heterogeneity, subgroup analysis by CVC type was carried out for CRI and lumen thrombosis.

Eighteen studies used only tunnelled catheters (AZEPTIC 2011; CHARTS 2008; Cooper 1999; D'Avella 2007; Dogra 2002; Geron 2008; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Solomon 2010; Vercaigne 2016a; Zhang 2009c) and five used only non-tunnelled catheters (CITRIM 2017; Davanipur 2011; Hermite 2012; Kim 2006a; Sofroniadou 2012). Four used both types of catheters (Betjes 2004; Bleyer 2005; Campos 2011; Weijmer 2005) however only three delivered data separating tunnelled and non-tunnelled catheters (Betjes 2004; Campos 2011; Weijmer 2005). For the purpose of the analysis, the studies including both types were included separately in the tunnelled or non-tunnelled group.

Due to insufficient data on included studies, it was not possible to explore other sources of heterogeneity, such as subgroups of diabetic participants or co-interventions to prevent CRI.

Catheter-related infection (tunnelled and non-tunnelled catheters)

Twenty-one studies reported data for tunnelled catheters (AZEPTIC 2011; CHARTS 2008; Cooper 1999; D'Avella 2007; Geron 2008; McIntyre 2004; Moghaddas 2015; Moran 2012; Mortazavi 2011; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Solomon 2010; Vercaigne 2016a; Zhang 2009c, Betjes 2004; Campos 2011; Dogra 2002; Weijmer 2005). Antimicrobial lock solutions probably reduce the incidence of CRI per 1000 catheter days compared to control in tunnelled catheters (Analysis 1.5: RR 0.40, 95% CI 0.30 to 0.53; I^2 = 14%).

Eight studies reported data for non-tunnelled catheters (Betjes 2004; Campos 2011; CITRIM 2017; Davanipur 2011; Hermite 2012; Kim 2006a; Sofroniadou 2012; Weijmer 2005). Antimicrobial lock solutions probably reduce the incidence of CRI per 1000 catheter days compared to control in non-tunnelled catheters (Analysis 1.6: RR 0.37, 95% CI 0.16 to 0.86; I^2 = 67%). Heterogeneity was high.

Heterogeneity disappears if only tunnelled catheters are analysed, therefore some heterogeneity in the main analysis might be explained on the basis of type of CVC.

Thrombosis (tunnelled and non-tunnelled catheters)

Ten studies reported data for tunnelled catheters (AZEPTIC 2011; Moghaddas 2015; Moran 2012; Nori 2006; Oguzhan 2012; Pervez 2002; Saxena 2006; Solomon 2010; Weijmer 2005; Zhang 2009c). Antimicrobial lock solutions probably make little or no difference to the risk of thrombosis in tunnelled catheters (Analysis 1.7: RR 0.83, 95% CI 0.50 to 1.37; I^2 = 76%). High heterogeneity was observed.

Four studies reported data for non-tunnelled catheters (Buturovic 1998; CITRIM 2017; Hermite 2012; Weijmer 2005). Antimicrobial lock solutions probably make little or no difference to the risk of thrombosis in non-tunnelled catheters (Analysis 1.8: RR 0.66, 95% CI 0.25 to 1.72; I^2 = 92%). High heterogeneity was observed.

For this outcome, the type of catheter does not explain the observed heterogeneity.

Sensitivity analyses

We carried out a sensitivity analyses by excluding the studies deemed as to be at high risk of bias (for any domain), to determine whether the results of the meta-analysis regarding the main outcomes were robust.

Catheter-related infection

Eighteen studies with low or unclear risk of bias were analysed (Betjes 2004; Campos 2011; CITRIM 2017; Corbett 2013; D'Avella 2007; Davanipur 2011; Dogra 2002; Geron 2008; Hermite 2012; Mortazavi 2011; Oguzhan 2012; Pervez 2002; Saxena 2006; Saxena 2012; Sofroniadou 2012; Solomon 2010: Weijmer 2005). There was no change to the results; there was less precision and heterogeneity remained the same (Analysis 2.1: (RR 0.47, 95% CI 0.32 to 0.68; I^2 = 58%).

Thrombosis

Nine studies with low or unclear risk of bias were analysed (Buturovic 1998; Campos 2011; CITRIM 2017; Hermite 2012; Oguzhan 2012; Pervez 2002; Saxena 2006; Solomon 2010; Weijmer 2005). There was no change to the results; either in direction or magnitude of effect (Analysis 2.2: (RR 0.85, 95% CI 0.48 to 1.52; I^2 = 88%).

Antibiotic lock solutions versus control

Catheter-related infection

Thirteen studies reported CRI per 1000 catheter-days (Bleyer 2005; Campos 2011; Cooper 1999; Davanipur 2011; Kim 2006a; McIntyre 2004; Moghaddas 2015; Mortazavi 2011; Nori 2006; Saxena 2006; Saxena 2012; Sofroniadou 2012; Zhang 2009c). Antibiotic lock solutions probably reduce the incidence of CRI per 1000 catheter days compared to control (Analysis 3.1: RR 0.30, 95% CI 0.22 to 0.42; I^2 = 18%; moderate certainty evidence). Heterogeneity was low.

One study (Al-Hwiesh 2007) reported antibiotic lock solutions reduced the incidence in CRI per dialysis session compared to control (Analysis 3.2: RR 0.18, 95% CI 0.05 to 0.59).

Thrombosis

Five studies reported thrombosis per 1000 catheter-days (Campos 2011; Moghaddas 2015; Nori 2006; Saxena 2006; Zhang 2009c). Antibiotic lock solutions probably make little or no difference to

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the risk of thrombosis per 1000 catheter-days compared to control (Analysis 3.3; RR 0.76, 95% CI 0.42 to 1.38; I^2 = 47%; moderate certainty evidence). Moderate heterogeneity was observed.

Colonisation

One study (Bleyer 2005) reported that antibiotic lock solutions reduced the incidence of catheter colonisation compared to heparin (Analysis 3.4: RR 0.10, 95% CI 0.01 to 0.79).

Subgroup analyses

Catheter-related infection

Nine studies reported data for tunnelled catheters (Campos 2011; Cooper 1999; McIntyre 2004; Moghaddas 2015; Mortazavi 2011; Nori 2006; Saxena 2006; Saxena 2012; Zhang 2009c). Antibiotic lock solutions probably reduce the incidence of CRI per 1000 catheter-days compared to control in tunnelled catheters (Analysis 3.5: RR 0.30, 95% CI 0.18 to 0.50; I^2 = 35%). Moderate heterogeneity was observed.

Four studies reported data for non-tunnelled catheters (Campos 2011; Davanipur 2011; Kim 2006a; Sofroniadou 2012). Antibiotic lock solutions probably reduce the incidence of CRI per 1000 catheter days compared to control in non-tunnelled catheters (Analysis 3.6: RR 0.14, 95% CI 0.05 to 0.36; I^2 = 0%).

Thrombosis

Three studies reported data for tunnelled catheters (Moghaddas 2015; Saxena 2006; Zhang 2009c). Antibiotic lock solutions probably make little or no difference to the risk of thrombosis per 1000 catheter-days compared to control for tunnelled catheters (Analysis 3.7: RR 0.61, 95% CI 0.31 to 1.23; I^2 = 45%).

No analysis was performed for non-tunnelled catheters as no separate data was reported in the three studies that used both types of catheters.

Sensitivity analyses

Sensitivity analyses excluding studies deemed as to be at high risk of bias (for any domain) were undertaken.

Catheter-related infection

Seven studies with low or unclear risk of bias were included in this analysis (Campos 2011; Cooper 1999; Davanipur 2011; Mortazavi 2011; Saxena 2006; Saxena 2012; Sofroniadou 2012). There was no change to the results with less heterogeneity and higher precision (Analysis 4.1: RR 0.37, 95% CI 0.28 to 0.48; I^2 = 4%).

Thrombosis

Two studies with low or unclear risk of bias were included in this analysis (Campos 2011; Saxena 2006). There was no change to results, however heterogeneity was higher (Analysis 4.2: RR 0.79, 95% CI 0.24 to 2.63; I^2 = 82%).

Non-antibiotic antimicrobial lock solutions versus control

Catheter-related infection

Eleven studies reported CRI per 1000 catheter-days (AZEPTIC 2011; Betjes 2004; CHARTS 2008; CITRIM 2017; D'Avella 2007; Geron 2008; Hermite 2012; Oguzhan 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005). Non-antibiotic antimicrobial lock solutions probably make little or no difference to the incidence of CRI per 1000 catheter days compared to control (Analysis 5.1: RR 0.65, 95% CI 0.41 to 1.05; I^2 = 51%). Heterogeneity was moderate.

One study (Hendrickx 2001) reported no difference in the incidence of CRI per 1000 dialysis sessions between non-antibiotic antimicrobial lock solutions and control (Analysis 5.2: RR 1.22, 95% CI 0.38 to 3.88).

Thrombosis

Eight studies reported thrombosis per 1000 catheter-days (AZEPTIC 2011; Buturovic 1998; CHARTS 2008; CITRIM 2017; Hermite 2012; Oguzhan 2012; Solomon 2010; Weijmer 2005). Seven studies used heparin as control and one study (Hermite 2012) used saline solution 0.9% as control lock solution. Non-antibiotic antimicrobial lock solutions probably make little or no difference to the risk of thrombosis per 1000 catheter-days compared to control (Analysis 5.3: RR 0.85, 95% CI 0.44 to 1.66; I^2 = 89%). Heterogeneity is high.

One study (Hendrickx 2001) reported a decrease in the incidence of thrombosis per 1000 dialysis sessions with non-antibiotic antimicrobial lock solutions versus heparin (Analysis 5.4 RR 0.11, 95% CI 0.04 to 0.32).

Colonisation

One study (Betjes 2004) reported no difference in the reduction of catheter colonisation between non-antibiotic antimicrobial lock solutions and control (Analysis 5.5: RR 0.99, 95%CI 0.27 to 3.68).

Subgroup analyses

Catheter-related infection

Nine studies reported data for tunnelled catheters (AZEPTIC 2011; Betjes 2004; CHARTS 2008; D'Avella 2007; Geron 2008; Weijmer 2005; Oguzhan 2012; Solomon 2010; Vercaigne 2016a). Non-antibiotic antimicrobial lock solutions probably reduce the incidence of CRI per 1000 catheter-days compared to control in tunnelled catheters (Analysis 5.6: RR 0.60, 95% CI 0.40 to 0.91; I^2 = 0%).

Four studies reported data for non-tunnelled catheters (Betjes 2004; CITRIM 2017; Hermite 2012; Weijmer 2005). Non-antibiotic antimicrobial lock solutions probably make little or no difference to the risk of CRI per 1000 catheter-days compared to control for tunnelled catheters (Analysis 5.7: RR 0.93, 95% CI 0.48 to 1.81; I^2 = 41%). Heterogeneity is moderate.

Thrombosis

Five studies reported data for tunnelled catheters (AZEPTIC 2011; CHARTS 2008; Oguzhan 2012; Solomon 2010; Weijmer 2005). Non-antibiotic antimicrobial lock solutions probably make little or no difference to the risk of thrombosis per 1000 catheter-days compared to control for tunnelled catheters (Analysis 5.8: RR 1.17, 95% CI 0.57 to 2.41; I^2 = 72%). Heterogeneity was high.

Four studies reported data for non-tunnelled catheters (Buturovic 1998; CITRIM 2017;Hermite 2012; Weijmer 2005) Non-antibiotic antimicrobial lock solutions probably make little or no difference to the risk of thrombosis per 1000 catheter-days compared to control

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for non-tunnelled catheters (Analysis 5.9: RR 0.66, 95% CI 0.25 to 1.72; I^2 = 92%). Heterogeneity was high.

Sensitivity analyses

Sensitivity analyses excluding studies deemed as to be at high risk of bias (for any domain) were undertaken.

Catheter-related infection

Nine studies with low or unclear risk of bias were included in this analysis (Betjes 2004; CITRIM 2017; Geron 2008; Hermite 2012; Oguzhan 2012; Solomon 2010; Vercaigne 2016a; Weijmer 2005). The analysis showed a similar magnitude of effect but with less precision and higher heterogeneity (Analysis 6.1: RR 0.65, 95% CI 0.38 to 1.12; I^2 = 61%).

Thrombosis

Six studies with low or unclear risk of bias were included in this analysis (Buturovic 1998; CITRIM 2017; Hermite 2012; Oguzhan 2012; Solomon 2010; Weijmer 2005). The analysis showed a similar magnitude of effect but with less precision and same heterogeneity (Analysis 6.2: RR 0.90, 95% CI 0.43 to 1.91; I^2 = 92%).

Combined antibiotic plus non-antibiotic antimicrobial lock solutions versus control

Catheter-related infection

Four studies reported CRI per 1000 catheter-days (Dogra 2002; Moran 2012; Nori 2006; Pervez 2002). Antibiotic plus non-antibiotic antimicrobial lock solution probably reduce the incidence of CRI per 1000 catheter-days compared to control (Analysis 7.1: RR 0.26, 95% CI 0.14 to 0.49; I^2 = 0%; moderate certainty evidence).

Thrombosis

Three studies reported thrombosis per 1000 catheter-days (Moran 2012; Nori 2006; Pervez 2002). Antibiotic plus non-antibiotic antimicrobial lock solution probably make little or no difference to the incidence of thrombosis per 1000 catheter-days compared to control (Analysis 7.2: RR 0.63, 95% CI 0.22 to 1.81; I^2 = 0%; moderate certainty evidence).

Colonisation

No study reported catheter colonisation.

Subgroup analyses

All four studies used tunnelled catheters.

Sensitivity analyses

Sensitivity analyses excluding studies deemed as to be at high risk of bias (for any domain) were undertaken.

Catheter-related infection

Two studies with low or unclear risk of bias were included in this analysis (Dogra 2002; Pervez 2002). The result no longer showed a reduction in CRI (Analysis 8.1: RR 0.16, 95% CI 0.02 to 1.03; I^2 = 0%).

Thrombosis

One study (Pervez 2002) showed a similar magnitude of effect but with less precision (Analysis 8.2: RR 0.66, 95% CI 0.18 to 2.44).

Other planned outcomes

Survival of the catheter, infection and thrombosis-free days, were reported in a small number of included studies, however the data was not presented in enough detail to be meta-analysed.

Mortality and adverse effects were not reported.

DISCUSSION

Summary of main results

Antimicrobial lock solutions reduced CRI in patients using CVC for HD, compared to standard lock solutions, usually heparin (moderate certainty evidence). This beneficial effect was best for antibiotic lock solutions and for combined (antibiotic plus non-antibiotic antimicrobial) lock solutions. Heterogeneity was low for antibiotic lock solutions and for combined lock solutions (I^2 = 18% and 0% respectively) but high for all antimicrobial lock solutions and non-antibiotic antimicrobial lock solutions (I^2 = 54% and 51% respectively). Therefore the type of antimicrobial lock solution might explain some of the heterogeneity in the main analysis. Type of catheter (tunnelled vs non- tunnelled) might also influence the effect of antimicrobial lock solutions. For both tunnelled (RR 0.40; 95% CI 0.30 to 0.53; I^2 = 14%) and non-tunnelled catheters, antimicrobial lock solutions (RR 0.37, 95% CI 0.16 to 0.86; I^2 = 67%) reduced CRI.

The difference between both types of catheters could be related to the pathogenesis of infection. In the case of non-tunnelled catheters the infection could be developed through the either external or the internal surface of the catheter. By contrast, the route for the development of infection of tunnelled catheters corresponds to the intraluminal surface, which is in contact with the antimicrobial lock solutions. However the type of catheter alone, does not explain heterogeneity, probably due to differences in characteristics of patients using one or the other type of catheter. Due to the quality of the evidence, our confidence in the effect of antimicrobial lock solutions on CRI is moderate.

The efficacy of antimicrobial lock solutions in reducing the incidence of CRI is still present in the sensitivity analysis, using the studies classified as having low or unclear risk of bias, however, even though these results are robust, our confidence in the effect on CRI is moderate due to the quality of the evidence.

Regarding the safety of antimicrobial lock solutions, they are no worse than heparin or other lock solutions on the incidence of thrombosis of CVC for HD. These results remain unaltered when analysed according to type of antimicrobial lock solutions, type of CVC, and quality of studies.

It is important to note that there is less evidence for thrombosis, due to a small number of studies reporting this outcome; therefore, these estimates are imprecise. These results are also heterogeneous, which might be due to a study that used saline solution instead of heparin as control lock solution or due to different definitions of thrombosis throughout the studies. Due to the quality of the evidence, our confidence in the effect of antimicrobial lock solutions on lumen thrombosis is low.

It is not possible to draw conclusions regarding CVC colonisation because this outcome was reported in only two studies that used different antimicrobial lock solutions. Survival of the catheter,

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infection- and thrombosis-free periods, mortality, and adverse effects were not reported.

Overall completeness and applicability of evidence

We included thirty studies in the analyses with a total of 3392 participants. Studies were conducted between 1998 and 2017 in adult participants undergoing HD through a CVC, mainly in an ambulatory setting. The studies compared antimicrobial with other control lock solutions, mainly heparin, in order to prevent CRI without increasing thrombosis.

Our review considered all types of antimicrobial lock solutions together and subsets of antibiotic, non-antibiotic and combination of both solutions. Other included outcomes were thrombosis and colonisation. Most studies rarely reported other adverse effects, follow-up were short or not reported so we do not have information regarding long term effects, such as antibiotic resistance.

Our review presents some limitations to its applicability, mainly because adverse effects other than thrombosis were not assessed in studies for all antimicrobial lock solutions.

It is important to remember that some literature shows that sodium citrate is associated with some adverse effects such as hypocalcaemia, ventricular arrhythmias, and few cases of sudden death (Aguinaga 2011), none of which were reported in our included studies. Additionally, antibiotic solutions could cause microbial resistance, especially when used for long periods(Korkor 2009). Antibiotic antimicrobial lock solutions were quite different among studies, so we were unable to determine if any of them was better than the others.

Quality of the evidence

Thirty nine studies were selected for this review including 4216 participants. Thirty-seven were RCTs and two quasi-randomised, 17 studies (44%) presented an appropriate sequence of randomizations whereas seven studies (18%) had low risk of bias for allocation concealment. Blinding method was reported in nine studies for participants and health personnel (23%), and seven studies for outcome assessment (18%). Complete data was reported in 22 studies (56%). Reporting bias was low in 28 studies (72%). It was not possible to determine others type of bias in 35 studies (90%), mainly because conflict of interest or funding was not declared (Figure 2; Figure 3)

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

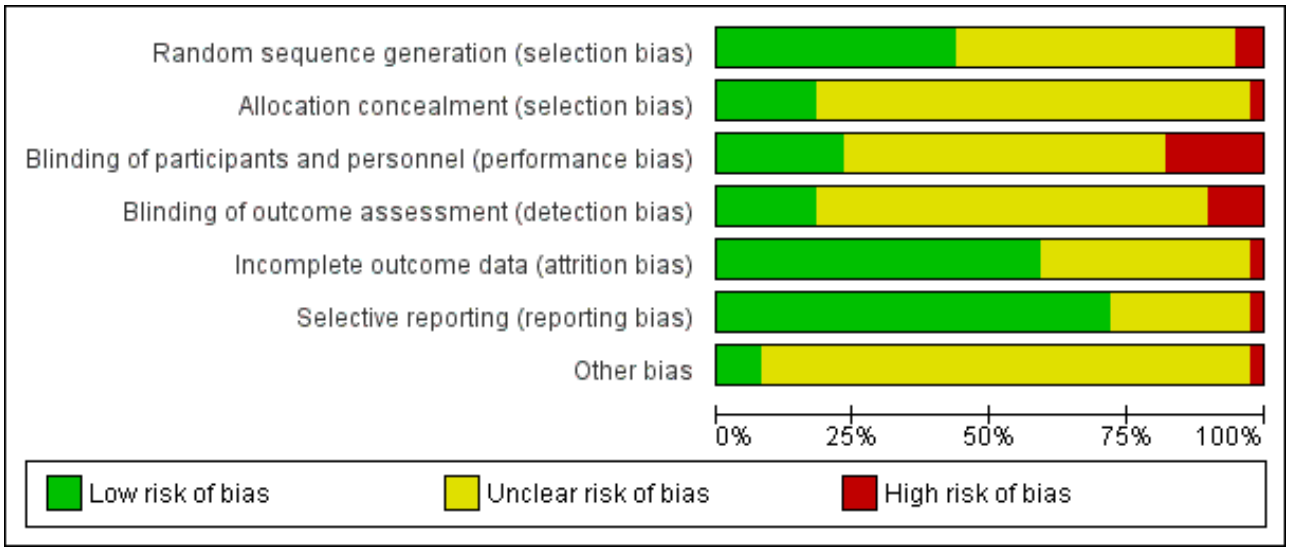

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Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

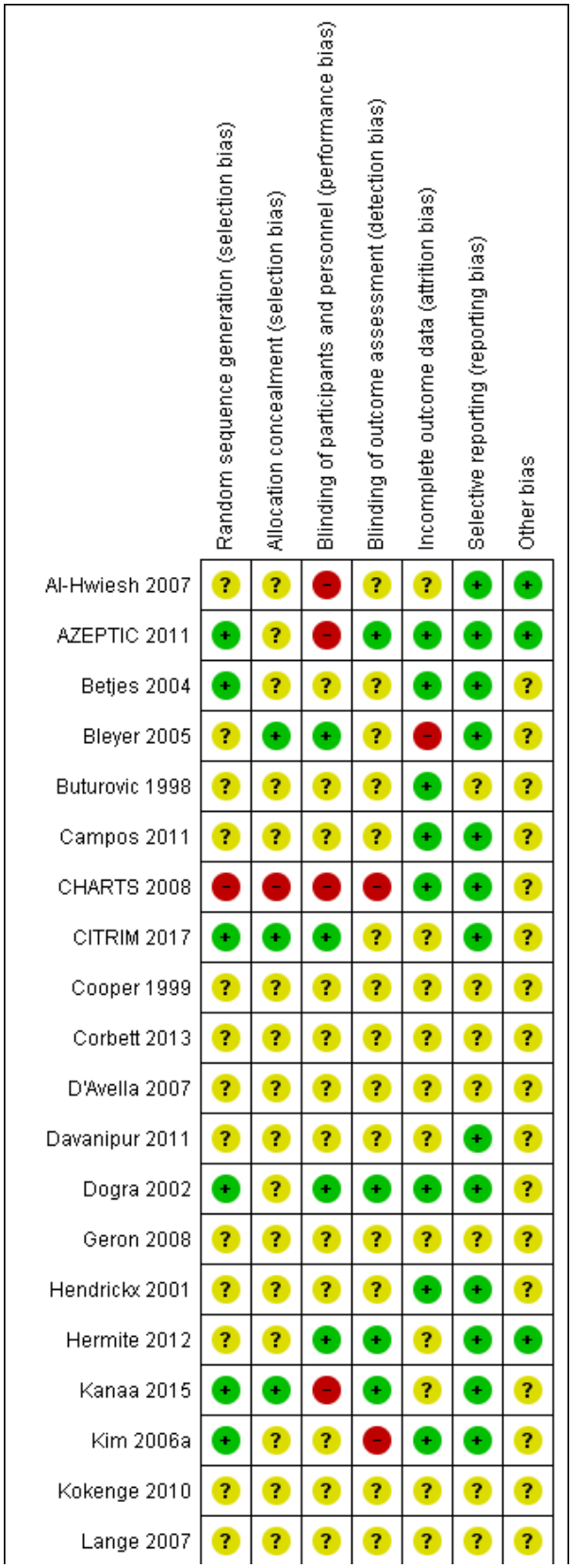

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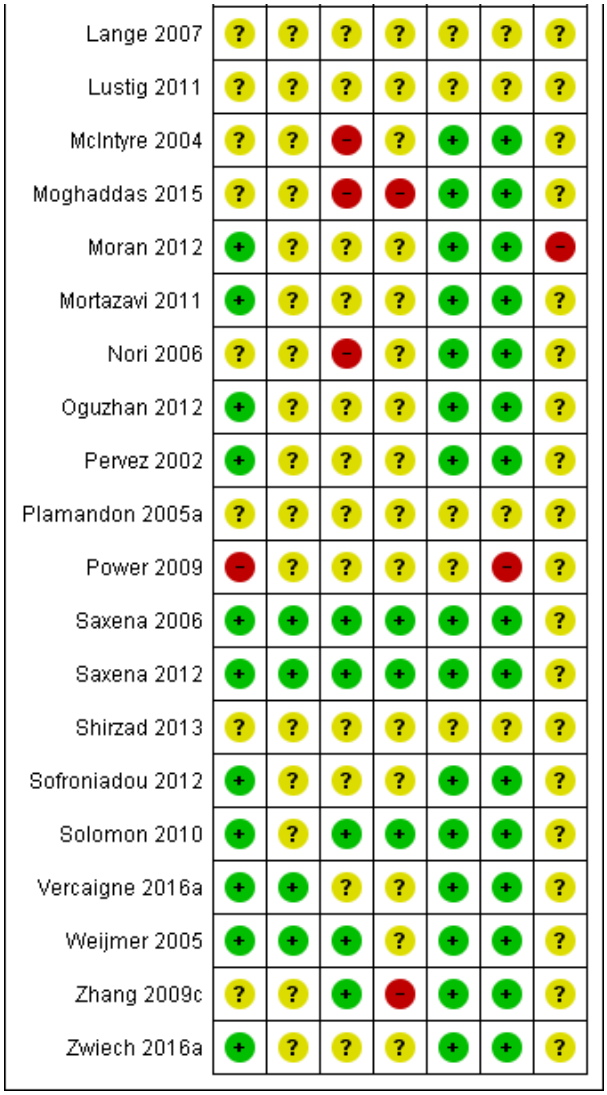
Figure 3. (Continued)



Publication bias is likely to occur in all comparisons based on the funnel plots (Figure 4; Figure 5; Figure 6).

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Figure 4. Funnel plot of comparison: 1 Antimicrobial (Antibiotic plus non-antibiotic) solutions versus control, outcome: 1.1 CVC-related infection (per 1000 catheter-days).

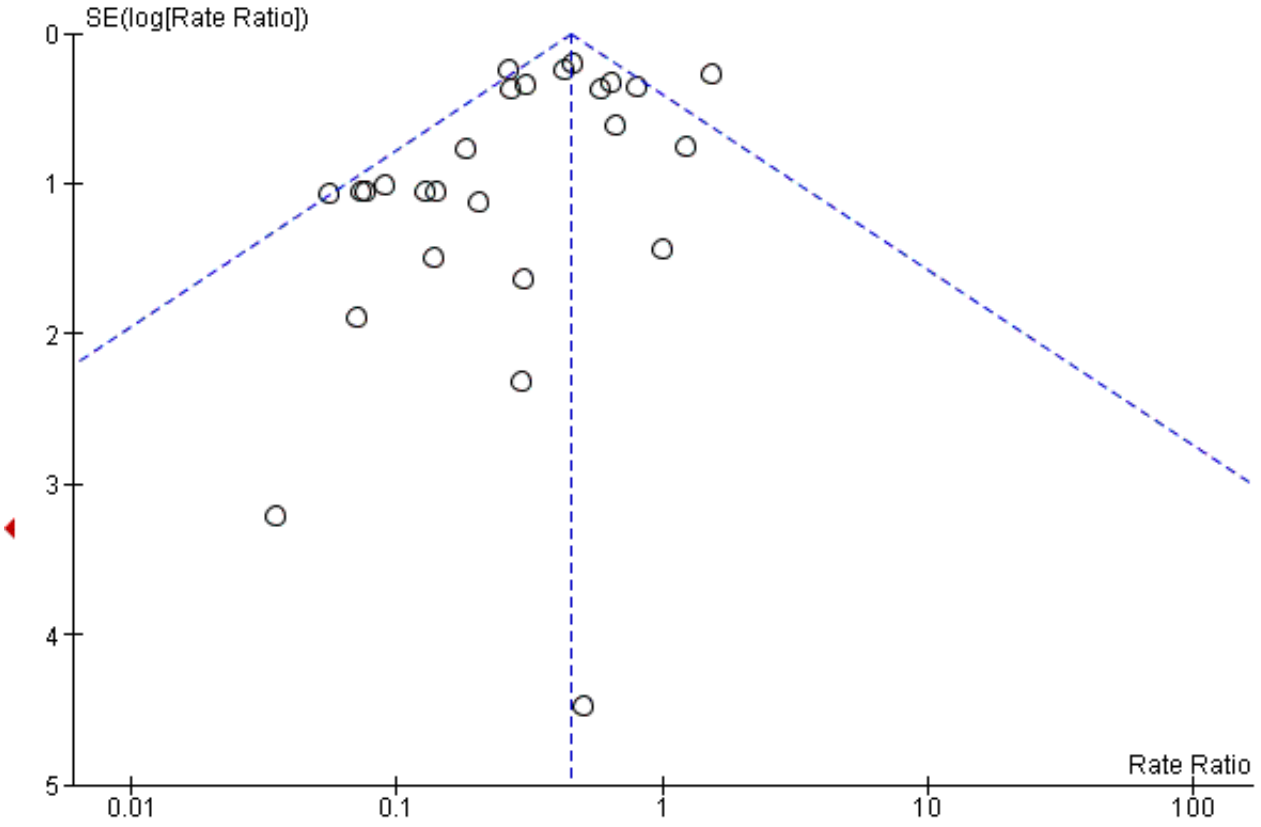

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Figure 5. Funnel plot of comparison: 1 Antimicrobial (antibiotic plus non-antibiotic) lock solutions versus control, outcome: 1.3 Thrombosis (per 1000 catheter-days).

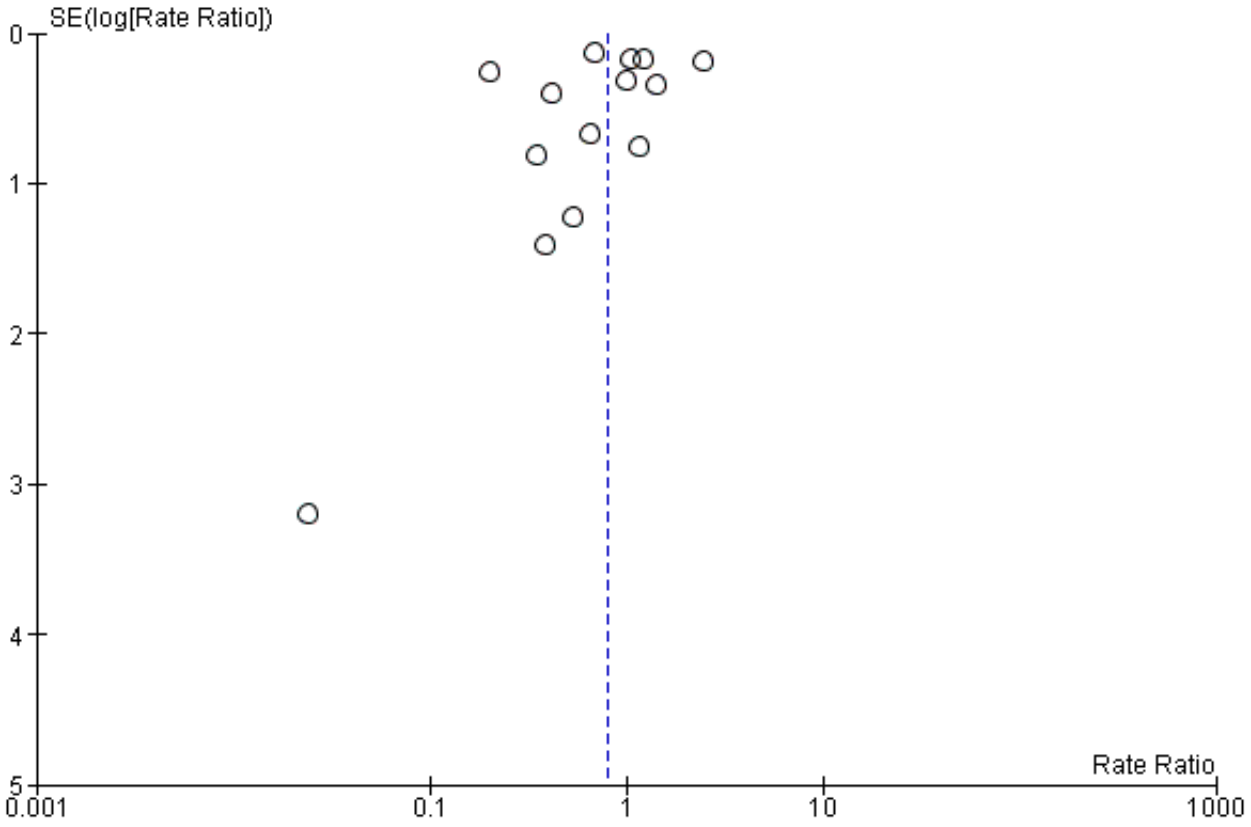

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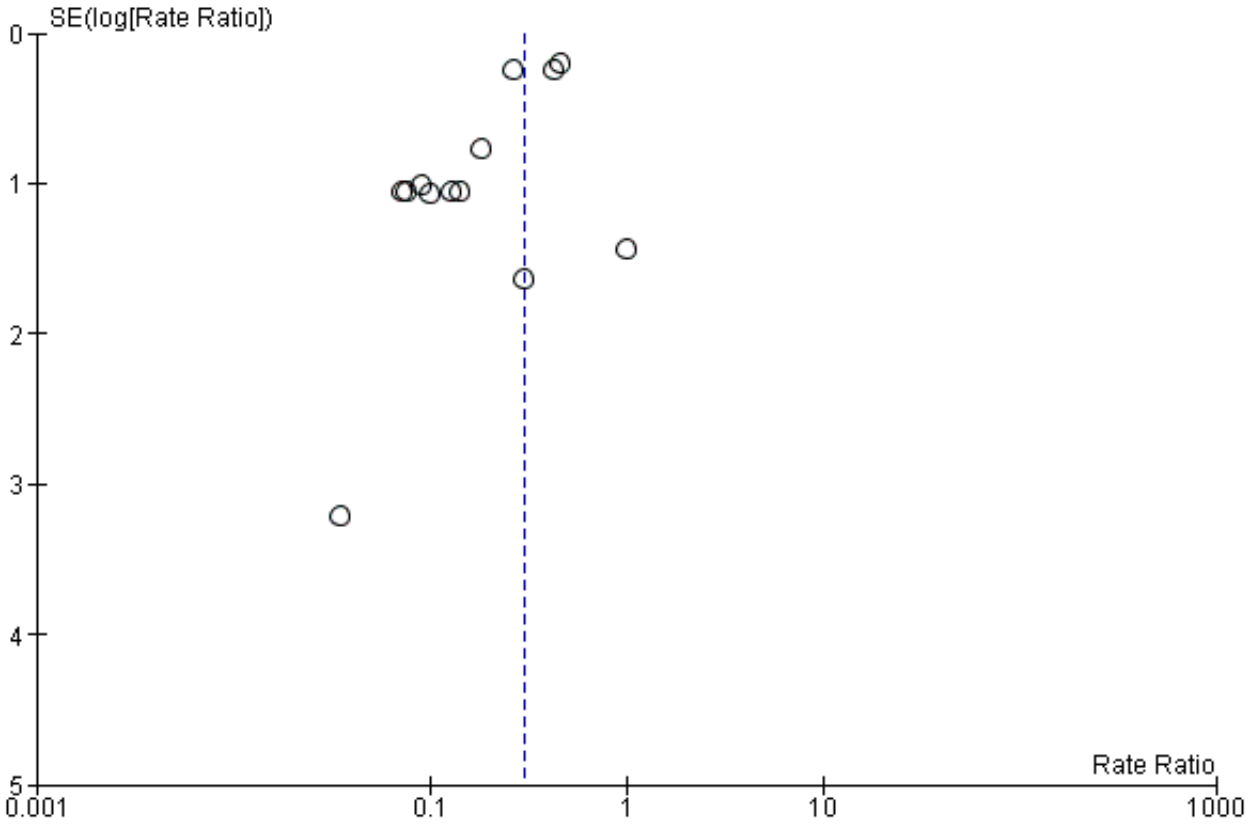
Figure 6. Funnel plot of comparison: 3 Antibiotic lock solutions versus control, outcome: 3.1 Catheter-related infection (per 1000 catheter-days).



Potential biases in the review process

A comprehensive search of the Cochrane Kidney and Transplant's Specialised Register was undertaken, thereby decreasing the likelihood of overlooking published studies. However, some studies may have been missed in the process, or may have been presented in some conferences not included in our search. Data was not complete for many studies; we contacted the authors via e-mail regarding any missing information, however only one responded.

This review was performed independently by two authors in the stages of selection of articles and two others in the extraction of data. A third author participated in both processes when no agreement was reached through consensus. Sensitivity analysis was performed on the main results. As several studies contained insufficient information to make a judgment of quality, we contacted the authors; unfortunately, with no response from them.

Agreements and disagreements with other studies or reviews

Yahav 2008 published a systematic review evaluating antimicrobial lock solutions for the prevention of HD CRI. This review included 16 studies using antibiotic lock solutions or non-antibiotic lock solutions. We included in our review 9 of the 11 comparing antibiotic lock solutions and 4 of the 5 comparing non-antibiotic lock solutions. The studies not included in our review did not meet of our inclusion criteria (i.e. inappropriate design or insufficient data reported). Snaterse 2010 published a review analysing the use of catheter locking with antimicrobial, antibiotic and non-antibiotic solutions for preventing the infection of CVC used for an extended period of time, including multiple indications of prolonged use. All studies that included participants who used catheter for HD were included in the review.

Zhao 2014 evaluated whether citrate is superior to heparin in the permeability of HD CVC and the prevention of infections. Eleven of the 12 studies included in the review are considered in the our systematic review. One study was not included because it was not randomised.

Grudzinski 2015 published a review whose objective was to evaluate the benefits and risks of catheter locks for HD catheters with sodium citrate. The five included studies are included in our review; however, it is not possible to compare these with our review because their aims are the benefits and harms of using citrate versus heparin as a CVC locking solution.

The results of our review are similar regarding the effect of antibiotic lock solutions to those reported by Yahav 2008 and Snaterse 2010, showing that antibiotic lock solutions for HD CVC reduce the incidence of CRI per 1000 catheter-days. In addition, Zhao 2014 found that citrate in combination with other antimicrobials (non-antibiotic antimicrobial lock solutions and antibiotic lock solutions) compared with heparin were associated with a lower incidence of CRI; however citrate alone was not shown to be better than heparin. Our review confirmed these findings.

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AUTHORS' CONCLUSIONS

Implications for practice

Our review shows that antibiotic antimicrobial and combined (antibiotic plus non-antibiotic) lock solutions decreased the incidence of CRI compared to control lock solutions, usually heparin, but non-antibiotic lock solutions did not significantly reduce CRI in participants undergoing HD through a CVC. This beneficial effect was also better established for tunnelled CVC. The effect on the incidence of thrombosis is uncertain for all antimicrobial lock solutions due to imprecision and heterogeneity of results. Our confidence on the evidence is low and very low ; better designed studies are needed to confirm the efficacy and safety of antimicrobial lock solutions. In addition, it is necessary to consider our uncertainty in other potential adverse effects such as ototoxicity from the use of gentamycin, risk of antibiotics resistance, among others, that were not assessed in the studies included in this review.

Implications for research

Although the available data show that some antimicrobial lock solutions are effective in preventing CRI, additional large, well-designed RCTs are required to evaluate incidence of CRI, thrombosis, and adverse events. These studies should consider a follow-up of patients sufficiently long to detect microbial resistance in the case of antimicrobial antibiotic solutions and other adverse effects in both the antibiotic and non-antibiotic antimicrobial lock solutions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Al-Hwiesh 2007

Methods	• Study design: parallel RCT • Study duration: February 2005 to July 2006 • Duration of follow-up: 12 months
Participants	• Setting: single centre • Country: Saudi Arabia • Patients on HD who had HD catheter • Number (patients/catheters): treatment group (36/39); control group (33/47) • Mean age ± SD (years): treatment group (47.4 ± 11.5); control group (45.5 ± 7.4) • Sex (M/F): treatment group (22/14); control group (21/12) • Exclusion criteria: not reported
Interventions	Treatment group

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Al-Hwiesh 2007 *(Continued)*

	• Vancomycin hydrochloride: 25 mg/mL • Gentamycin sulphate: 40 mg/mL • Heparin: 5000 U/mL Control group • Heparin: 5000 U/mL
Outcomes	• Bacteraemia • Clinical sepsis
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Study protocol not available but published results include all expected outcomes
Other bias	Low risk	Study appears free of other biases

AZEPTIC 2011

Methods	• Study design: parallel RCT • Study duration: May 1999 to June 2001 • Duration of follow-up: 6 months
Participants	• Setting: multicentre (25 centres) • Country: USA • Adult with ESKD > 18 years receiving HD 3 times/wk through a cuffed and tunnelled internal jugular venous catheter with a mean baseline flow rate of 300 mL/min, if they had no clinical or laboratory evidence of active infection within the preceding 30 days and a negative pre-enrolment blood culture • Number (patients randomised/analysed/catheters): treatment group (209/201/201); control group (207/206/206) • Mean age ± SD (years): treatment group (62.2 ± 15.4); control group (61.7 ± 15.2)

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AZEPTIC 2011 *(Continued)*

	• Sex (M): treatment group (48.8%); control group (51.5%) • Exclusion criteria: femoral and subclavian catheters; catheters with antithrombotic or antimicrobial coatings; pregnancy; thrombocytopenia or other chronic coagulopathy; history of heparin-induced thrombocytopenia; antibiotic therapy within 14 days of enrolment (30 days for vancomycin); hypersensitivity to heparin, sodium citrate, methylene blue, methylparaben, or propylparaben; current infection or who were under antibiotic therapy
Interventions	Treatment group • Sodium citrate: 0.24 M (7.0%) • Methylene blue: 0.05% • Methylparaben: 0.15% • Propylparaben: 0.015% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Patency failure • Adverse effects
Notes	• Funding source: " Supported, in part, by National Institute of Diabetes and Digestive and Kidney Diseases 5 R44 DK071369-03; the Indiana 21st Century Research and Technology Fund; the Oscar Rennebohm Foundation of Madison, WI; the National Institutes of Health; and Ash Access Technology" • "Dr. Ash is the founder and reports ownership of Ash Access Technology. Dr. Ash has stock ownership and options in Ash Access Technology and received patents from Ash Access Technology related to this product. Mr. Winger is employed by Ash Access Technology and reports ownership and stock options. Dr. Lavin is employed by Averion International. Averion International was compensated by Ash Access Technology for clinical monitoring, statistical analysis, and clinical event committee support for this study."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible consenting participants were randomised 1:1 to one of the two treatment groups from computer-generated randomizations lists
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent committee assessed the outcome and was blinded to patient treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol

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AZEPTIC 2011 *(Continued)*

Other bias	Low risk	Study appears free of other biases

Betjes 2004

Methods	• Study design: parallel RCT • Study duration: May 2002 to June 2003 • Duration of follow-up: 90 days
Participants	• Setting: single centre • Country: Netherlands • Patients who needed a HD catheter for starting or continuing HD treatment • Number: 58 randomised, 76 catheters; treatment group (37 catheters); control group (39 catheters) • Mean age ± SD (years): treatment group (58.3 ± 16.3); control group (50.3 ± 20.4) • Sex (M): treatment group (56.8%); control group (61.5%) • Exclusion criteria: HD catheter was used on the ICU or for reasons other than HD; using antibiotics
Interventions	Treatment group • Sodium citrate: 4% • Taurolidine: 1.35% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Clinical exit-site infection • Bacterial colonisation • CRS or bacterial colonisation-free survival
Notes	• Nasal mupirocin was administered to participants • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...computer-generated table of random numbers. The randomization procedure was done independent of type of catheter or place of insertion"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement

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Betjes 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Study protocol not available but published results include all expected outcomes
Other bias	Unclear risk	Funding sources not reported

Bleyer 2005

Methods	• Study design: parallel RCT • Study duration: 1 August 1998 to 17 November 1999 • Duration of follow-up: to 31 December 2000
Participants	• Setting: multicentre (4 centres) • Country: USA • Participants to remain in the hospital for more than 30 days or if they were expected it receive HD at one of four dialysis centres in the vicinity • Number (patients/catheters): treatment group (30/30); control group (30/30) • Mean age ± SD (years): treatment group (50.1 ± 19.6); control group (58.7 ± 13.5) • Sex (F): treatment group (36.7%); control group (48.2%) • Exclusion criteria: active catheter infection; active infection at any site within the previous 48 hours; known allergies to heparin, minocycline, or EDTA; serum calcium < 7.5 mg/dL with symptoms; previous enrolment in the study
Interventions	Treatment group • Minocycline-EDTA: minocycline (3 mg/mL); EDTA (30 mg/mL) Control group • Heparin: 5000 U/mL
Outcomes	• Catheter clotting • Catheter colonisation • CRI
Notes	• Funding source: not reported • "One of the investigators at the study site (RJS) is a co-patent holder on the minocycline–EDTA flush solution being studied. Another author at a distant site (IIR) is the other patent holder. The study was blinded and the data analyses were done by AJB and GR to minimize any potential conflicts"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomised according to a block design, with each block consisting of four patients"; however method of randomisation not reported
Allocation concealment (selection bias)	Low risk	"Only the pharmacist who prepared and distributed the catheter solutions knew the randomizations code"

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Bleyer 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study. "Each solution was drawn up into a syringe, and each syringe was wrapped in orange plastic so that differences in color between the two solutions (minocycline–EDTA, orange; heparin, clear) could not be identified."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Three losses in the control group were not considered in the analysis
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported; 2 authors were patent holders for treatment solution

Buturovic 1998

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: USA • Patients with subclavian or jugular single lumen catheters inserted as temporary blood access for HD expected to be used for at least 7 days • Number (patients/catheters): treatment group 1 (10/10); treatment group 2 (10/10); control group (10/10) • Mean age ± SD: 63.1 ± 8 years • Sex (M/F): 13/17 • Exclusion criteria: not reported
Interventions	Treatment group 2 • Trisodium citrate: 3mL of 4% Treatment group 2 • Polygeline: 3 mL of 3.5% Control group • Unfractioned heparin: 1 mL (5000 IU) • Saline: 2 mL
Outcomes	• Thrombosis
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

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Buturovic 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Unclear risk	Study protocol not available but published results include all expected outcomes
Other bias	Unclear risk	Insufficient information to permit judgement

Campos 2011

Methods	• Study design: parallel RCT • Study duration: March 2008 to July 2009 • Duration of follow-up: 90 days
Participants	• Setting: multicentre (3 centres) • Country: not reported • Patients > 18 years, had reached ESKD and required planned HD by a catheter for at least 2 weeks, had no evidence of active infection, and had discontinued any antibiotic at least 7 days before catheter implantation; only catheters implanted in jugular and subclavian veins • Number: 150 patients; treatment group (102 catheters); control group (102 catheters) • Mean age ± SD (years): treatment group (54.56 ± 16.86); control group (55.55 ± 15.35) • Sex (M): treatment group (62%); control group (53.7%) • Exclusion criteria: in the first two sessions of HD, the catheter did not allow a pump blood flow rate of > 200 mL/min for non-tunnelled catheters and > 250 mL/min for tunnelled catheters; protocol violation
Interventions	Treatment group • Minocycline: 3 mg/mL • EDTA: 30 mg/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Catheter dysfunction
Notes	• Funding source: not reported

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Campos 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation was performed by sealed envelope, but did not state if they were opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data was reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported

CHARTS 2008

Methods	• Study design: quasi-RCT • Study duration: December 2004 to June 2005 • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: Canada • Participants receiving chronic HD 3 times/week, 4 h/session, at the in-centre HD Unit with cuffed catheters as primary vascular access; enrolled in the study until their catheters were removed or until the study completion date • Number (patients/catheters): treatment group (32/32); control group (29/29) • Mean age ± SD (years): treatment group (63 ± 16); control group (69 ± 15) • Sex (M/F): treatment group (21/11); control group (14/15) • Exclusion criteria: previously randomised to the study; AV fistula or AV graft was already in use at the time of the study; currently on antibiotics; unable or unwilling to give informed consent
Interventions	Treatment group • Citrate: 4% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Exit side Infection

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CHARTS 2008 *(Continued)*

	• Local bleeding • Systemic bleeding complication (epistaxis, fistula hematoma, prolonged fistula bleeding 30 min, hemarthrosis, gastrointestinal bleeding, haemoptysis, and intracerebral haemorrhage) • Thrombocytopenia
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomised according to their last name
Allocation concealment (selection bias)	High risk	No allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data was reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported

CITRIM 2017

Methods	• Study design: parallel RCT • Study duration: July 2012 to July 2014 • Duration of follow-up: 180 days
Participants	• Setting: single centre • Country: Brazil • Patients > 18 years; CKD or AKI requiring HD through a catheter; admitted to ICU • Number (catheters): treatment group (233); control group (231) • Mean age ± SD (years): Treatment group (58.61 ± 17.14); control group (57.44 ± 18.27) • Sex (males): treatment group (50.21%); control group (47.82%) • Exclusion criteria: patients with a tunnelled catheter; suspected heparin-induced thrombocytopenia; allergy to heparin or trisodium citrate; systemic or localised infection; pregnant women
Interventions	Treatment group • Trisodium citrate: 30% (Citra-Lock™ 30 %, Fresenius MedicalCare). Control group

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CITRIM 2017 *(Continued)*

	• Unfractionated sodium heparin: 5000 U/mL
Outcomes	• CRI • Catheter dysfunction
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...computer-generated list of random numbers in blocks of six."
Allocation concealment (selection bias)	Low risk	"...was performed using opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and investigators were unaware of the treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported

Cooper 1999

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: not reported • Country: USA • Chronic HD patients with permanent HD catheter access • Number: treatment group (19); control group (17) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Gentamicin: 40 mg/lumen Control group

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Cooper 1999 *(Continued)*

	• Heparin: 5000 U/lumen
Outcomes	• CRI: diagnosed by positive blood cultures with no other identifiable infection source • Probable CRI: diagnostic when clinical suspicion of infection was high but blood cultures were negative
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Corbett 2013

Methods	• Study design: parallel RCT • Study duration: no reported • Duration of follow-up: 6 months
Participants	• Setting: within centre and satellite dialysis units • Country: UK • All patients on established HD with evidence of a CRI and who had commenced treatment for catheter salvage • Number: treatment group (14); control group (13) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Citrate

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Corbett 2013 *(Continued)*

	• Taurolidine • Heparin: 500 U/mL Control group • Heparin: 5000 U/mL
Outcomes	• Recurrence of CRI
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

D'Avella 2007

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: USA • Chronic HD patients with permanent catheter • Number: treatment group (46); control group (45) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group

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D'Avella 2007 *(Continued)*

	• Saline: 18% • Heparin: 7000 U/mL Control group • Saline: 0.9% • Heparin: 10,000 U/mL
Outcomes	• CRI
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Davanipur 2011

Methods	• Study design: parallel RCT • Study duration: 2007 to 2008 • Duration of follow-up: 6 months
Participants	• Setting: multicentre (3) • Country: Iran • Adults on long-term HD (twice or three times per week), regardless of the cause of kidney failure, with newly inserted uncuffed temporary double-lumen catheters • Number (participants/catheters): treatment group (50/50); control group (50/50) • Mean age (years): treatment group (50.1); control group (52.3) • Sex (M/F): treatment group (22/28); control group (28/22)

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Davanipur 2011 *(Continued)*

	• Exclusion criteria: not reported
Interventions	Treatment group • Cloxacillin: 100 mg/mL • Heparin: 1000 IU/mL Control group • 2.5 mL of solution composed of heparin and normal saline
Outcomes	• CRI • Infection-free catheter survival • Colonisation
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported. "Participants were randomly divided into 2 groups."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported

Dogra 2002

Methods	• Study design: parallel RCT • Study duration: May 1999 to June 2001 • Duration of follow-up: 270 days
Participants	• Setting: multicentre (2) • Country: Australia • Participants required insertion of a tunnelled catheter for the maintenance or commencement of HD • Number (participants/catheters): treatment group (44/55); control group (39/57)

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Dogra 2002 *(Continued)*

- Mean age ± SD (years): treatment group (55.7 ± 2.5); control group (59.3 ± 2.1)
- Sex (% M/F): treatment group (45/55); control group (47/53)
- Exclusion criteria: active sepsis; were on parenteral or prolonged (> 5 d) oral antibiotic therapy; allergy to gentamicin and/or citrate

Interventions	Treatment group • Gentamicin: 2 mL of 40 mg/mL • Tri-sodium citrate: 1mL of 3.13% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Infection-free catheter survival
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomization using random number tables was performed by Clinical Trials Pharmacists, thereby ensuring allocation concealment"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of microbiology staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Funding source not reported

Geron 2008

Methods	• Study design: parallel RCT • Study duration: 6 months • Duration of follow-up: not reported
Participants	• Setting: not reported • Country: Israel • Patients with newly inserted tunnel cuffed catheter

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Geron 2008 *(Continued)*

- Number: treatment group 1 (5); treatment group 2 (7); control group (5)
- Mean age ± SD (years): not reported
- Sex (M/F): not reported
- Exclusion criteria: not reported

Interventions	Treatment group 1 • Taurolock Treatment group 2 • Taurolock • Heparin: 500 U/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Patency dysfunction
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Hendrickx 2001

Methods	• Study design: parallel RCT • Study duration: April to October 2000

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Hendrickx 2001 *(Continued)*

	• Duration of follow-up: not reported
Participants	• Setting: single centre • Country: Belgium • Patients with a single lumen CVC as permanent access • Number: treatment group (10); control group (9) • Mean age (years): treatment group (74.6); control group (71.4) • Sex (M/F): treatment group (4/6); control group (4/5) • Exclusion criteria: temporary catheter; previous history of catheter position-related inadequate blood flow; known history of haemorrhagic diathesis or systemic thrombo-embolic events; liver failure; on chronic anticoagulation therapy (low dose aspirin excluded)
Interventions	Treatment group • Trisodium citrate: 5% Control group • Heparin: 5000 U/mL
Outcomes	• Non-occlusive clot formation • Complete occlusion of the catheter • Necessity for urokinase therapy • Incidence of flow problems • CRI.
Notes	• Most of the outcome were not defined • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported "...patients were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported

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Hermite 2012

Methods	• Study design: parallel RCT • Study duration: May 2009 to August 2010 • Duration of follow-up: not reported
Participants	• Setting: Single centre (2 units) • Country: France • ICU adult participants ≥18 years with AKI requiring continuous or intermittent HD • Number (participants/catheters): treatment group (39/39); control group (39/39) • Mean age ± SD (years): treatment group (64 ± 15); control group (65 ± 16) • Sex (M/F): treatment group (23/16); control group (30/9) • Exclusion criteria: allergy to citrate; pregnancy; liver failure; history of thromboembolic disease
Interventions	Treatment group • Citrate solution: 46.7% Control group • Saline solution: 10 mL
Outcomes	• CRI • Probable CRI • Catheter malfunction
Notes	• Funding source: "This work was financed by the University Hospital of Dijon Clinical Research Division"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was an open-label trial; but "as far as possible, the nurses and physicians in the unit in charge of the routine care were blinded to each patient's treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were evaluated by an independent clinical event committee who were blinded to participants' treatment group assignments.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Low risk	Study appears free of other biases

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Kanaa 2015

Methods	• Study design: parallel RCT • Study duration: August 2006 to October 2008 • Duration of follow-up: terminated early
Participants	• Setting: multicentre (4) • Country: UK • Maintenance HD patients with confirmed uncolonised tunnelled HD catheters • Number: treatment group (59); control group (58) • Mean age, range (years): treatment group (61, 24 to 83); control group (60, 21 to 4) • Sex (M/F): treatment group (44/15); control group (38/20) • Exclusion criteria: any medical, social or psychological condition that would compromise participation and follow-up in study; pregnant or lactating; tunnelled catheter with an expected duration of placement or use of less than 60 days; enrolled in another clinical study, or had participated in the study; life expectancy of less than 3 months; existing tunnelled CVC who had positive blood cultures or received antimicrobial therapy, including antibiotic lock solution and/or antimicrobial catheters, for documented or suspected CRI within 14 days prior to enrolment; evidence of systemic infection or catheter exit site infection at the time of enrolment; colonized catheters (screening quantitative through catheter blood cultures (QTCBC) yielding >20 CFU/mL bacteria or yeasts); catheters demonstrated signs of dysfunction in 2 or more dialysis sessions during the last 2 weeks prior to enrolment
Interventions	Treatment group • Cathasept: 4% Control group • Heparin: 5000 U/mL
Outcomes	• Clinically significant microbial colonisation: through-catheter quantitative blood culture yielding ≥ 1000 CFU/mL of bacteria or yeast • CRI • Catheter patency • Biomarkers of inflammation and anaemia
Notes	• Funding source: "...Tyco Healthcare Group LP, doing business as Covidien (Mansfield, MA), for funding the study and contributing to the study design and data collection; and Yorkshire Kidney Research Fund for an educational grant to support Dr Kanaa. The sponsors had no role in analysis or interpretation of data, writing the report, or the decision to submit the report for publication." • Study terminated early by the sponsors due to slow recruitment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using a random number table and blocking factor of 10 in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	Was performed using opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants and personnel

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Kanaa 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of microbiology staff
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	"The sponsors had no role in analysis or interpretation of data, writing the report, or the decision to submit the report for publication." However the study was terminated early

Kim 2006a

Methods	• Study design: parallel RCT • Study duration: March 2001 and February 2003 • Duration of follow-up: 60 days
Participants	• Setting: single centre • Country: Korea • Participants requiring a temporary catheter while waiting for placement and maturation of an AV fistula or graft • Number (participants/catheters): treatment group (60/60); control group (60/60) • Mean age ± SD (years): treatment group (53.68 ± 15.201); control group (56.18 ± 15.684) • Sex (M/F): treatment group (33/27); control group (28/32) • Exclusion criteria: already had an infection; under antibiotic therapy
Interventions	Treatment group • Cefazolin: 10 mg/mL • Gentamicin: 5 mg/mL • Heparin: 1000 U/mL Control group • Heparin: 1000 U/mL
Outcomes	• CRI
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomizations method was made using table of random number
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Kim 2006a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	High risk	Researchers assessed the outcomes were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were performed on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Funding source not reported

Kokenge 2010

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: stopped for adverse events
Participants	• Setting: not reported • Country: Germany • Maintenance HD patients • Number: treatment group (35); control group (39) • Mean age: 70.12 years • Sex (M/F): 43/31 • Exclusion criteria: not reported
Interventions	Treatment group • Sodium citrate: 3.13% Control group • Standard heparin
Outcomes	• Malfunctioning of catheter, due to thrombosis or bleeding.
Notes	• Abstract-only publication • "The study was stopped because of a significant (P = 0.04) higher adverse event rate in group A"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Kokenge 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Lange 2007

Methods	• Study design: parallel RCT • Study duration: January to December 2006 • Duration of follow-up: not reported
Participants	• Setting: not reported • Country: Germany • Maintenance HD patients • Number: 64; treatment group: (unclear); control group (unclear) • Mean age ± SD: 68 ± 12 years • Sex (M/F): 38/28 • Exclusion criteria: dialysis for < 3 days
Interventions	Treatment group • Sodium citrate: 3.13% Control group • Standard heparin
Outcomes	• Malfunctioning of catheter: thrombosis
Notes	• Abstract-only report • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Lange 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Lustig 2011

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: not reported • Country: Israel • Participants with a dialysis catheter • Number: 100 participants; 140 catheters; treatment group (not reported); control group (not reported) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: not reported
Interventions	Treatment group • Trisodium citrate • Ethanol • Methylene blue Control group • Heparin
Outcomes	• CRI • Thrombosis • Sepsis • Exit site infections
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

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Lustig 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

McIntyre 2004

Methods	• Study design: parallel RCT • Study duration: March 2002 to April 2003 • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: UK • Participants to have had no evidence of CRI, having been antibiotic free for at least 28 days before catheter insertion • Number (participants/catheters): treatment group (25/25); control group (25/25) • Mean age ± SD (years): treatment group (63.6 ± 2.8); control group (57.8 ± 3.2) • Sex (M/F): treatment group (18/7); control group (14/11) • Exclusion criteria: catheter was an exchange reinsertion; insertion at a separate site (with previous catheter still in situ); recent infection; those on immunosuppressant medications
Interventions	Treatment group • Gentamicin: 5 mg/mL • Heparin: 5000 IU/mL. Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Catheter malfunction
Notes	• Funding source: not reported

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McIntyre 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study was block randomised; method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Randomisation was performed by sealed envelope, but not opaque
Blinding of participants and personnel (performance bias) All outcomes	High risk	By the characteristics of the solution used, blinding of intervention was not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were performed on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Insufficient information to permit judgement

Moghaddas 2015

Methods	• Study design: parallel RCT • Study duration: February 2013 of March 2014 • Duration of follow-up: patients' follow-up length was 6 months based on the study protocol; however, we followed most, but not all, patients for 1 year
Participants	• Setting: multicentre (3) • Country: Iran • Adult patients who were dialysed by tunnelled, cuffed HD catheter using polysulfone, low-flux dialyzer and bicarbonate buffer solution 3 times a week for 4 h in each dialysis session • Number: treatment group (46); control group (41) • Mean age ± SD (years): treatment group (63.63 ± 10.63); control group (60.68 ± 14.40) • Sex (M/F): treatment group (20/26); control group (23/18) • Exclusion criteria: history of infection within the week before study's entrance or who were treating with an antibiotic; known sulfa antibiotics hypersensitivity; glucose-6-phosphate dehydrogenase enzyme deficiency
Interventions	Treatment group • Cotrimoxazole (based on trimethoprim): 10 mg/mL • Unfractionated heparin: 2500 U/mL Control group • Heparin: 2500 U/mL

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Moghaddas 2015 *(Continued)*

Outcomes	• CRI (definition CDC) • CRI-free survival: the number of days from the start of the study to diagnosis of CRI • Catheter dysfunction: as the requirement for catheter removal or the need for thrombolytic drugs administration via the dialysis catheter because a pump blood ow of more than 250 mL/min that is needed for tunnelled, cuffed catheters was not achieved during HD or there was clinical suspicious for thrombosis formation • Exit site infection as a symptoms including erythema, tenderness and/or induration within 2 cm of the dialysis catheter exit site with or without purulent exudates or microbiological exit site infection where the exudates lead to microorganism's growth in the culture
Notes	• Funding source: "This study was part of an Iranian BCPS thesis that has been supported by Tehran University of Medical Sciences (grant number 92-01-33-21582)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was made using cluster randomization among three dialysis units."; method for doing this was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were performed on an intention-to-treat basis
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Insufficient information to permit judgement

Moran 2012

Methods	• Study design: parallel RCT • Study duration: September 2003 to May 2008 • Duration of follow-up: not reported
Participants	• Setting: multicentre (16) • Country: USA • All adult participants with either newly placed or existing tunnelled cuffed catheters • Number (participants/catheters): Treatment group (155/155); control group (148/148) • Mean age ± SD (years): treatment group (63.4 ± 15.6); control group (62.8 ± 16.8) • Sex (% M/F): treatment group (49/51); control group (54.7/45.3)

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Moran 2012 *(Continued)*

	• Exclusion criteria: active exit-site or tunnel infection or other systemic or localized infection that was unresponsive to antibiotic therapy and/or was life-threatening; any infection associated with one or more positive blood culture results until 14 days after blood culture results had become negative and clinical resolution of the episode had occurred; known allergy to heparin or gentamicin; known IV drug use
Interventions	Treatment group • Gentamicin: 320 µg/mL • sodium citrate: 4% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Thrombosis
Notes	• Funding source: "This study was entirely funded by Satellite Healthcare, the study sponsor. Dr Moran, Ms Khababa, Ms Sun, Ms Doss, and Dr Schiller were employees of Satellite Healthcare at the time the study was conducted."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomly assigned 1:1 to treatment or control groups using a central randomization system with participants randomly assigned within centers in blocks of 2 and 4 to ensure an approximate balance in the number of participants in each group within each centre"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	High risk	This study was entirely funded by Satellite Healthcare, the study sponsor. Most investigators were employees of Satellite Healthcare at the time the study was conducted

Mortazavi 2011

Methods	• Study design: parallel RCT

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Mortazavi 2011 *(Continued)*

	• Study duration: December 2009 to March 2010 • Duration of follow-up:
Participants	• Setting: multicentre (2) • Country: Iran • Participants > 18 years, being dialysed with central tunnelled catheter (only if placed in the internal jugular vein), with a maximum time of 1 month post catheterisation, dialysis 3 times a week and having accepted to participate • Number (participants/catheters): treatment group (15/15); control group (15/15) • Mean age ± SD (years): treatment group (52 ± 10.30); control group (56 ± 9.6) • Sex (M/F): treatment group (7/8); control group (6/9) • Exclusion criteria: allergy to cefotaxime; antibiotic treatment within 2 weeks prior to enrolment; participants requiring a surrogate decision maker; catheters with blood flow rates < 300 mL/min, or requiring frequent thrombolytic solution dwells in the catheter lumen because of malfunction
Interventions	Treatment group • Cefotaxime: 10 mg/mL • Heparin: 5000 UI/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI
Notes	• Funding source: " No financial support received in support of the study:

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used randomisation computerized block protocol
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind study, probably were blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Insufficient information to permit judgement

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Nori 2006

Methods	• Study design: parallel RCT • Study duration: 4 October 2003 and 30 April 2004 • Duration of follow-up: not reported
Participants	• Setting: multicentre (3) • Country: USA • Participants with either tunnelled or non tunnelled (only if placed in the internal jugular vein) catheter as their primary vascular access • Number (randomised/analysed/catheters): treatment group 1 (20/20/20); treatment group 2 (21/21/21); control group (21/20/21) • Mean age ± SEM (years): treatment group 1 (58 ± 3);treatment group 2 (58 ± 3) control group (59 ± 4) • Sex (M/F): treatment group 1 (11/9); treatment group 2 (13/8); control group (10/10) • Exclusion criteria: < 18 years; required a surrogate decision maker; antibiotic treatment within 2 weeks before the date of enrolment; catheters with blood flow rates < 300 mL/min; required frequent thrombolytic solution dwells in the catheter lumen for malfunction; admitted to an outside hospital for any illness; required thrombolytics for catheter thromboses on more than 3 occasions
Interventions	Treatment group 1 • Gentamicin: 4 mg/mL • Citrate: 3.13 % Treatment group 1 • Minocycline: 3 mg/mL • EDTA: 30 mg/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI
Notes	• Funding source: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Permuted block randomisation was performed at each centre; method not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias)	Low risk	All patient data reported

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Nori 2006 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Describes the outcomes according to objectives
Other bias	Unclear risk	Insufficient information to permit judgement

Oguzhan 2012

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: multicentre (central unit plus associated satellites) • Country: Turkey • Adults > 18 years receiving HD through a central venous tunnelled catheter. These included participants with AKI and those with chronic ESKD, both incident and prevalent • Number (participants/catheters): treatment group (26/26); control group (30/30) • Mean age ± SD (years): treatment group (60.2 ± 15.2); control group (58 ± 14.3) • Sex (% M/F): treatment group I (50/50); control group (36.6/63.4) • Exclusion criteria: < 18 years; pregnant; active sepsis; on antibiotic therapy; needed the reinsertion of a tunnelled catheter through the same exit site or a new entry site; or if the tunnelled catheter was used for another purpose other than HD
Interventions	Treatment group • NaCl: 26% • Heparin: 500 U/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Thrombosis
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomization using random number tables was performed"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to permit judgement

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Oguzhan 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data was reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Insufficient information to permit judgement

Pervez 2002

Methods	• Study design: parallel RCT • Study duration: January 1999 to April 2000 • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: USA • Participants who underwent tunnelled catheter placement, including participants who had a tunnelled catheter changed over guide wire • Number (participants/catheters): treatment group (14/14); control group (22/22) • Mean age ± SE (years): treatment group I (53.7 ± 4.0); control group (47.6 ± 3.3) • Sex (M/F): treatment group I (10/4); control group (10/12) • Exclusion criteria: not reported
Interventions	Treatment group • Tricitrasol: 46:7% • Gentamicin: 40 mg/mL Control group • Heparin: 1000 U/mL
Outcomes	• CRI
Notes	• Catheter hub covered with a sterile plastic bag after cleaning with a 10% povidone iodine solution • Funding source: "This study was supported by the Dialysis Clinic Inc."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use computer-generated number list
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement

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Pervez 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Was supported by the Dialysis Clinic Inc

Plamandon 2005a

Methods	• Study design: crossover RCT • Study duration: 4 weeks • Duration of follow-up: not reported
Participants	• Setting: not reported • Country: Canada • Participants with prevalent cuffed double lumen catheters • Number: 44 • Mean age: 72.9 years • Sex (males): 57% • Exclusion criteria: not reported
Interventions	Treatment group • sodium citrate: 4% Control group • Heparin: 5000 U/mL
Outcomes	• Thrombosis • Catheter dysfunction
Notes	• Abstract-only publication • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Insufficient information to permit judgement

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Plamandon 2005a *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Power 2009

Methods	• Study design: quasi-RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: multicentre (4) • Country: UK • Participants who had been on dialysis therapy for longer than 90 days • Number (participants/catheters): treatment group (132/132); control group (100/100) • Mean age ± SD (years): treatment group I (63 ± 14); control group (62 ± 13) • Sex (M/F): treatment group (73/59); control group (59/41) • Exclusion criteria: bleeding diathesis; an intervention, or pathological state within 3 months of entry that would heighten the risk of bleeding; hypocalcaemia
Interventions	Treatment group • Sodium citrate: 46.7% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Catheter dysfunction
Notes	• Funding source: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Single random- numbers method of odd and even numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

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Power 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patient data reported
Selective reporting (reporting bias)	High risk	Outcomes of interest reported incompletely
Other bias	Unclear risk	Insufficient information to permit judgement

Saxena 2006

Methods	• Study design: RCT • Study duration: March 2002 to February 2003 • Duration of follow-up: 18 months
Participants	• Setting: single centre • Country: Saudi Arabia • Elderly participants who underwent reinsertion of a tunnelled central catheter through a new access site • Number (randomised/analysed/catheters): treatment group (60/59/61); control group (58/55/63) • Mean age ± SD (years): treatment group (78 ± 19); control group (75.5 ± 17) • Sex (M/F): Treatment group (36/22); control group (32/23) • Exclusion criteria: active sepsis, receiving prolonged (> 7 days) antibiotic therapy (oral/parenteral); allergies to cephalosporins; could not be randomised within 3 dialysis sessions of new tunnel catheter insertion; had the exchange over guidewires of a tunnelled catheter through the same exit site were also excluded
Interventions	Treatment group • Cefotaxime: 10 mg/mL • Heparin: 5000 U/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Thrombosis
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

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Saxena 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Use computer-generated random number list
Allocation concealment (selection bias)	Low risk	Numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patient's and HD staff were blinded of the treatment assigned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The microbiologist was blinded of the treatment assigned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Insufficient information to permit judgement

Saxena 2012

Methods	• Study design: RCT • Study duration: April 2005 to March 2006 • Duration of follow-up: not reported
Participants	• Setting: multicentre (2) • Country: Saudi Arabia • Participants > 18 years carrying *S. aureus* that would require the installation of a tunnelled central catheter for HD start or maintenance • Number (participants/catheters): treatment group (39/41); control group (43/47) • Mean age ± SD (years): treatment group (53.7 ± 17.2); control group (51.9 ± 19.1) • Sex (M/F): treatment group (23/16); control group (26/17) • Exclusion criteria: active sepsis receiving prolonged antibiotic therapy; hypersensitivity to heparin or cephalosporins; catheter exchanged over a guidewire; existing exit-site or tunnel infection; pregnant women
Interventions	Treatment group • Cefotaxime: 10 mg/mL • Heparin: 5000 U/mL Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Death related to CRI • Exit site infection

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Saxena 2012 *(Continued)*

Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random number
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes, numbered in sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The pharmacy dispensed equal number of identical syringes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Microbiologist was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient outcome data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Insufficient information to permit judgement

Shirzad 2013

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: Iran • Participants who underwent reinsertion of a tunnelled central catheter through a new access site • Number (participants/catheters): treatment group (58/59); control group (55/60) • Mean age ± SD (years): treatment group (78 ± 19); control group (75.5 ± 17) • Sex (M/F): treatment group (36/22); control group (32/23) • Exclusion criteria: active sepsis, receiving prolonged (> 7 days) antibiotic therapy (oral/parenteral) or allergies to cephalosporins; who could not be randomised within 3 dialysis sessions of new catheter insertion; catheter exchange over guidewires through the same exit site
Interventions	Treatment group • Cefazolin: 5 mg/dL • Heparin: 2500 IU Control group • Heparin: 2500 IU

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Shirzad 2013 *(Continued)*

Outcomes	• Infection
Notes	• Funding source: not reported • Translated from Persian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Sofroniadou 2012

Methods	• Study design: parallel RCT • Study duration: December 2004 and June 2008 • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: Greece • Participants required a temporary non-tunnelled catheter for commencement or maintenance of HD on the basis of ESKD • Number (participants/catheters): 135/156; treatment group 1 (not reported/49); treatment group 2 (not reported/52); control group (not reported/51) • Mean age, range (years): treatment group 1 (72, 62 to 80); treatment group 2 (67.5, 47 to 75); control group (72, 65 to 77) • Sex (males): treatment group 1 (30); treatment group 2 (28); control group (33) • Exclusion criteria: active systemic or localized infection under antibiotic treatment; sepsis; allergy to heparin, vancomycin or linezolid; heparin-induced thrombocytopenia and thrombosis mediated by antiheparin antibodies; pregnancy; catheter was used for any other reason than for HD; AKI requiring HD use of immunosuppressive drugs; diagnosis of a current malignancy
Interventions	Treatment group 1

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Sofroniadou 2012 *(Continued)*

	• Vancomycin: 5 mg/mL • Unfractionated heparin: 2000 U/mL Treatment group 2 • Linezolid: 2 mg/mL • Unfractionated heparin: 2000 U/mL Control group • Heparin: 2000 U/mL
Outcomes	• CRI • CRI-free survival • Exit site infections • Bacterial colonisation • Thrombosis
Notes	• Funding source: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Insufficient information to permit judgement

Solomon 2010

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: multicentre (13 centres) • Country: UK

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Solomon 2010 *(Continued)*

- Participants aged > 18 years receiving tunnelled intravascular catheters for HD and able to give informed consent
- Number (randomised/analysed/catheters): treatment group (55/53/56); control group (55/54/58)
- Mean age ± SD (years): treatment group (59.8 ± 14.7); control group (56.7 ± 17.4)
- Sex (M/F): treatment group (26/27); control group (41/13)
- Exclusion criteria: not reported

Interventions	Treatment group • Taurolidine: 1.35% • Citrate: 4% Control group • Heparin: 5000 U/mL
Outcomes	• Bacteraemia • Thrombosis (defined by need for thrombolytic therapy) • All-cause mortality
Notes	• Funding source: "This work was supported in part by a grant from the Preston branch of the North West Kidney Research Association and a grant from the Liverpool Regional Dialysis Unit Fund."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use computer-generated randomised permuted blocks of 10 participants stratified among the 3 main centres
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Insufficient information to permit judgement

Vercaigne 2016a

Methods	• Study design: parallel RCT • Study duration: August 2011 to May 2013

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Vercaigne 2016a *(Continued)*

	• Duration of follow-up: not reported
Participants	• Setting: multicentre (2) • Country: Canada • Participants: treatment group (20); control group (19) • Mean age, range (years): treatment group (63, 22.4 to 83.2); control group (62.3, 36.1 to 88.0) • Sex (M/F): treatment group (12/8); control group (9/10) • Exclusion criteria: critically ill in ICU setting; AKI and unlikely to require prolonged vascular access; maturing or planned AV fistula/graft creation within 2 months; planned antibiotics treatment courses not lasting longer than 4 weeks from the date of the new catheter insertion
Interventions	Treatment group • Ethanol: 30% • Sodium citrate: 4% Control group • Heparin: 1000 U/mL
Outcomes	• Serious adverse events • CRI • Catheter dysfunction
Notes	• Pilot study • Funding source: "This study was supported in part by MedXL Inc., Pointe-Claire, QC, Canada."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...randomised centrally in permuted blocks of four using computer software (Microsoft Excel 2010 Microsoft Corporation). Randomization was stratified based on whether the catheter was inserted into a new location or changed over a guide wire."
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Ethanol has a distinctive smell
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Study parted funded by MedXL Inc (medical devices and prefilled syringes)

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Weijmer 2005

Methods	• Study design: parallel RCT • Study duration: April 2001 to September 2002 • Duration of follow-up: not reported
Participants	• Setting: multicentre (9) • Country: Netherlands and Belgium • Participants > 18 years, not admitted to the ICU, and experienced CKD or AKI that required HD treatment by means of a HD catheter. Only participants with a newly inserted, well-positioned HD catheter that was expected to be needed for 1 week • Number (participants/catheters): treatment group (148/148); control group (143/143) • Mean age ± SD (years): treatment group (61.6 ± 14.8); control group (61.3 ± 16.0) • Sex (M/F): treatment group (61/87); control group (56/87) • Exclusion criteria: suspected heparin-induced thrombocytopenia or heparin-induced thrombosis; systemic bacterial infection; localised infection requiring systemic antibiotics; proven or suspected allergy to heparin or trisodium citrate; pregnancy
Interventions	Treatment group • Trisodium citrate: 30% Control group • Heparin: 5000 U/mL
Outcomes	• CRI • Exit-side infection • Thrombosis • Adverse effects (bleeding episodes)
Notes	• Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...computer-generated list of random numbers in blocks of six and stratified according to the dialysis centre and to the type of catheter inserted (tunneled cuffed or untunneled)."
Allocation concealment (selection bias)	Low risk	"The randomization codes were kept by the central department of pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Patients and investigators were unaware of the treatment assignments"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	All analyses were performed on an intention-to-treat basis

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Weijmer 2005 *(Continued)*

Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Insufficient information to permit judgement

Zhang 2009c

Methods	• Study design: parallel RCT • Study duration: January 2005 to June 2007 • Duration of follow-up: not reported
Participants	• Setting: National, dialysis units • Country: China • Participants > 18 years and suffered from ESKD that required HD treatment, with a newly inserted, well-positioned permanent tunnelled cuffed HD catheter • Number (participants/catheters): treatment group (71/71); control group (69/69) • Mean age ± SD (years): treatment group (52 ± 16.3); control group (52.1 ± 16.7) • Sex (M/F): treatment group (51/20); control group (50/19) • Exclusion criteria: systematic bacterial infection; local infection requiring systemic antibiotics; pregnancy; dizziness; tinnitus; immunosuppressive treatment
Interventions	Treatment group • Gentamicin: 4 mg/mL • Heparin: 5500 IU/mL Control group • Heparin: 5500 U/mL
Outcomes	• CRI • Thrombosis • Adverse effects (bleeding, tinnitus and vertigo)
Notes	• Funding source:

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants and dialysis nurses were blinded of the treatment assignments
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study investigators who assessed outcomes were not blinded

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Zhang 2009c *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All patient data reported
Selective reporting (reporting bias)	Low risk	Describes the outcome according to objective
Other bias	Unclear risk	Insufficient information to permit judgement

Zwiech 2016a

Methods	• Study design: parallel RCT • Study duration: not reported • Duration of follow-up: not reported
Participants	• Setting: single centre • Country: Poland • Participants on chronic HD, fitted with a permanent HD catheter for < 3 months or a newly implanted non-tunnelled or tunnelled catheter for continuing HD treatment • Participants (randomised/analysed): treatment group (29/28); control group (24/24) • Mean age SD (years): treatment group: (57.11 ± 14.46); control group (56.24 ± 11.98) • Sex (M/F): treatment group (14/12); control group (11/13) • Exclusion criteria: antibiotic treatment in the previous 4 weeks; presence of any infections during the study period needing antibiotic treatment; *S. aureus* in a nasal swab
Interventions	Treatment group • Tauloridine: 1.35% • Citrate: 4% • Heparin: 500 IU Control group • Heparin: 5000 IU/mL
Outcomes	• CRI
Notes	• Study in two phases. Phase 1 is included in the present review • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use computer-generated random number list
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement

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Zwiech 2016a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Describes the outcome according to protocol
Other bias	Unclear risk	Insufficient information to permit judgement

AKI - acute kidney injury; AV - arteriovenous; CFU - colony-forming units; CKD - chronic kidney disease; CRI - catheter-related infection; CRS - catheter-related sepsis; CVC - central venous catheter; ESKD - end-stage kidney disease; HD - haemodialysis; ICU - intensive care unit; IV - intravenous; M/F - male/female; RCT - randomised controlled trial; SD - standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beigi 2010	Wrong population: treating infection rather than preventing
Bosma 2010	Wrong outcome: colonisation *in vitro*
Chen 2014b	Wrong intervention: NaCl at concentrations less than 12% has not proven to be antimicrobial solution
Chu 2016	Wrong intervention: low to high dose heparin (no antimicrobial lock solutions)
Coli 2010	Wrong intervention: compared urokinase lock therapies (no antimicrobial lock solutions)
HEALTHY-CATH 2009	Wrong intervention: weekly 70% ethanol + heparin lock versus heparin lock (no antimicrobial lock solutions)
Hryszko 2013	Wrong intervention: low versus high dose heparin (no antimicrobial lock solutions)
Hu 2011	Wrong intervention: low versus high dose heparin (no antimicrobial lock solutions)
ISRCTN27307877	Protocol no longer available on the National Research Register website; no full text publication identified
Khosroshahi 2006b	Wrong population: treating infection rather than preventing
Khosroshahi 2015	Wrong population: treating infection rather than preventing
Malo 2010	Wrong intervention: low molecular weight heparin versus unfractionated heparin (no antimicrobial lock solutions)
Meeus 2005	Wrong intervention: 5% versus 10% citrate
Mohammad 2016	Wrong intervention: taurolock + heparin versus taurolock + urokinase
NCT00862966	Citrate versus heparin. The recruitment status of this study is unknown; the completion date has passed and the status has not been verified in more than two years. Last verified March 2009

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Study	Reason for exclusion
NCT01989091	B-lock versus heparin. This study has been terminated (did not meet predetermined primary endpoint)
Onder 2008	Wrong population: treating infection rather than preventing
Oran 2008	Wrong intervention: timing of heparin lock (3 times/week versus 6 times/week) (no antimicrobial lock solutions)
PreCLOT 2006	Wrong intervention: tissue plasminogen activator versus heparin (no antimicrobial lock solutions)
Ray 1999	Wrong intervention: twice-daily heparin flushes or twice-daily heparin flushes with once-weekly urokinase instillation (no antimicrobial lock solutions)
Sishir 2014	Wrong intervention: 70% ethanol versus heparin (no antimicrobial lock solutions)
Thomson 2011	Wrong intervention: low versus high dose heparin (no antimicrobial lock solutions)

Characteristics of studies awaiting assessment *[ordered by study ID]*

CLOCK 2017

Methods	• Study design: parallel RCT • Study duration: March 2014 to November 2016 • Duration of follow-up: 100 days
Participants	• Setting: single centre • Country: Brazil • Participants aged between 18 to 75 years and with a CKD 5D diagnosis; on high efficiency HD and long-term CVC for HD, with a subclavian insertion on either the right and left sides • Number: treatment group 1 (25); treatment group 2 (25); control group (25) • Mean age ± SD (years): treatment group 1 (53.3 ± 15.5); treatment group 2 (55 ± 13); control group (53.2 ± 15.5) • Sex (M/F): treatment group 1 (12/13); treatment group 2 (12/13); control group (12/13) • Exclusion criteria: pregnant females; on oral anticoagulant treatment; signs of subclinical or active infection; poor catheter care
Interventions	Treatment group 1 • Trisodium citrate: 30% Treatment group 2 • M-EDTA Control group • Heparin: 1000 IU/mL
Outcomes	• Increased hydraulic resistance • CRI • Infection (clinical signs and laboratory findings) • Adverse drug reactions

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CLOCK 2017 *(Continued)*

Notes	• Funding source: "We also thank the following institutions for grants: University of Sao Paulo, Conselho Nacional de Desenvolvimento Cientıfico e Tecnol ogico (CNPq), Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (FAPESP)."

CKD - chronic kidney disease; CRI - catheter-related infection; CVC - central venous catheter; HD - haemodialysis; M/F - male/female; RCT - randomised controlled trial; SD - standard deviation

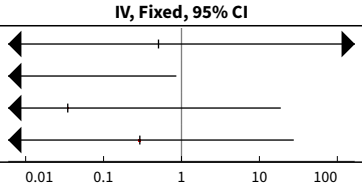
DATA AND ANALYSES

Comparison 1. All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	27		Rate Ratio (Fixed, 95% CI)	0.45 [0.38, 0.54]
2 Catheter-related infection (per 1000 dialysis sessions)	2		Rate Ratio (Fixed, 95% CI)	0.49 [0.21, 1.12]
3 Thrombosis (per 1000 catheter-days)	14		Rate Ratio (Random, 95% CI)	0.79 [0.52, 1.22]
4 Colonisation	2		Rate Ratio (Random, 95% CI)	0.37 [0.04, 3.36]
5 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in tunnelled catheters	21		Rate Ratio (Random, 95% CI)	0.40 [0.30, 0.53]
6 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in non-tunnelled catheters	8		Rate Ratio (Random, 95% CI)	0.37 [0.16, 0.86]
7 Subgroup analysis: thrombosis (per 1000 catheter-days) in tunnelled catheters	10		Rate Ratio (Random, 95% CI)	0.83 [0.50, 1.37]
8 Subgroup analysis: thrombosis (per 1000 catheter-days) in non-tunnelled catheters	4		Rate Ratio (Random, 95% CI)	0.66 [0.25, 1.72]

Analysis 1.1. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 1 Catheter-related infection (per 1000 catheter-days).

Study or subgroup	Antimicrobial N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Fixed, 95% CI	Weight	Rate Ratio IV, Fixed, 95% CI
Geron 2008	0	0	-0.7 (4.47)		0.04%	0.51[0,3232.59]
Vercaigne 2016a	0	0	-6.6 (3.3)		0.07%	0[0,0.86]
Cooper 1999	0	0	-3.4 (3.21)		0.08%	0.03[0,18.76]
AZEPTIC 2011	0	0	-1.2 (2.32)		0.15%	0.29[0,27.58]



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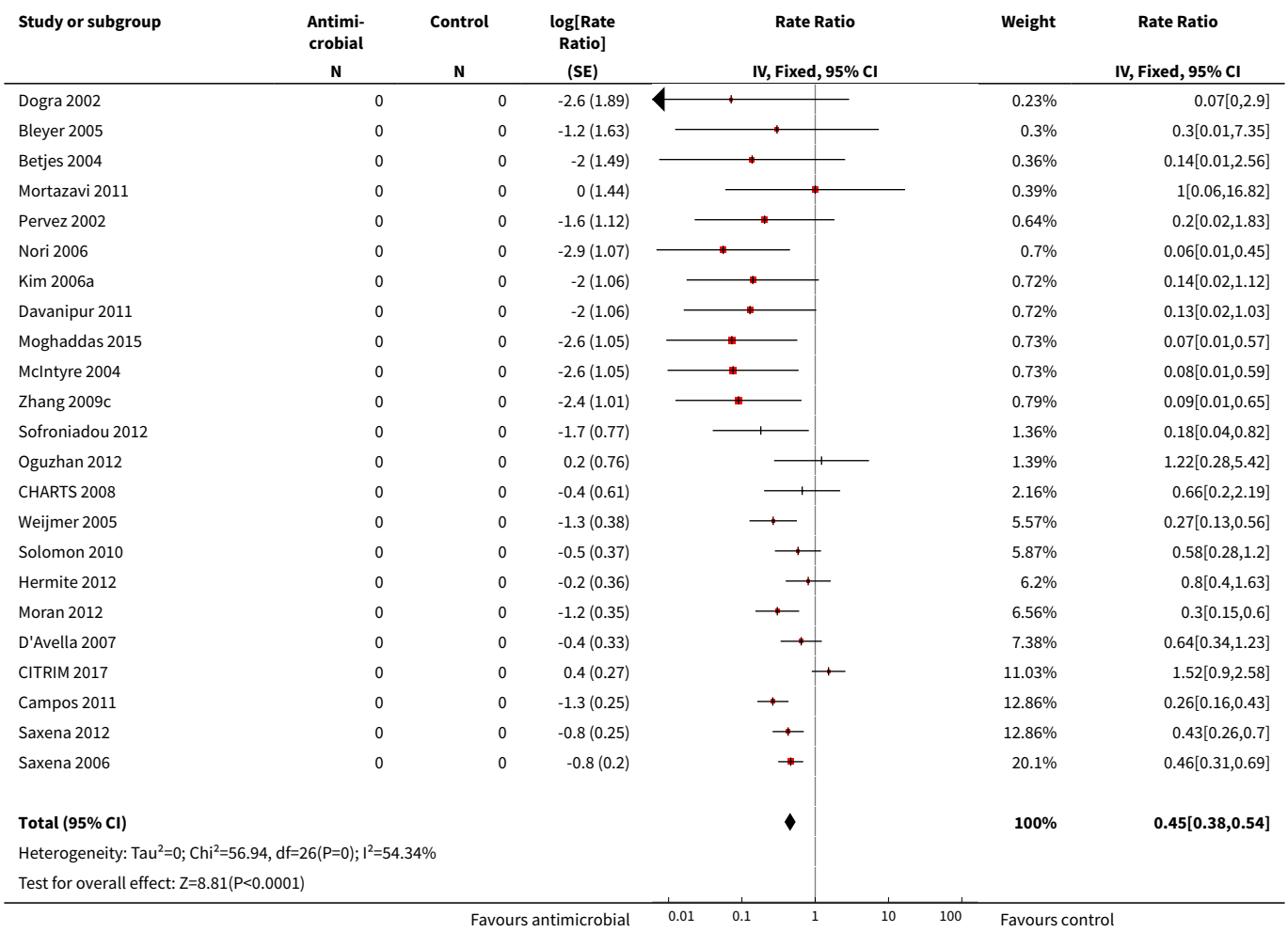
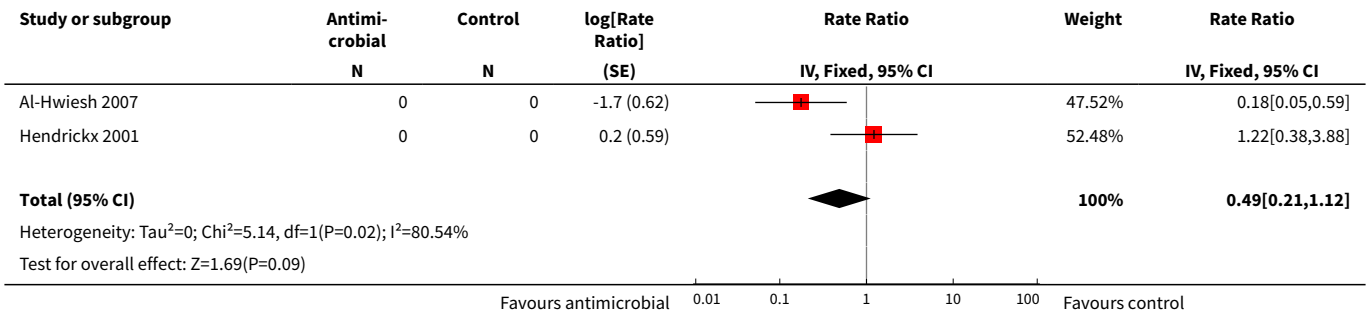


Analysis 1.2. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 2 Catheter-related infection (per 1000 dialysis sessions).



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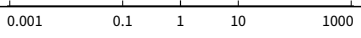
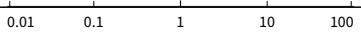
Analysis 1.3. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 3 Thrombosis (per 1000 catheter-days).

Study or subgroup	Antimicrobial N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
AZEPTIC 2011	0	0	-3.7 (3.2)		0.44%	0.02[0,12.83]
Nori 2006	0	0	-0.9 (1.41)		1.96%	0.39[0.02,6.19]
Buturovic 1998	0	0	-0.6 (1.22)		2.48%	0.54[0.05,5.88]
Moghaddas 2015	0	0	-1 (0.82)		4.37%	0.35[0.07,1.75]
Oguzhan 2012	0	0	0.1 (0.76)		4.79%	1.15[0.26,5.1]
Pervez 2002	0	0	-0.4 (0.67)		5.52%	0.66[0.18,2.44]
Saxena 2006	0	0	-0.9 (0.4)		8.36%	0.42[0.19,0.92]
Campos 2011	0	0	0.4 (0.34)		9.08%	1.43[0.74,2.79]
Zhang 2009c	0	0	0 (0.32)		9.32%	1.01[0.54,1.89]
Hermite 2012	0	0	-1.6 (0.26)		10.02%	0.2[0.12,0.34]
Solomon 2010	0	0	0.9 (0.19)		10.74%	2.46[1.69,3.57]
CITRIM 2017	0	0	0.2 (0.18)		10.83%	1.21[0.85,1.72]
Weijmer 2005	0	0	0.1 (0.17)		10.92%	1.05[0.75,1.47]
Moran 2012	0	0	-0.4 (0.14)		11.16%	0.69[0.52,0.91]
Total (95% CI)					**100%**	**0.79[0.52,1.22]**
Heterogeneity: Tau^2=0.4; Chi^2=76.71, df=13(P<0.0001); I^2=83.05%						
Test for overall effect: Z=1.06(P=0.29)						



Analysis 1.4. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 4 Colonisation.

Study or subgroup	Antimicrobial N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Bleyer 2005	0	0	-2.3 (1.05)		43.72%	0.1[0.01,0.79]
Betjes 2004	0	0	-0 (0.67)		56.28%	0.99[0.27,3.68]
Total (95% CI)					**100%**	**0.37[0.04,3.36]**
Heterogeneity: Tau^2=1.83; Chi^2=3.35, df=1(P=0.07); I^2=70.18%						
Test for overall effect: Z=0.89(P=0.37)						



Analysis 1.5. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 5 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in tunnelled catheters.

Study or subgroup	Antimicrobial N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Geron 2008	0	0	-0.7 (4.47)		0.1%	0.51[0,3232.59]
Vercaigne 2016a	0	0	-6.6 (3.3)		0.19%	0[0,0.86]
Cooper 1999	0	0	-3.4 (3.21)		0.2%	0.03[0,18.76]
AZEPTIC 2011	0	0	-1.2 (2.32)		0.38%	0.29[0,27.58]

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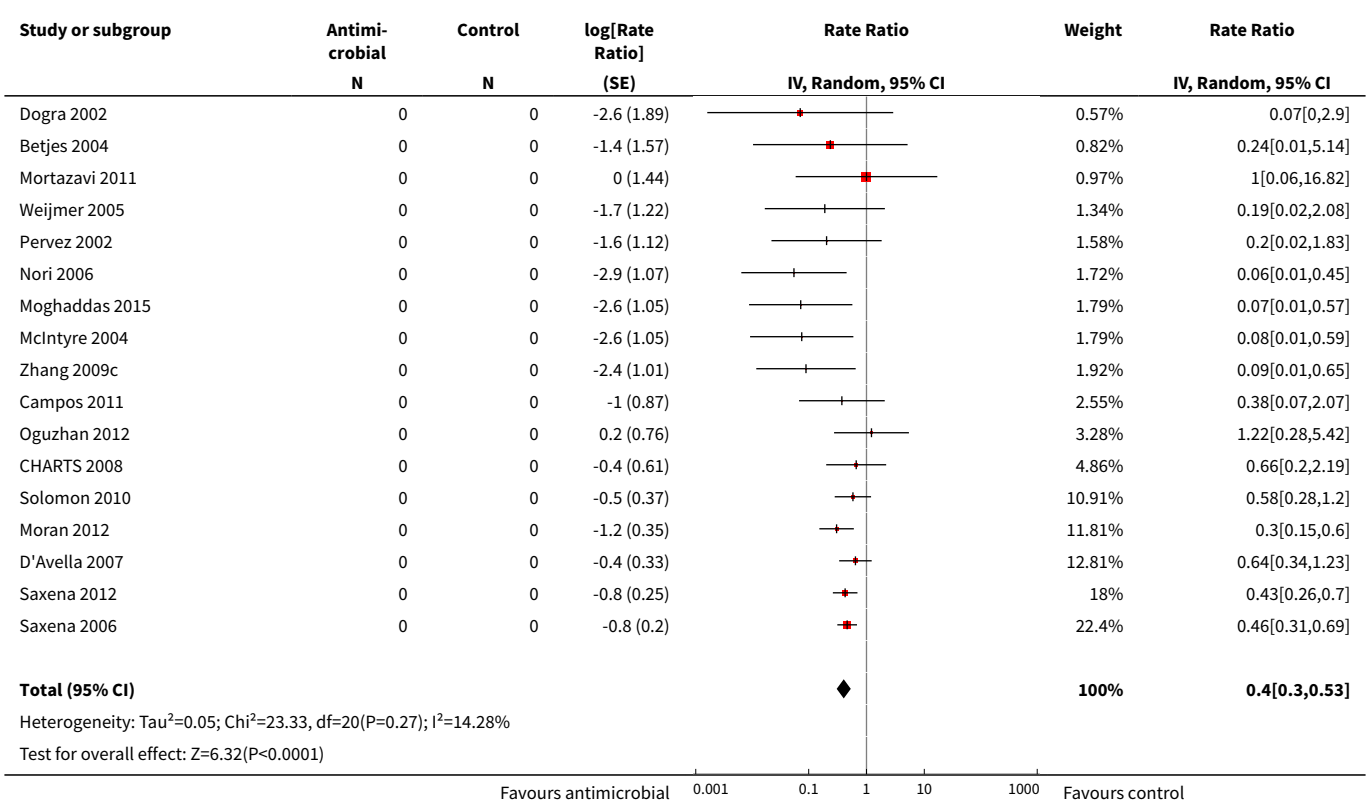
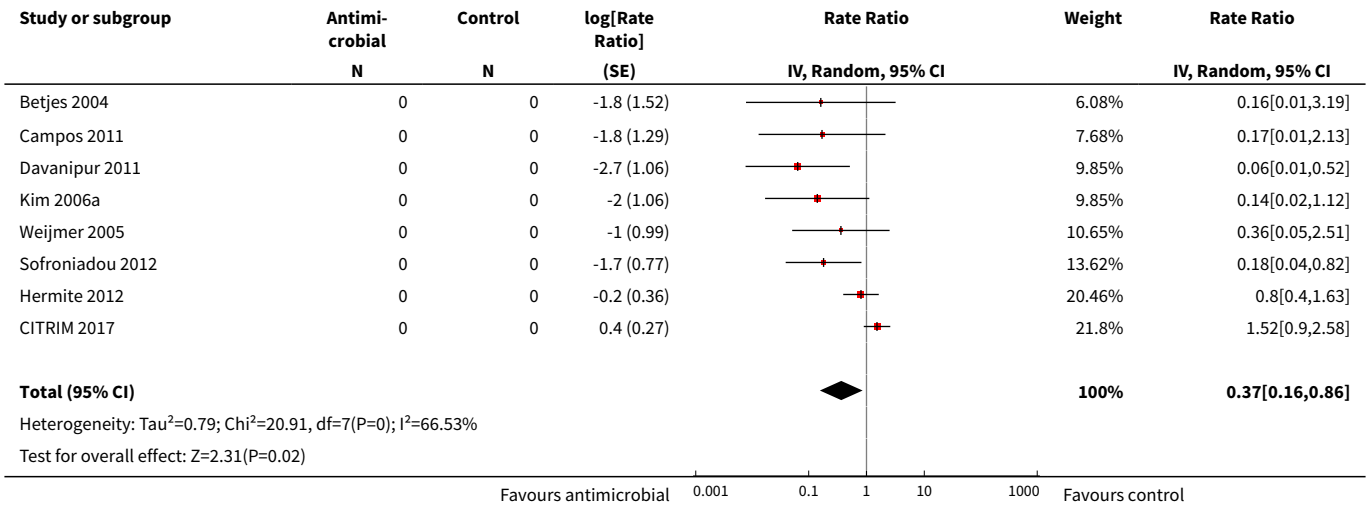


Analysis 1.6. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 6 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in non-tunnelled catheters.



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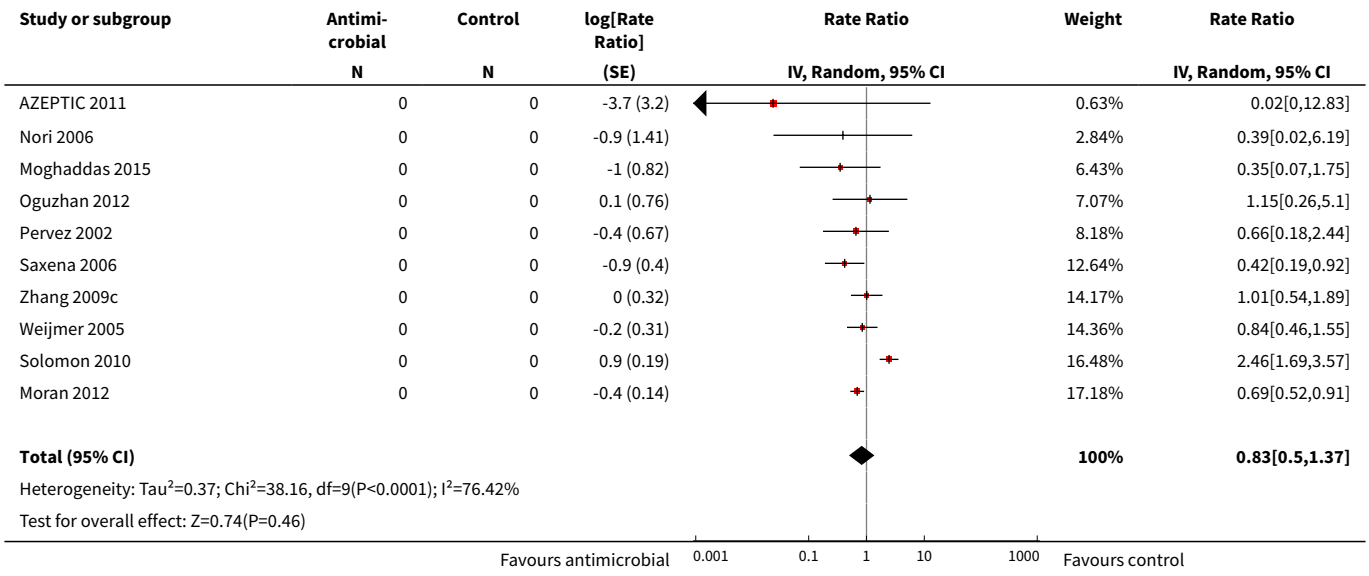
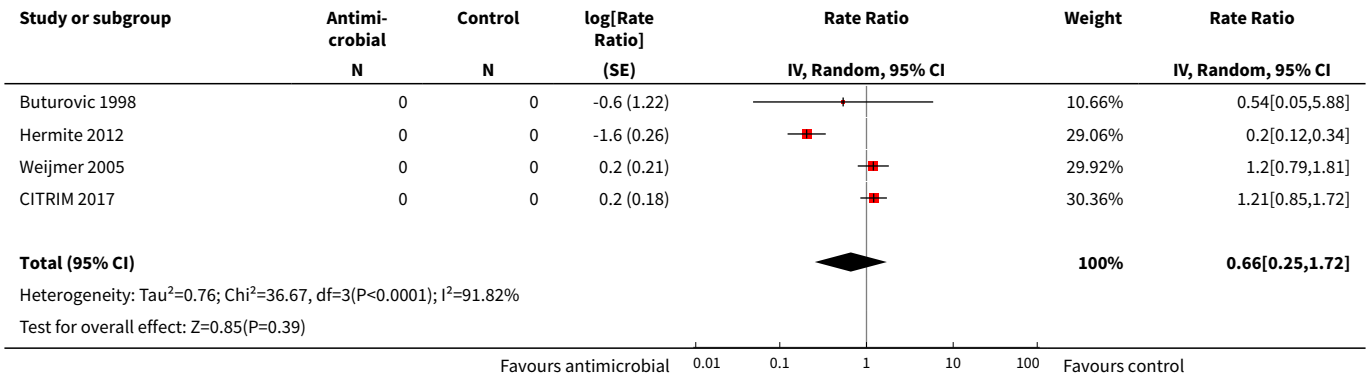
Analysis 1.7. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 7 Subgroup analysis: thrombosis (per 1000 catheter-days) in tunnelled catheters.



Analysis 1.8. Comparison 1 All antimicrobial (antibiotic plus non-antibiotic plus the combination) solutions versus control, Outcome 8 Subgroup analysis: thrombosis (per 1000 catheter-days) in non-tunnelled catheters.



Comparison 2. Sensitivity analysis: all antimicrobial lock solutions versus control excluding studies deemed with high-risk bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	18		Rate Ratio (Random, 95% CI)	0.47 [0.32, 0.68]
2 Thrombosis (per 1000 catheter-days)	9		Rate Ratio (Random, 95% CI)	0.85 [0.48, 1.52]

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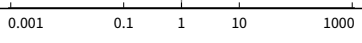
Analysis 2.1. Comparison 2 Sensitivity analysis: all antimicrobial lock solutions versus control excluding studies deemed with high-risk bias, Outcome 1 Catheter-related infection (per 1000 catheter-days).

Study or subgroup	Favours antimicrobials N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Geron 2008	0	0	-0.7 (4.47)		0.17%	0.51[0,3232.59]
Vercaigne 2016a	0	0	-6.6 (3.3)		0.31%	0[0,0.86]
Cooper 1999	0	0	-3.4 (3.21)		0.33%	0.03[0,18.76]
Dogra 2002	0	0	-2.6 (1.89)		0.92%	0.07[0,2.9]
Betjes 2004	0	0	-2 (1.49)		1.42%	0.14[0.01,2.56]
Mortazavi 2011	0	0	0 (1.44)		1.51%	1[0.06,16.82]
Pervez 2002	0	0	-1.6 (1.12)		2.33%	0.2[0.02,1.83]
Davanipur 2011	0	0	-2 (1.06)		2.55%	0.13[0.02,1.03]
Sofroniadou 2012	0	0	-1.7 (0.77)		4.16%	0.18[0.04,0.82]
Oguzhan 2012	0	0	0.2 (0.76)		4.23%	1.22[0.28,5.42]
Weijmer 2005	0	0	-1.3 (0.38)		8.86%	0.27[0.13,0.56]
Solomon 2010	0	0	-0.5 (0.37)		9.04%	0.58[0.28,1.2]
Hermite 2012	0	0	-0.2 (0.36)		9.21%	0.8[0.4,1.63]
D'Avella 2007	0	0	-0.4 (0.33)		9.74%	0.64[0.34,1.23]
CITRIM 2017	0	0	0.4 (0.27)		10.82%	1.52[0.9,2.58]
Saxena 2012	0	0	-0.8 (0.25)		11.18%	0.43[0.26,0.7]
Campos 2011	0	0	-1.3 (0.25)		11.18%	0.26[0.16,0.43]
Saxena 2006	0	0	-0.8 (0.2)		12.04%	0.46[0.31,0.69]
Total (95% CI)					**100%**	**0.47[0.32,0.68]**

Heterogeneity: Tau^2=0.25; Chi^2=40.59, df=17(P=0); I^2=58.12%

Test for overall effect: Z=4.04(P<0.0001)

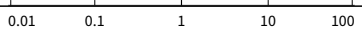


Analysis 2.2. Comparison 2 Sensitivity analysis: all antimicrobial lock solutions versus control excluding studies deemed with high-risk bias, Outcome 2 Thrombosis (per 1000 catheter-days).

Study or subgroup	Antimicrobial N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Buturovic 1998	0	0	-0.6 (1.22)		4.19%	0.54[0.05,5.88]
Oguzhan 2012	0	0	0.1 (0.76)		7.49%	1.15[0.26,5.1]
Pervez 2002	0	0	-0.4 (0.67)		8.42%	0.66[0.18,2.44]
Saxena 2006	0	0	-0.9 (0.4)		11.7%	0.42[0.19,0.92]
Campos 2011	0	0	0.4 (0.34)		12.45%	1.43[0.74,2.79]
Hermite 2012	0	0	-1.6 (0.26)		13.36%	0.2[0.12,0.34]
Solomon 2010	0	0	0.9 (0.19)		14.05%	2.46[1.69,3.57]
CITRIM 2017	0	0	0.2 (0.18)		14.13%	1.21[0.85,1.72]
Weijmer 2005	0	0	0.1 (0.17)		14.21%	1.05[0.75,1.47]
Total (95% CI)					**100%**	**0.85[0.48,1.52]**

Heterogeneity: Tau^2=0.58; Chi^2=67.33, df=8(P<0.0001); I^2=88.12%

Test for overall effect: Z=0.54(P=0.59)



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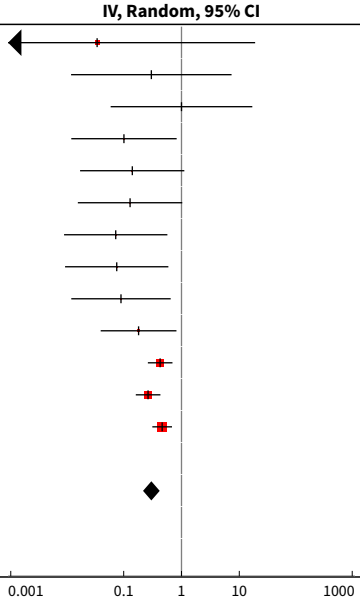
Comparison 3. Antibiotic lock solutions versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	13		Rate Ratio (Random, 95% CI)	0.30 [0.22, 0.42]
2 Catheter-related infection (per 1000 dialysis sessions)	1		Rate Ratio (Random, 95% CI)	Totals not selected
3 Thrombosis (per 1000 catheter-days)	5		Rate Ratio (Random, 95% CI)	0.76 [0.42, 1.38]
4 Colonisation	1		Rate Ratio (Random, 95% CI)	Totals not selected
5 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in tunnelled catheters	9		Rate Ratio (Random, 95% CI)	0.30 [0.18, 0.50]
6 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in non-tunnelled catheters	4		Rate Ratio (Random, 95% CI)	0.14 [0.05, 0.36]
7 Subgroup analysis: thrombosis per 1000 catheter-days in tunnelled catheters	3		Rate Ratio (Random, 95% CI)	0.61 [0.31, 1.23]

Analysis 3.1. Comparison 3 Antibiotic lock solutions versus control, Outcome 1 Catheter-related infection (per 1000 catheter-days).

Study or subgroup	Antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Cooper 1999	0	0	-3.4 (3.21)		0.28%	0.03[0,18.76]
Bleyer 2005	0	0	-1.2 (1.63)		1.06%	0.3[0.01,7.35]
Mortazavi 2011	0	0	0 (1.44)		1.36%	1[0.06,16.82]
Nori 2006	0	0	-2.3 (1.07)		2.4%	0.1[0.01,0.82]
Kim 2006a	0	0	-2 (1.06)		2.45%	0.14[0.02,1.12]
Davanipur 2011	0	0	-2 (1.06)		2.45%	0.13[0.02,1.03]
Moghaddas 2015	0	0	-2.6 (1.05)		2.49%	0.07[0.01,0.57]
McIntyre 2004	0	0	-2.6 (1.05)		2.49%	0.08[0.01,0.59]
Zhang 2009c	0	0	-2.4 (1.01)		2.68%	0.09[0.01,0.65]
Sofroniadou 2012	0	0	-1.7 (0.77)		4.44%	0.18[0.04,0.82]
Saxena 2012	0	0	-0.8 (0.25)		24.11%	0.43[0.26,0.7]
Campos 2011	0	0	-1.3 (0.25)		24.11%	0.26[0.16,0.43]
Saxena 2006	0	0	-0.8 (0.2)		29.68%	0.46[0.31,0.69]
Total (95% CI)					**100%**	**0.3[0.22,0.42]**
Heterogeneity: Tau^2=0.06; Chi^2=14.72, df=12(P=0.26); I^2=18.49%						
Test for overall effect: Z=7.06(P<0.0001)						



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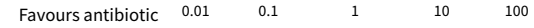
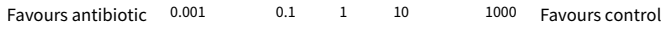
Analysis 3.2. Comparison 3 Antibiotic lock solutions versus control, Outcome 2 Catheter-related infection (per 1000 dialysis sessions).

Study or subgroup	Antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Rate Ratio IV, Random, 95% CI
Al-Hwiesh 2007	0	0	-1.7 (0.62)		0.18[0.05,0.59]



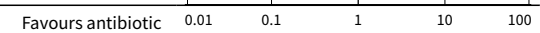
Analysis 3.3. Comparison 3 Antibiotic lock solutions versus control, Outcome 3 Thrombosis (per 1000 catheter-days).

Study or subgroup	Antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Nori 2006	0	0	-1.4 (1.63)		3.2%	0.23[0.01,5.72]
Moghaddas 2015	0	0	-1 (0.82)		10.53%	0.35[0.07,1.75]
Saxena 2006	0	0	-0.9 (0.4)		25.84%	0.42[0.19,0.92]
Campos 2011	0	0	0.4 (0.34)		29.56%	1.43[0.74,2.79]
Zhang 2009c	0	0	0 (0.32)		30.88%	1.01[0.54,1.89]
Total (95% CI)					**100%**	**0.76[0.42,1.38]**
Heterogeneity: Tau^2=0.19; Chi^2=7.58, df=4(P=0.11); I^2=47.2%						
Test for overall effect: Z=0.9(P=0.37)						



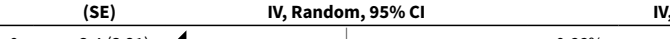
Analysis 3.4. Comparison 3 Antibiotic lock solutions versus control, Outcome 4 Colonisation.

Study or subgroup	Antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Rate Ratio IV, Random, 95% CI
Bleyer 2005	0	0	-2.3 (1.05)		0.1[0.01,0.79]



Analysis 3.5. Comparison 3 Antibiotic lock solutions versus control, Outcome 5 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in tunnelled catheters.

Study or subgroup	Antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Cooper 1999	0	0	-3.4 (3.21)		0.66%	0.03[0,18.76]
Mortazavi 2011	0	0	0 (1.44)		3.08%	1[0.06,16.82]
Nori 2006	0	0	-2.9 (1.07)		5.29%	0.06[0.01,0.45]
Moghaddas 2015	0	0	-2.6 (1.05)		5.46%	0.07[0.01,0.57]
McIntyre 2004	0	0	-2.6 (1.05)		5.46%	0.08[0.01,0.59]
Zhang 2009c	0	0	-2.4 (1.01)		5.85%	0.09[0.01,0.65]
Campos 2011	0	0	-1 (0.87)		7.53%	0.38[0.07,2.07]



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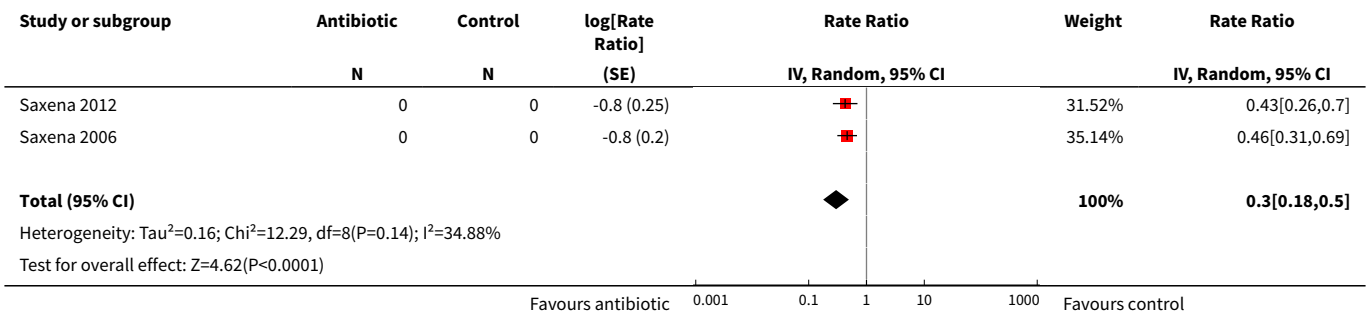
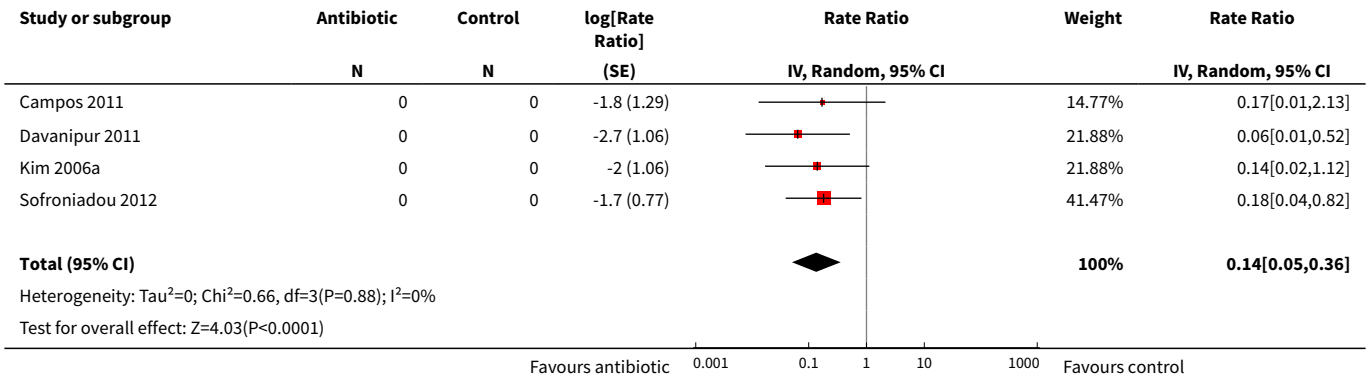
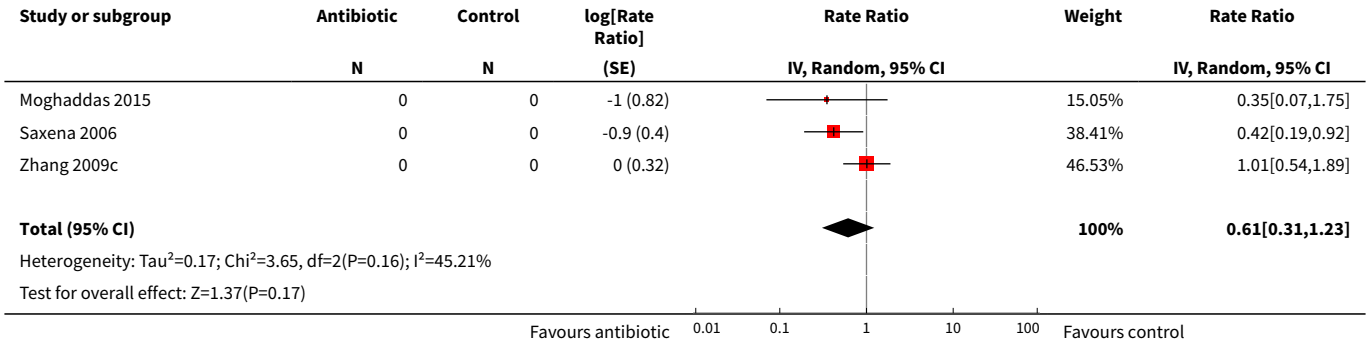


Analysis 3.6. Comparison 3 Antibiotic lock solutions versus control, Outcome 6 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in non-tunnelled catheters.



Analysis 3.7. Comparison 3 Antibiotic lock solutions versus control, Outcome 7 Subgroup analysis: thrombosis per 1000 catheter-days in tunnelled catheters.



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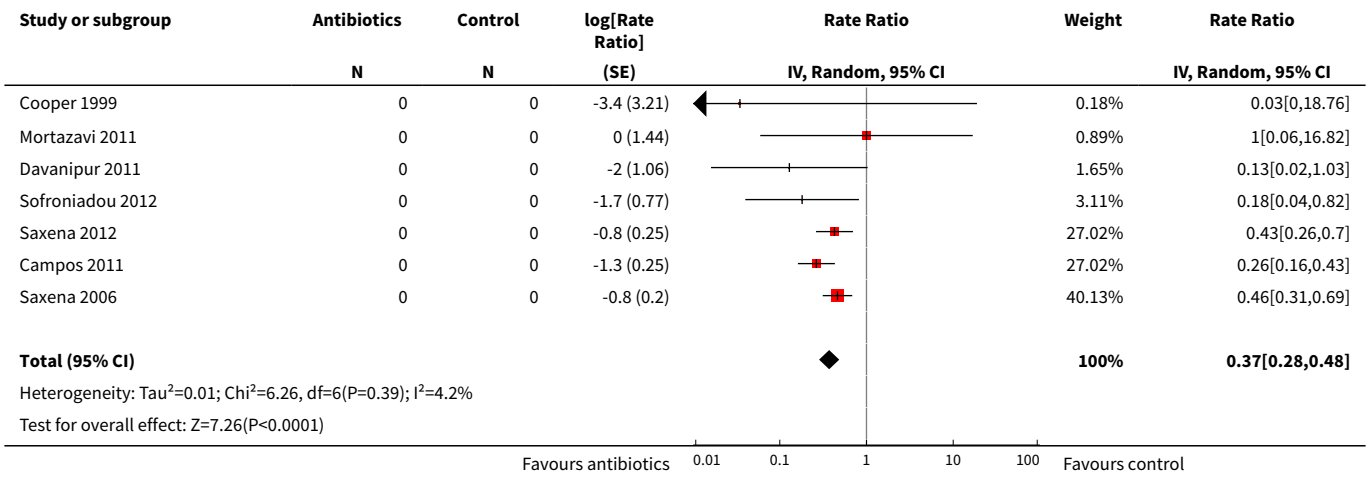
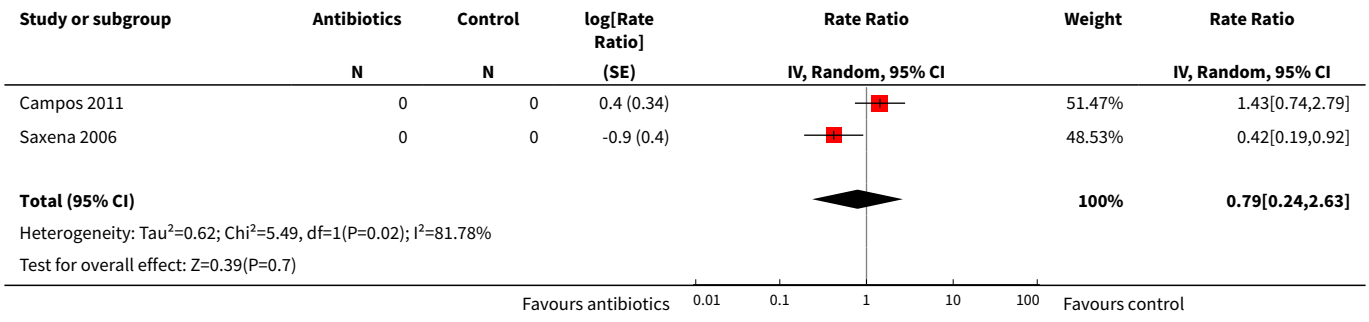
Comparison 4. Sensitivity analysis: antibiotic lock solutions versus control excluding studies judged to be at high-risk bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	7		Rate Ratio (Random, 95% CI)	0.37 [0.28, 0.48]
2 Thrombosis (per 1000 catheter-days)	2		Rate Ratio (Random, 95% CI)	0.79 [0.24, 2.63]

Analysis 4.1. Comparison 4 Sensitivity analysis: antibiotic lock solutions versus control excluding studies judged to be at high-risk bias, Outcome 1 Catheter-related infection (per 1000 catheter-days).



Analysis 4.2. Comparison 4 Sensitivity analysis: antibiotic lock solutions versus control excluding studies judged to be at high-risk bias, Outcome 2 Thrombosis (per 1000 catheter-days).



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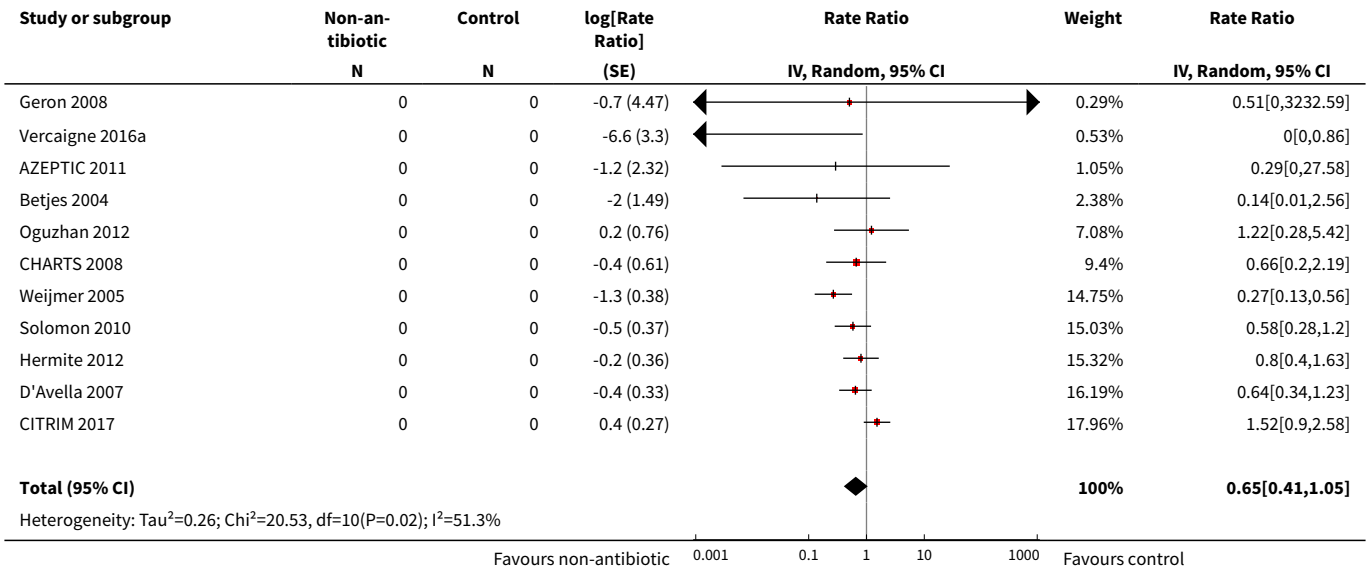
Comparison 5. Non-antibiotic antimicrobial lock solutions versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	11		Rate Ratio (Random, 95% CI)	0.65 [0.41, 1.05]
2 Catheter-related infection (per 1000 dialysis sessions)	1		Rate Ratio (Random, 95% CI)	Totals not selected
3 Thrombosis (per 1000 catheter-days)	8		Rate Ratio (Random, 95% CI)	0.85 [0.44, 1.66]
4 Thrombosis (per 1000 dialysis sessions)	1		Rate Ratio (Random, 95% CI)	Totals not selected
5 Colonisation	1		Rate Ratio (Random, 95% CI)	0.99 [0.27, 3.68]
6 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in tunnelled catheters	9		Rate Ratio (Random, 95% CI)	0.60 [0.40, 0.91]
7 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in non-tunnelled catheters	4		Rate Ratio (Random, 95% CI)	0.93 [0.48, 1.81]
8 Subgroup analysis: thrombosis (per 1000 catheter-days) in tunnelled catheters	5		Rate Ratio (Random, 95% CI)	1.17 [0.57, 2.41]
9 Subgroup analysis: thrombosis (per 1000 catheter-days) in non-tunnelled catheters	4		Rate Ratio (Random, 95% CI)	0.66 [0.25, 1.72]

Analysis 5.1. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 1 Catheter-related infection (per 1000 catheter-days).



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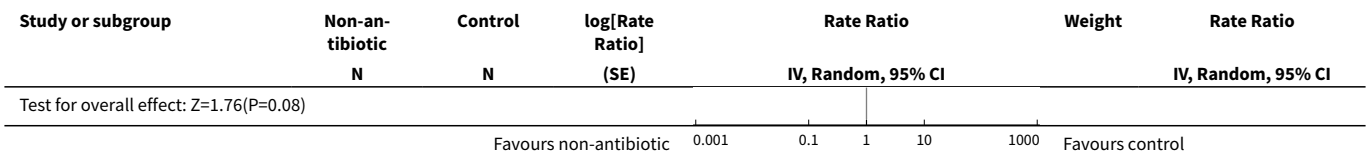
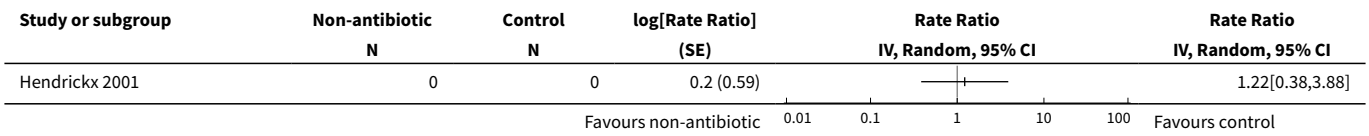
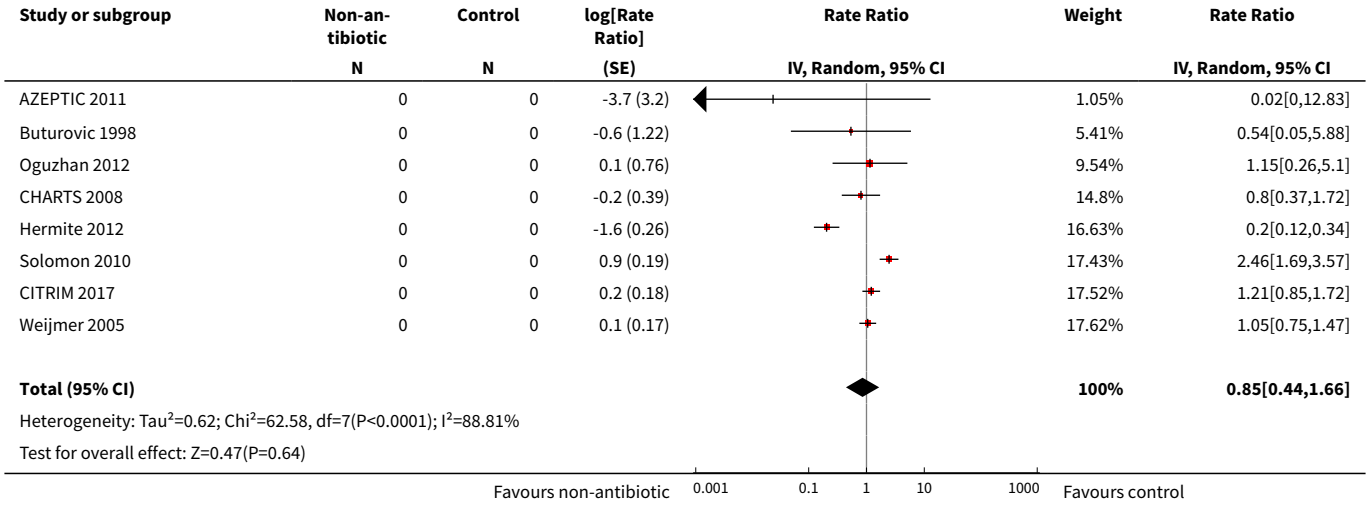


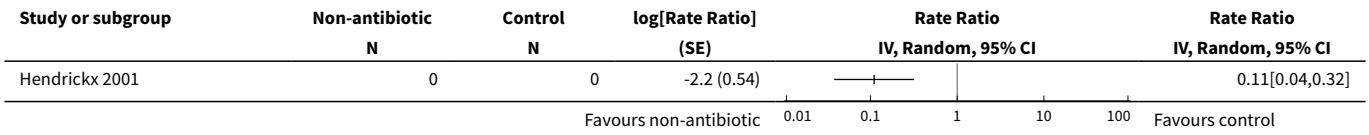
Analysis 5.2. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 2 Catheter-related infection (per 1000 dialysis sessions).



Analysis 5.3. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 3 Thrombosis (per 1000 catheter-days).



Analysis 5.4. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 4 Thrombosis (per 1000 dialysis sessions).



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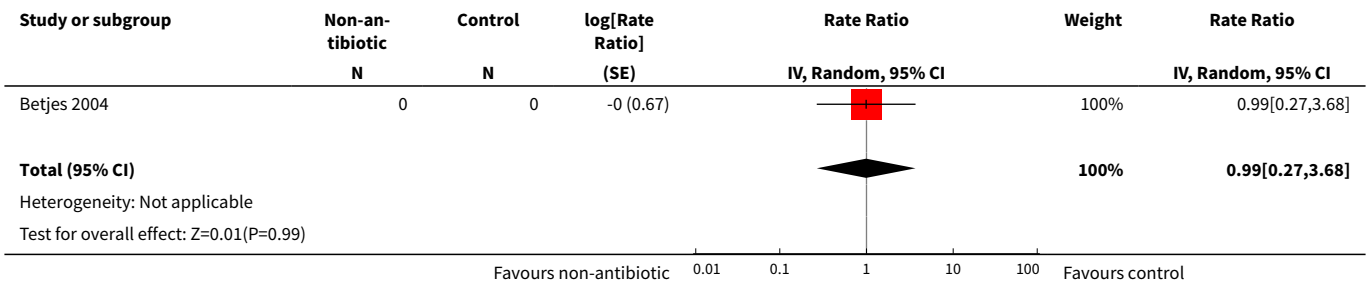
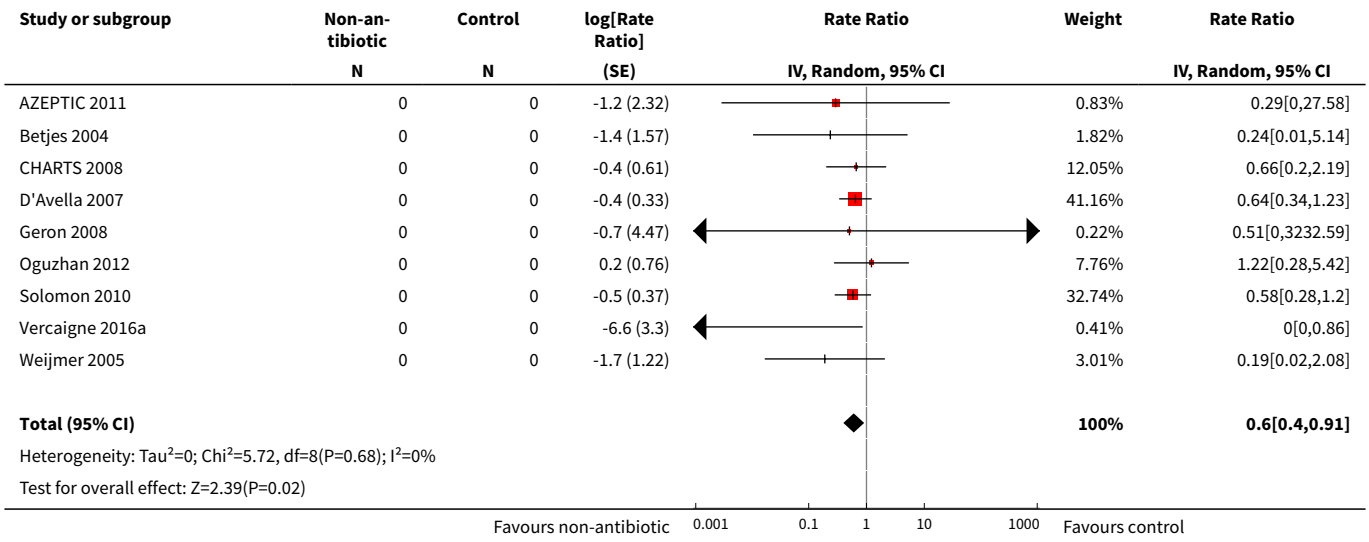
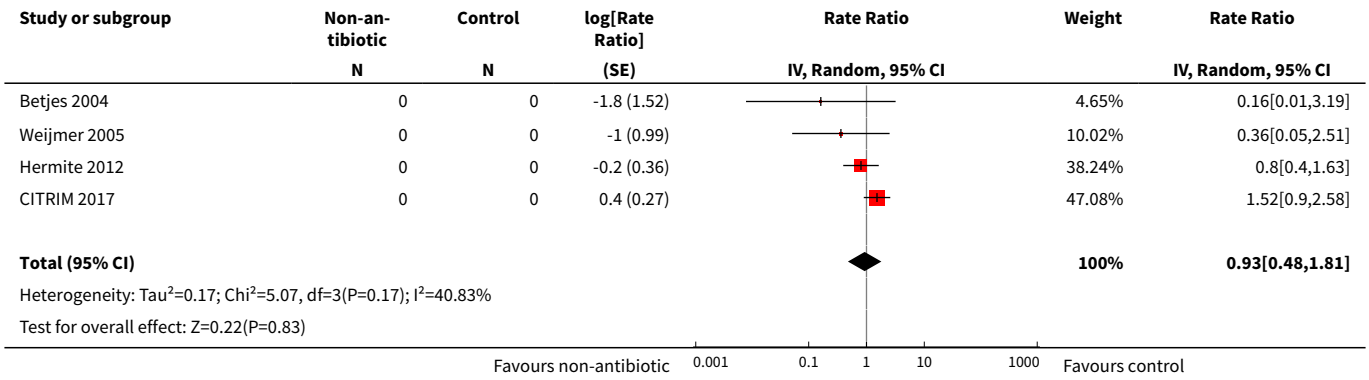
Analysis 5.5. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 5 Colonisation.



Analysis 5.6. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 6 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in tunnelled catheters.



Analysis 5.7. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 7 Subgroup analysis: catheter-related infection (per 1000 catheter-days) in non-tunnelled catheters.



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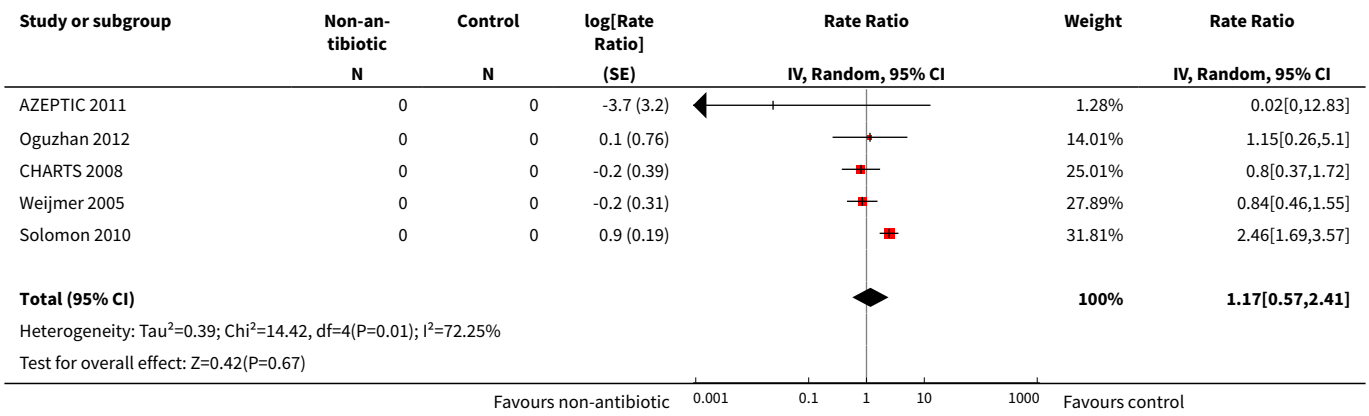
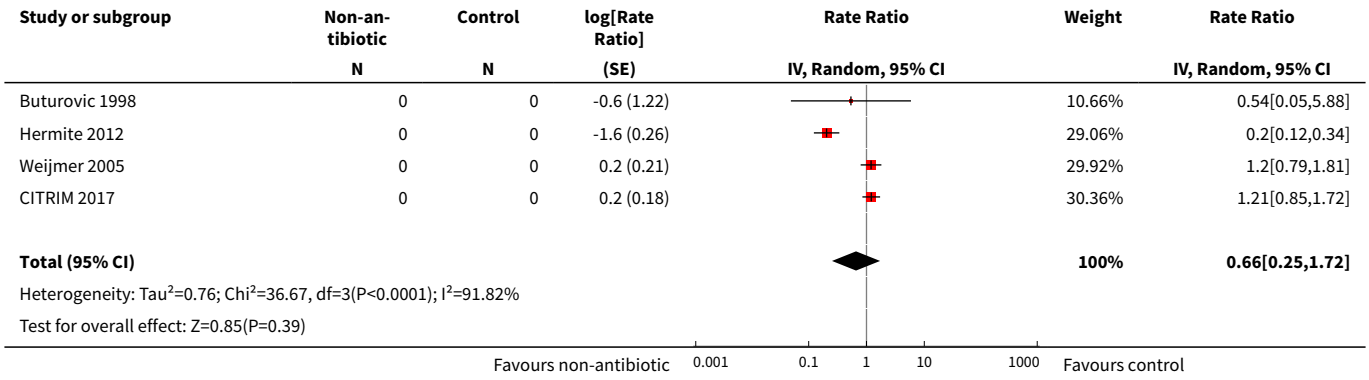
Analysis 5.8. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 8 Subgroup analysis: thrombosis (per 1000 catheter-days) in tunnelled catheters.



Analysis 5.9. Comparison 5 Non-antibiotic antimicrobial lock solutions versus control, Outcome 9 Subgroup analysis: thrombosis (per 1000 catheter-days) in non-tunnelled catheters.



Comparison 6. Sensitivity analysis: non-antibiotic lock solutions versus control excluding studies judged to be at high-risk bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	9		Rate Ratio (Random, 95% CI)	0.65 [0.38, 1.12]
2 Thrombosis (per 1000 catheter-days)	6		Rate Ratio (Random, 95% CI)	0.90 [0.43, 1.91]

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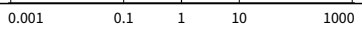
Analysis 6.1. Comparison 6 Sensitivity analysis: non-antibiotic lock solutions versus control excluding studies judged to be at high-risk bias, Outcome 1 Catheter-related infection (per 1000 catheter-days).

Study or subgroup	Non-antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Geron 2008	0	0	-0.7 (4.47)		0.38%	0.51[0,3232.59]
Vercaigne 2016a	0	0	-6.6 (3.3)		0.69%	0[0,0.86]
Betjes 2004	0	0	-2 (1.49)		3.04%	0.14[0.01,2.56]
Oguzhan 2012	0	0	0.2 (0.76)		8.56%	1.22[0.28,5.42]
Weijmer 2005	0	0	-1.3 (0.38)		16.45%	0.27[0.13,0.56]
Solomon 2010	0	0	-0.5 (0.37)		16.71%	0.58[0.28,1.2]
Hermite 2012	0	0	-0.2 (0.36)		16.98%	0.8[0.4,1.63]
D'Avella 2007	0	0	-0.4 (0.33)		17.79%	0.64[0.34,1.23]
CITRIM 2017	0	0	0.4 (0.27)		19.4%	1.52[0.9,2.58]
Total (95% CI)					**100%**	**0.65[0.38,1.12]**

Heterogeneity: Tau^2=0.33; Chi^2=20.35, df=8(P=0.01); I^2=60.68%

Test for overall effect: Z=1.56(P=0.12)



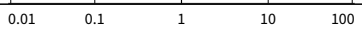
Favours non-antibiotic — Favours control

Analysis 6.2. Comparison 6 Sensitivity analysis: non-antibiotic lock solutions versus control excluding studies judged to be at high-risk bias, Outcome 2 Thrombosis (per 1000 catheter-days).

Study or subgroup	Non-antibiotic N	Control N	log[Rate Ratio] (SE)	Rate Ratio IV, Random, 95% CI	Weight	Rate Ratio IV, Random, 95% CI
Buturovic 1998	0	0	-0.6 (1.22)		6.77%	0.54[0.05,5.88]
Oguzhan 2012	0	0	0.1 (0.76)		11.68%	1.15[0.26,5.1]
Hermite 2012	0	0	-1.6 (0.26)		19.66%	0.2[0.12,0.34]
Solomon 2010	0	0	0.9 (0.19)		20.52%	2.46[1.69,3.57]
CITRIM 2017	0	0	0.2 (0.18)		20.63%	1.21[0.85,1.72]
Weijmer 2005	0	0	0.1 (0.17)		20.73%	1.05[0.75,1.47]
Total (95% CI)					**100%**	**0.9[0.43,1.91]**

Heterogeneity: Tau^2=0.68; Chi^2=60.62, df=5(P<0.0001); I^2=91.75%

Test for overall effect: Z=0.27(P=0.79)



Favours non-antibiotic — Favours control

Comparison 7. Combined antimicrobial lock solutions versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	4		Rate Ratio (Random, 95% CI)	0.26 [0.14, 0.49]
2 Thrombosis (per 1000 catheter-days)	3		Rate Ratio (Random, 95% CI)	0.63 [0.22, 1.81]

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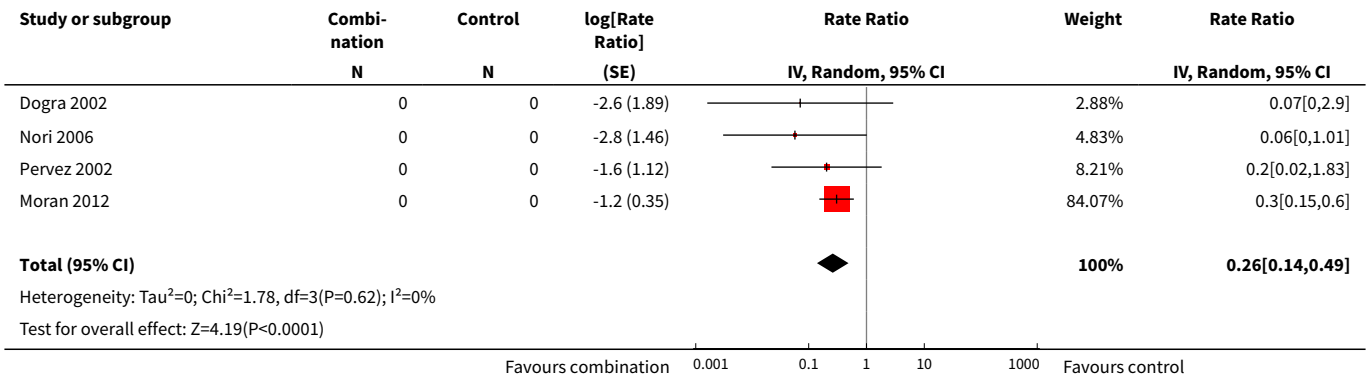
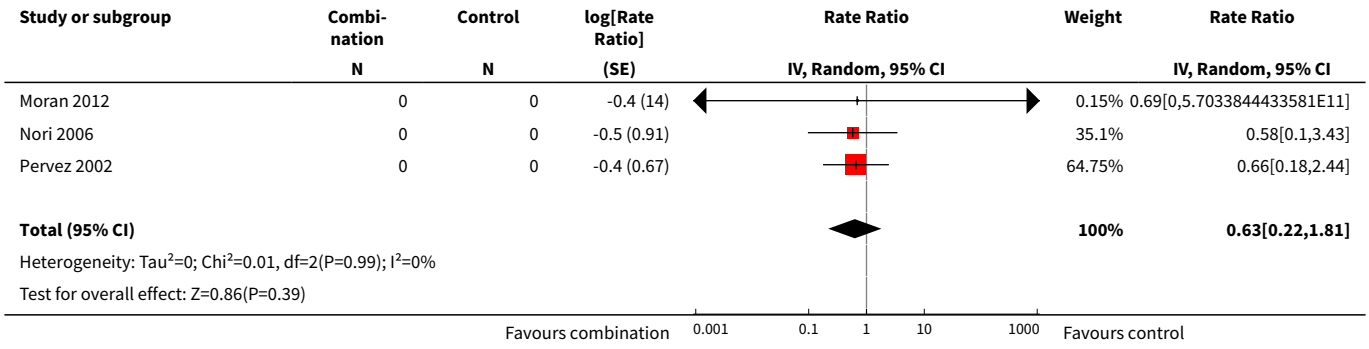
Analysis 7.1. Comparison 7 Combined antimicrobial lock solutions versus control, Outcome 1 Catheter-related infection (per 1000 catheter-days).



Analysis 7.2. Comparison 7 Combined antimicrobial lock solutions versus control, Outcome 2 Thrombosis (per 1000 catheter-days).



Comparison 8. Sensitivity analysis: combined antimicrobial lock solutions versus control excluding studies deemed with high-risk bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Catheter-related infection (per 1000 catheter-days)	2		Rate Ratio (Random, 95% CI)	0.16 [0.02, 1.03]
2 Thrombosis (per 1000 catheter-days)	1		Rate Ratio (Random, 95% CI)	0.66 [0.18, 2.44]

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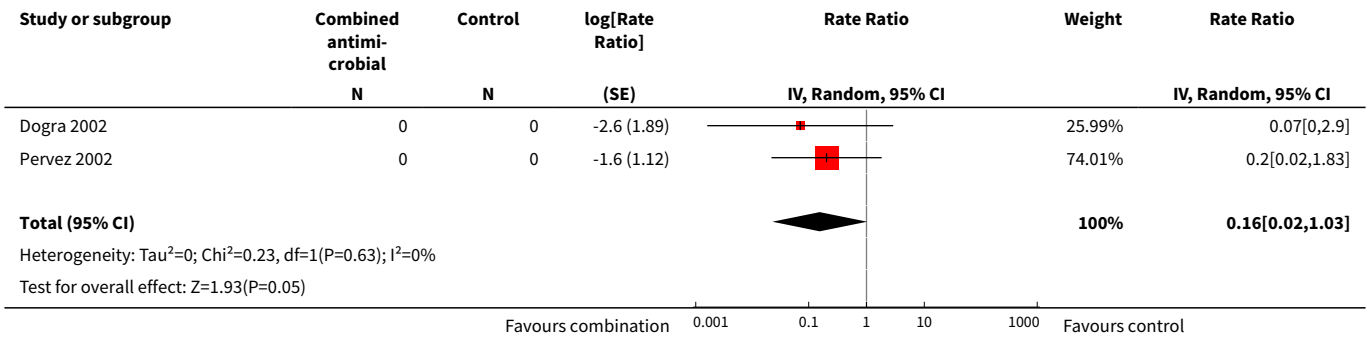
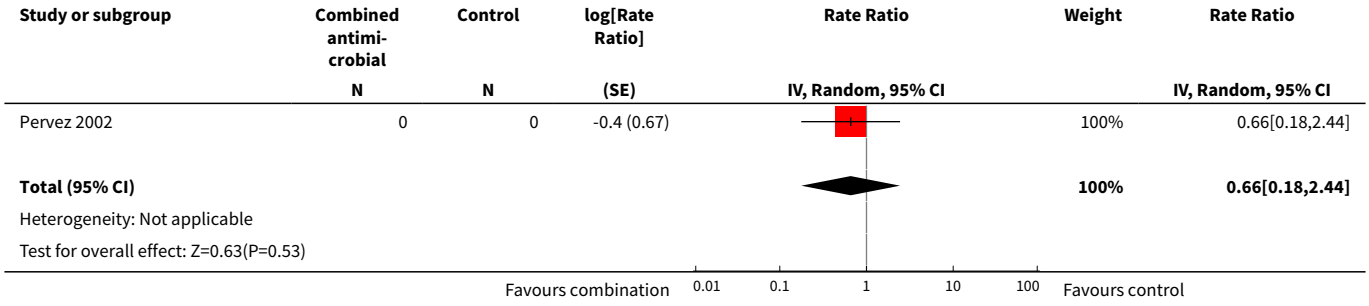
Analysis 8.1. Comparison 8 Sensitivity analysis: combined antimicrobial lock solutions versus control excluding studies deemed with high-risk bias, Outcome 1 Catheter-related infection (per 1000 catheter-days).



Analysis 8.2. Comparison 8 Sensitivity analysis: combined antimicrobial lock solutions versus control excluding studies deemed with high-risk bias, Outcome 2 Thrombosis (per 1000 catheter-days).



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (lock* NEAR/5 (solution* or antiinfective* or anti-infective* or antibiotic* or antimicrobial* or nonantibiotic* or non-antibiotic* or disinfect*)):ti,ab,kw 2. lock*:ti,ab,kw 3. MeSH descriptor Anti-Infective Agents explode all trees 4. gentam*cin*:ti,ab,kw 5. vancom*cin*:ti,ab,kw 6. (minocyclin* or minomycin):ti,ab,kw 7. (cefotaxim* or cephotaxim*):ti,ab,kw 8. (cefazolin or cephazolin):ti,ab,kw 9. tobram*cin*:ti,ab,kw 10.(citrate* or citric acid):ti,ab,kw 11.taurolidine:ti,ab,kw 12.Taurine:ti,ab,kw 13.(#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

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(Continued)

	14.catheter*:ti,ab,kw 15.CVC:ti,ab,kw 16.(central next venous next line*):ti,ab,kw 17.(central next line*):ti,ab,kw 18.(#14 OR #15 OR #16 OR #17) 19.dialysis:ti,ab,kw 20.h*emodialysis:ti,ab,kw 21.h*emofiltration:ti,ab,kw 22.h*emodiafiltration:ti,ab,kw 23.(continuous next renal next replacement):ti,ab,kw 24.((slow next continuous next ultrafiltration) or SCUF or CVVH or CVVHD or CVVHDF):ti,ab,kw 25.("endstage kidney" or "endstage renal" or "end stage kidney" or "end stage renal"):ti,ab,kw 26.(ESKD or ESKF or ESRD or ESRF):ti,ab,kw 27.("acute kidney" or "acute renal" or AKI or AKF or ARF):ti,ab,kw 28.(#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27) 29.(#1 AND #28) 30.(#2 AND #13 AND #28) 31.(#13 AND #18 AND #28) 32.(#29 OR #30 OR #31)
MEDLINE	1. (lock* adj5 (solution* or antiinfective* or anti-infective* or antibiotic* or antimicrobial* or nonantibiotic* or non-antibiotic* or disinfect*)).tw. 2. lock*.tw. 3. exp Anti-Infective Agents/ 4. gentam#cin*.tw. 5. vancom#cin*.tw. 6. (minocyclin* or minomycin).tw. 7. (cefotaxim* or cephotaxim*).tw. 8. (cefazolin or cephazolin).tw. 9. tobram#cin*.tw. 10.exp Citrates/ 11.citrate*.tw. 12.taurolidine.tw. 13.Taurine/ 14.or/3-13 15.exp Catheters/ 16.Catheterization/ 17.Catheterization, Central Venous/ 18.catheter*.tw. 19.CVC.tw. 20.central venous line*.tw. 21.central line*.tw. 22.or/15-21 23.Renal Dialysis/ 24.exp Hemofiltration/ 25.dialysis.tw. 26.(haemodialysis or hemodialysis).tw. 27.(hemofiltration or haemofiltration).tw. 28.(haemodiafiltration or hemodiafiltration).tw. 29.continuous renal replacement.tw. 30.(slow continuous ultrafiltration or SCUF or CVVH or CVVHD or CVVHDF).tw. 31.(endstage kidney or endstage renal or end stage kidney or end stage renal).tw.

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(Continued)

	32.(ESKD or ESKF or ESRD or ESRF).tw. 33.exp Acute Kidney Insufficiency/ 34.(acute kidney or acute renal or AKI or AKF or ARF).tw. 35.or/23-34 36.and/1,35 37.and/2,14,35 38.and/14,22,35 39.or/36-38
EMBASE	1. (lock* adj5 (solution* or antiinfective* or anti-infective* or antibiotic* or antimicrobial* or nonantibiotic* or non-antibiotic* or disinfect*)).tw. 2. lock*.tw. 3. Antiinfective Agent/ 4. gentam#cin*.tw. 5. vancom#cin*.tw. 6. (minocyclin* or minomycin).tw. 7. (cefotaxim* or cephotaxim*).tw. 8. (cefazolin or cephazolin).tw. 9. tobram#cin*.tw. 10.Citric Acid/ 11.(citrate* or citric acid).tw. 12.taurolidine.tw. 13.or/3-12 14.Catheter/ 15.exp Central Venous Catheter/ 16.Dialysis Catheter/ 17.Subclavian Vein Catheter/ 18.Catheterization/ 19.Central Venous Catheterization/ 20.catheter*.tw. 21.CVC.tw. 22.central venous line*.tw. 23.central line*.tw. 24.or/14-23 25.Hemodialysis/ 26.Hemofiltration/ 27.Hemodiafiltration/ 28.exp Continuous Renal Replacement Therapy/ 29.dialysis.tw. 30.(haemodialysis or hemodialysis).tw. 31.(hemofiltration or haemofiltration).tw. 32.(haemodiafiltration or hemodiafiltration).tw. 33.continuous renal replacement.tw. 34.(slow continuous ultrafiltration or SCUF or CVVH or CVVHD or CVVHDF).tw. 35.(endstage kidney or endstage renal or end stage kidney or end stage renal).tw. 36.(ESKD or ESKF or ESRD or ESRF).tw. 37.Acute Kidney Failure/ 38.(acute kidney or acute renal or AKI or AKF or ARF).tw. 39.or/25-38 40.and/1,39 41.and/2,13,39 42.and/13,24,39

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(Continued)

	43.or/40-42

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Sequence Generation Randomise	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation may be implemented without a random element, and this is considered to be equivalent to being random)
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention
	Unclear: Insufficient information about the sequence generation process to permit judgement
Allocation Concealed Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes)
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear: Randomisation stated but no information on method used is available
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect esti-

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(Continued)

	mate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation
	Unclear: Insufficient information to permit judgement
Selective outcome reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon)
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: MCA, MIC, JCC, LML, MC
2. Develop a search strategy: MCA, MIC
3. Search for studies: MCA, MIC
4. Obtain copies of studies: MCA
5. Study selection: MCA, MIC
6. Extract data from studies: NR, MR
7. Enter data into RevMan: MCA, MIC, JCC
8. Carry out the analysis: JCC, MCA, MIC
9. Interpret the analysis: MCA, MIC, JCC, LML
10. Draft the final review: MCA, MIC, JCC, LML
11. Disagreement resolution: MCA, MIC, JCC, LML
12. Update the review: MCA, MIC, JCC, LML

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INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Anti-Bacterial Agents [therapeutic use]; Anti-Infective Agents [*therapeutic use]; Anticoagulants [therapeutic use]; Catheter-Related Infections [epidemiology] [*prevention & control]; Catheterization, Central Venous [*adverse effects]; Heparin [therapeutic use]; Incidence; Randomized Controlled Trials as Topic; Venous Thrombosis [epidemiology] [*prevention & control]

MeSH check words

Humans

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