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Review

Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials

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SUMMARY

Catheter-related bloodstream infection (CRBSI) is associated with high rates of morbidity. This systematic review assesses the efficacy of antibiotic-based lock solutions to prevent CRBSI. A secondary goal of our review is to determine which antibiotic-based lock solution is most effective in reducing CRBSI. We searched Medline and the Cochrane Library for relevant trials up to April 2009. Data from the original publications were used to calculate the overall relative risk of CRBSI. Data for similar outcomes were combined in the analysis where appropriate, using a random-effects model. Sixteen trials were included in the review, nine conducted in haemodialysis patients, six in oncology patients (mainly children) and one study concerned critically ill neonates. Three haemodialysis patients needed to be treated with antibiotics to prevent one CRBSI, given a mean insertion time of 146 days (range: 37–365) and an average baseline risk of 3.0 events per 1000 catheter-days. In the oncology patients a number needed to treat (NNT) was calculated of eight patients to prevent one BSI, given a mean insertion time of 227 days (range: 154–295) and average baseline risk of 1.7 events per 1000 catheter-days. There are indications that antibiotic-based lock solutions as compared to heparin lock solutions are effective in the prevention of CRBSI in haemodialysis patients. In trials studying oncology patients the estimated effect showed only a marginal significant benefit in favour of antibiotic-based lock solutions. Our review supports the Centers for Disease Control and Prevention in not recommending routine use of antibiotic-based catheter lock solutions.

Introduction

Central venous catheters (CVCs) are commonly used for the intravenous administration of fluids and therapeutic agents or measurements of haemodynamic variables. Unfortunately, CVCs bring about thrombotic, mechanical and infectious complications. The National Nosocomial Infections Surveillance System reported a rate of catheter-related bloodstream infection (CRBSI) of 5 per 1000 central catheter-days.[1] Infections related to CVCs are an important cause of morbidity and mortality for hospitalised patients as well as outpatients.

Colonisation of the catheter is a precondition of infection. Catheters are mainly colonised by the extraluminal or by the endoluminal route.[2] For short-term use CVCs (mean duration less than 7–10 days), the skin around the catheter insertion site is the most common source of organisms.[3,4] Skin flora migrates along the external surface into the subcutaneous catheter tract. For long-term use CVCs, contaminated catheter hubs from which organisms migrate along the internal surface of the catheter, are the most common source of organisms.[5,6]

CVCs in patients treated with chemotherapy or haemodialysis are used intermittently for a long time. A major complication associated with the intermittent and long-term use of CVCs is catheter occlusion caused by blood clot formation. In order to improve catheter patency, catheter lumens are filled (locked) with anticoagulant solutions when they are not in use. Different lock regimens exist as there is no standard regimen. In general, the solutions dwell in the lumen for a specific time. Thereafter, the solutions are aspirated and discarded or flushed into the bloodstream. A diluted heparin solution has been the traditional locking solution for many years. An experimental strategy is adding

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antibiotics to the standard lock solution, thereby limiting intraluminal catheter colonisation and therefore the development of CRBSI.[7]

A meta-analysis performed in 2006 demonstrated that the use of vancomycin-containing lock solutions is effective in reducing bloodstream infections (BSIs) in a high-risk immunosuppressive patient population.[8] However, the authors limited their review to vancomycin-containing lock solutions.

The Centers for Disease Control and Prevention (CDC, Atlanta, Georgia, USA) guideline does not recommend antibiotic lock solutions to prevent CRBSI, except for some special circumstances (e.g. in patients with long-term cuffed catheter or port, or a history of multiple CRBSIs despite adherence to aseptic technique).[9] However, the CDC did not base its recommendation on a systematic review. Therefore, we decided to conduct a systematic review on antibiotic-based lock solution policies.

The aim of this review of randomised controlled trials was to summarise the evidence on the effectiveness of antibiotic-based catheter lock solutions as compared to heparin lock solutions to prevent CRBSI in all patients with long-term intermittent use of CVCs.

Long-term effects of antibiotic-based solutions, catheter occlusion, bleeding, mortality or cost-effectiveness were not scrutinised in this review.

Methods

Search strategy

Publications were retrieved by searching the following databases: Medline (1966–2009) and the Cochrane Central Register of Controlled Trials (CENTRAL) up to April 2009. No language restrictions were applied. Additionally, the reference lists of all selected trials were searched. The following search strategies were used: in the Cochrane Library: (lock* OR flush*) AND antibiotic*; in Medline: ((((((((((((bacteremia) OR ((“line infection”))) OR ((“line infections”))) OR ((“catheter-related infection”))) OR ((“catheter-related infections”))) OR ((“catheter-associated infection”))) OR ((“catheter-associated infections”))) OR ((“bloodstream infections”))) OR ((“bloodstream infection”))) OR ((sepsis))) OR ((septicemia))) AND ((((((((((intravascular catheter))) OR ((“intravascular device”))) OR ((“intravascular devices”))) OR ((“intravascular catheter”))) OR ((“intravascular catheters”))) OR ((catheterization))) OR ((indwelling catheters))) OR ((indwelling catheter))) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR comparative study[mh] OR evaluation studies[mh] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospective*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]))))) AND ((lock*) OR (flush*)).

Selection

We included studies in which the following criteria were met: planned as a randomised controlled trial, quasi-randomised trial or systematic review/meta-analysis of randomised or quasi-randomised trials; published as an article; the effects of one or more preventive antibiotic-based lock solutions were studied in patients with CVCs for intermittent use; and presentation of sufficient data for calculating the risks of CRBSI in the treatment and control group. Two reviewers independently scanned all titles and abstracts identified by the search and eliminated any obviously irrelevant studies. The remaining studies classified as clearly relevant or unclear were retrieved in full text and assessed for inclusion. Disagreements were solved by discussion between the authors.

Quality assessment

Two reviewers independently assessed trial quality using the following components: concealment of allocation (classified as adequate if based on central randomisation, sealed envelopes, or similar); ‘blinding’ during treatment and at outcome assessment (classified as double blind when patients, patients’ physician and nurses, the research microbiologist and the principal investigator of the study were blinded); description of drop-outs (classified as adequate if the number of patients lost and reasons why patients were lost were reported according to allocation to treatment); and analysis (classified as adequate if performed according to the intention-to-treat principle). Disagreements were solved by discussion.

Data extraction and analysis

Data were extracted from the original studies by both reviewers independently and cross-checked. Only trial data related to the topic of the review were considered. If necessary, additional primary data were requested from the original trial authors. CDC definitions for infections were used.[9] CRBSI was defined as isolation of the same organism from catheter segment and peripheral blood or simultaneous quantitative blood cultures with a $\geq$5:1 ratio CVC versus peripheral blood. BSI was considered as symptoms of infection and at least one positive blood culture. For the dichotomous outcome CRBSI the overall incidence density ratio (IDR) was calculated with a 95% confidence interval (CI) and the incidence density difference (IDD) with a 95% CI by using Review Manager (Version 4.2.7). The incidence density was calculated by dividing the total number of CRBSIs by the total catheter-days of follow-up. The number of catheterisation days needed to treat (NNT) was calculated as the inverse of the IDD. Meta-analyses were undertaken using a random-effects model for the IDDs or the IDRs to calculate pooled estimates and their 95% CIs. If there were sufficient studies, subgroup meta-analyses were carried out where applicable. Subgroups were not defined a priori. We used the bivariate meta-analysis model to calculate the regression of the logit-transformed risk in treatment group versus control.[10] A funnel plot was used as a visual aid to detect publication bias or systematic heterogeneity.

Results

Selection

A total of 253 potentially relevant publications were initially identified by our search (Figure 1). After scanning 253 titles and abstracts, 19 potentially relevant publications were retrieved in full text. Screening references yielded another four possibly relevant studies.[11–14] Twenty-three studies appeared to fulfil the selection criteria. Of these, seven studies were excluded after reading the whole article.[8,11,14–18] The reasons for exclusion are listed in Table I. Sixteen trials were included in the review, of which nine trials studied haemodialysis patients, six trials studied oncology patients and one trial high risk neonates.[12,13,19–24,26–32]

Quality assessment

Trials studying haemodialysis patients

Nine trials were described as parallel group randomised controlled trials (Table II). In four trials concealment of allocation

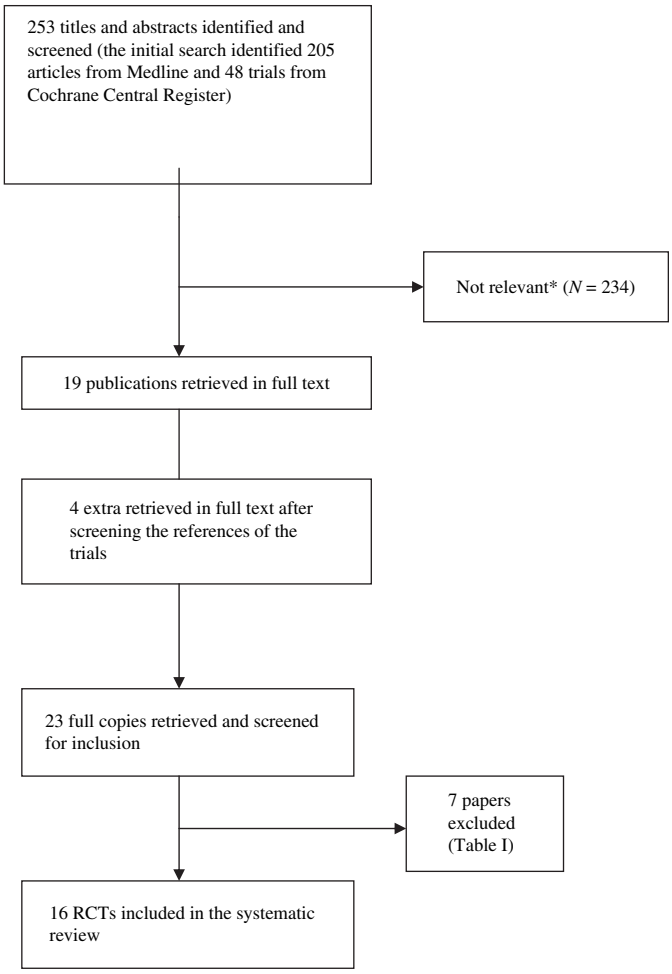

Figure 1. Flow diagram of reviewed articles. *Excluded because a non-antibiotic lock solution was used, lock solution was used for treatment rather than prevention, no central venous catheter (CVC) but subcutaneous ports, vancomycin added to total parenteral nutrition solution, study protocol instead of randomised controlled trial, review for effective management of CVC. RCT, randomised controlled trial.

was adequate.[13,28,30,32] None of the trials was clearly described as double blind. Description of drop-outs was adequate in five trials.[13,27,28,31,32] Only one trial performed analysis by intention to treat.[30]

Trials studying oncology patients

Six trials were described as parallel group randomised controlled trials (Table II). Concealment of allocation was adequate in two trials and both were described as double blind.[20,21] Description of drop-outs was adequate in two trials.[20,22] None of the trials was clearly based on an intention-to-treat principle.

Table I
Excluded studies

Study	Reasons for exclusion
Al-Hwiesh[18]	Double publication
Betjes and van Agteren[15]	Addressed another question
Jurewitsch and Jeejeebhoy[16]	Not randomised controlled trial
Kacica *et al.*[11]	Addressed another question
Safdar and Maki[8]	Addressed only a part of our question
Spafford *et al.*[14]	Addressed another question
Weijmer *et al.*[17]	Addressed another question

Trials studying high risk neonates

In this single RCT, concealment of allocation and description of drop-outs were adequately described (Table II).[25] The analysis was not performed by the intention-to-treat principle and it was unclear whether the trial was double blind.

Data extraction and analysis

Our main research question was: do antibiotic-based lock solutions reduce the occurrence of CRBSI compared to heparin lock solution?

Antibiotic-based lock solution versus standard heparin lock solution

Trials studying haemodialysis patients. In nearly all trials the CVCs were tunnelled and cuffed (Table III). The haemodialysis patients had comparable baseline risks for CRBSI between trials. The mean baseline risk was 3.0 CRBSIs per 1000 line-days. The catheter insertion time ranged from 37 to 365 days, with a mean of 146 days. Patients were randomised to locking the CVC by an antibiotic-based solution or a heparin solution alone. Data on the different antibiotic–anticoagulant solutions and the definitions of CRBSI are shown in Table III.

All nine studies found that CRBSI was more common in the heparin group; in seven of these the difference reached statistical significance (Figure 2). The results expressed as IDD derived from all trials showed a significant benefit in the advantage of antibiotic–anticoagulant solutions (IDD: −1.96; 95% CI: −2.63 to −1.30) (Figure 2). Since the mean incidence density for CRBSI was 3.0 per 1000 catheter-days in the control groups, this is equivalent to about three CVCs with a mean insertion time of 146 days being used to avoid one case of CRBSI.

Subgroup meta-analysis was carried out according to the anticoagulant used in the antibiotic group. The pooled results of the five trials comparing antibiotic–heparin with heparin lock solutions and those of the three trials comparing antibiotic–citrate with heparin lock solutions showed a statistically significant reduction in CRBSI (Figure 2, comparison 03 and 04). The study comparing antibiotic–EDTA with heparin lock solution showed an advantage of the antibiotic–EDTA lock solution, but this was not statistically significant (Figure 2, comparison 04).

Trials studying oncology patients. Five trials studied children, nearly all with tunnelled CVCs for chemotherapy (Table III).[19,21–24] The baseline risks for BSI were comparable between the trials. The mean baseline risk was 1.7 BSIs per 1000 catheter-days. The catheter insertion time ranged from 154 to 295 days, with a mean of 227 days. Most of the trials did not report CRBSI as the outcome but BSI. Data on the different antibiotic–heparin solutions and the definitions of BSI are shown in Table III.

A single trial studied neutropaenic adults (120 patients) with non-tunnelled CVCs for chemotherapy.[20] Patients in the control group in this study ran a mean risk for BSI of 27.1 per 1000 catheter-days. The CVCs were inserted for a mean of 10 days. Patients were randomised to a vancomycin–heparin or heparin lock solution.

In four out of the five trials studying paediatric populations the results were in favour of the antibiotic-based lock solutions, but the effect reached statistical significance in only one trial (Figure 3). The pooled results expressed as IDD showed a borderline statistically significant benefit of the antibiotic-based lock solutions (IDD −0.52 per 1000 catheter-days; 95% CI: −1.07 to 0.02) (Figure 3). Since the mean incidence density for BSI was 1.7 per 1000 catheter-days in the control groups, this is equivalent to about eight CVCs with a mean insertion time of 227 days being used to avoid one case of BSI.

The trial studying adults did not show any difference (IDD: −2.11; 95% CI: −20.17 to 15.95) (Figure 3, comparison 02).[20]

Table II
Data on quality assessment

	Concealment of allocation	Double blind	Description of drop-outs	Analysis by intention to treat
Al-Hwiesh and Abdul-Rahman[26]	Unclear	No	Inadequate (NR)	Unclear
Barriga *et al.*[19]	Unclear	Unclear	Inadequate (NR)	Unclear
Bleyer *et al.*[27]	Unclear	Unclear	Adequate (5%)	No
Carratala *et al.*[20]	Adequate	Yes	Adequate (3%)	No
Daghistani *et al.*[21]	Adequate	Yes	Inadequate (6%)	No
Dogra *et al.*[28]	Adequate	Unclear	Adequate (5%)	No
Garland *et al.*[25]	Adequate	Unclear	Adequate (6%)	No
Henrickson *et al.*[22]	Unclear	Unclear	Adequate	No
Kim *et al.*[29]	Unclear	No	Inadequate (NR)	Unclear
McIntyre *et al.*[30]	Adequate	No	Inadequate (NR)	Yes
Nori *et al.*[31]	Unclear	No	Adequate (2%)	No
Pervez *et al.*[12]	Unclear	No	Inadequate (NR)	Unclear
Saxena *et al.*[13]	Adequate	Unclear	Adequate (4%)	No
Saxena *et al.*[32]	Adequate	Unclear	Adequate (5%)	No
Rackoff *et al.*[23]	Unclear	No	Inadequate (NR)	Unclear
Schwartz *et al.*[24]	Unclear	Unclear	Inadequate (NR)	Unclear

NR, not reported.

Trials studying high risk neonates. A single trial studied critically ill neonates with a peripheral CVC inserted for a mean period of 20 days. The baseline risk for CRBSI was 15.4 per 1000 catheter-days. Neonates were randomised to a vancomycin–heparin or heparin lock solution. The result showed a strong benefit for the use of a vancomycin-heparin lock solution IDD for CRBSI: −13.15 per 1000 catheter-days (95% CI: −24.73 to −1.56) (Figure 3, comparison 03).[25]

Funnel plot analysis for detection of possible publication bias

Publication bias could not be ruled out in trials studying haemodialysis patients. The funnel plot shows underpresentation of small studies with negative or no effect (Figure 4).

For trials concerning oncology patients the funnel plot did not indicate publication bias (Figure 5).

Comparison of various antibiotic lock regimes

We could not determine which antibiotic-based lock solution is most effective in reducing CRBSI. Only two small trials compared different antibiotics head-to-head.

A small trial in haemodialysis patients compared gentamicin–citrate with minocycline–EDTA-containing lock solution.[31] The result was in favour of the gentamicin–citrate solution but with wide confidence intervals (IDD: −0.41; 95% CI: −1.21, 0.39). Also it is not possible to attribute this effect to the gentamicin, to the citrate or to both, as we could not determine the antimicrobial effect of citrate.

The other trial was performed in oncology patients and compared vancomycin–heparin versus vancomycin/ciprofloxacin–heparin lock solution.[22] It did not show any difference in the occurrence of CRBSI (IDD: −0.03; 95% CI: −0.33, 0.27).

Discussion

The aim of this review of randomised controlled trials was to summarise the evidence on the effectiveness of antibiotic-based catheter lock solutions in preventing CRBSI in all patients with long-term intermittent use of CVCs. Meta-analysis of nine RCTs showed a significant benefit in favour of the antibiotic-based solutions in haemodialysis patients with tunnelled and cuffed CVCs. Average insertion time was 146 days and CRBSI baseline risk was 3.0 per 1000 catheter-days, corresponding with NNT of three patients to prevent one CRBSI.

Meta-analysis of five RCTs in mainly paediatric oncology patients showed a small but statistically significant benefit of the antibiotic-based lock solutions in the prevention of BSI (not CRBSI).

It is worth mentioning that there was an overlap of 42 elderly patients between two trials.[13,32] Based on meta-analytical aspects, we felt it justified to retain the two studies in this review as this had no far-reaching consequences on the pooled IDD.

Overall, we think the included trials are flawed in various ways. Shortcomings may have introduced bias, as only two out of 16 trials clearly prevent performance bias and in eight trials methods of blinding were unclear. Nine trials had unclear allocation concealment and only one single trial performed analysis by intention-to-treat. Baseline comparability of groups did not differ. Design and methodology of included studies were sufficient to analyse and pool data.

A meta-analysis demonstrated that vancomycin-containing lock or flush solutions are effective in reducing the risk of BSI in oncology patients.[8] The review by Safdar *et al.* compared trails that were clinically heterogeneous, taking into account that a sensitivity analysis only highlighted statistical heterogeneity.[8] The summary risk ratio calculated in a heterogeneous population with a different mean duration of catheter placement resulted in a protective effect of vancomycin–heparin lock solution. In our review we focused on all antibiotic-based lock studies. In our statistical analyses we preferred to summarise the occurrence of BSI by the incidence per 1000 catheter-days rather than as a relative risk, as the duration of catheterisation is an important risk factor for the occurrence of BSI.

We merely included studies with a comparable population and catheterisation duration in the meta-analysis.

A Cochrane review also demonstrated a significant reduction of Gram-positive CRBSI, using vancomycin flush solutions in child oncology patients.[33] Results should be interpreted with caution because of the small number of studies.

In trials with haemodialysis patients we found that distinction should be made between the antibiotic–heparin-based lock solutions, antibiotic–citrate-based lock solutions and antibiotic–EDTA-based lock solutions. Non-antibiotic antimicrobial agents were expected to have a positive effect on CRBSI compared to heparin alone, a recent review confirmed.[34]

Another topic is the difference between a lock and flush solution as suggested by Safar *et al.*[8] Flush solutions were flushed into the bloodstream and lock solutions dwell in the lumen for a prescribed period of time and dispense after that time. In our opinion, in both cases a few millilitres are injected in the lumen of the catheter for a specified time, so that the effect is the same. For this reason we did not differentiate between lock and flush solutions in our analysis.

The results of the trials studying oncology patients should be considered with care. There is a lack of specificity when using BSI as a measure for CRBSI. The consequence of this is that the effect (expressed as NNT) of antibiotic-based lock solutions as derived

Table III
Study populations, interventions and definition of catheter-related bloodstream infection

Study	Setting	Type of CVC	Interventions (total no. of study catheters)	Duration of CVC catheterisation, mean or median days (total catheter-days)	No. of episodes	Baseline incidence density per 1000 catheter-days in C	Definition of outcome
Al-Hwiesh and Abdul-Rahman[26]	Haemodialysis	Tunnelled Cuffed	T (37): VA (25 mg/mL), GE (40 mg/mL), H (5000 U/mL)[a] C (44): H (5000 U/mL)[a]	T: (7212) C: (7656)	CRBSI T: 2 C: 16	2.1	CRBSI: Isolation of the same MO from the CVC blood and peripheral blood.
Barriga *et al.*[19]	Oncology	Tunnelled	T (39[b]): VA (25 μg/mL), H (25 U/mL)[c] C (44[b]): H (25 U/mL)[c]	T: (8011) C: (8666)	BSI T: 18 C: 26	3.0	BSI: Febrile episode + positive blood culture obtained from the CVC and/or peripheral blood.
Bleyer *et al.*[27]	Haemodialysis	Tunnelled Non-tunnelled	T (30): MI (3 mg/mL), EDTA (30 mg/mL)[d] C (27): H[d]	T: 77.9 (2336) C: 78.4 (2118)	CRBSI T: 0 C: 1	0.5	CRBSI: Febrile episode + CVC colonised with the same MO as isolated from peripheral blood.
Carratala *et al.*[20]	Oncology (neutropenic adults)	Non-tunnelled	T (60): VA (25 μg/mL), H (10 U/mL)[e] C (56): H (10 U/mL)[e]	T: 10 (600) C: 11 (627)	CRBSI T: 0 C: 4 BSI T: 15 C: 17	6.4 (ECRBSI) 27.1 (BSI)	Endoluminal CRBSI (ECRBSI): Febrile episode + identical MO from peripheral blood and the inner surface of the catheter hub (molecular typing). BSI: Febrile episode + positive peripheral blood culture.
Daghistani *et al.*[21]	Oncology (children)	ICVC	T (30): VA (25 μg/mL), AM (25 μg/mL), H (100 U/mL)[c] C (34): H (100 U/mL)[c]	T: 350 (9814) C: 295 (10 033)	BSI T: 2 C: 3	0.3	BSI: Febrile episode + positive blood culture obtained from the CVC and or peripheral blood.
Dogra *et al.*[28]	Haemodialysis	Tunnelled Cuffed	T (53): GE 40 mg/mL (2 mL) and 3.13% trisodium citrate (1 mL)[b] C (55): H (5000 U/mL)[b]	T: (3280)/ C: (2643)	CRBSI T: 0 T: 7	2.6	CRBSI: Febrile episode with no other apparent source of infection + (a) isolation of the same MO from catheter and catheter blood and peripheral blood; (b) defervescence of symptoms after catheter removal + positive catheter and peripheral blood; (c) defervescence of symptoms after catheter removal + catheter colonisation.
Garland *et al.*[25]	Critically ill neonates (NICU)	PICC	T (42): VA (25 μg/mL), H (10 U/mL)[f] C (43): H (10 U/mL)[f]	T: 20.3 (852.6) C: 19.6 (842.8)	CRBSI T: 2 C: 13 BSI T: 7 C: 18	15.4 (CRBSI) 21.4 (BSI)	CRBSI: Febrile episode + (a) identical MO from peripheral blood + the catheter hub or tip (molecular typing); (b) CoNS from peripheral blood + CoNS from hub or tip; (c) identical MO from catheter blood + hub or tip (molecular typing). BSI: Febrile episode + positive blood culture obtained from the CVC and/or peripheral blood.
Henrickson *et al.*[22]	Oncology (children)	Tunnelled	T1 (38): VA (25 μg/mL), H (9.73 U/mL)[c] T2 (35): VA (25 μg/mL), H (9.73 U/mL), CI (2 μg/mL)[c] C (80): H (9.73 U/mL)[c]	T1: 201 (8059) T2: 247 (10 840) C: 247 (18 045)	CRBSI T1: 1 T2: 1 C: 12 BSI T1: 8 T2: 3 C: 31	0.7 (CRBSI) 1.7 (BSI)	CRBSI: Febrile episode + (a) positive catheter blood and negative peripheral blood; (b) colony count catheter blood ≥10-fold cfu peripheral blood. BSI: Febrile episode + positive blood culture obtained from the CVC and/or peripheral blood.
Kim *et al.*[29]	Haemodialysis	Non-tunnelled	T (60): CEF (10 mg/mL), GE (5 mg/mL), H (1000 U/mL)[a] C (60): H (1000 U/mL)[a]	T: 37.68 (2261) C: 37.37 (2242)	CRBSI T: 1 C: 7	3.1	CRBSI: Isolation of the same MO from catheter and catheter blood and peripheral blood.
McIntyre *et al.*[30]	Haemodialysis	Tunnelled Cuffed	T (25): GE (5 mg/mL), H (5000 U/mL)[d] C (25): H (5000 U/mL)[d]	T: 130.1 (3252) C: 103 (2470)	CRBSI T: 1 C: 10	4.0	CRBSI: Febrile episode with no other apparent source of infection + isolation of the same MO from catheter and catheter blood and peripheral blood.

(*continued on next page*)

Table III (*continued*)

Study	Setting	Type of CVC	Interventions (total no. of study catheters)	Duration of CVC catheterisation, mean or median days (total catheter-days)	No. of episodes	Baseline incidence density per 1000 catheter-days in C	Definition of outcome
Nori *et al.*[31]	Haemodialysis	Tunnelled Cuffed	T1 (20): GE (4 mg/mL), 3.13% trisodium citrate[a] T2 (21): MI (3 mg/mL), EDTA (30 mg/mL)[a] C (20): H (5000 U/mL)[a]	T1: (2002) T2: (2453) C: (1734)	CRBSI T1: 0 T2: 1	4.0	CRBSI: Febrile episode with no other apparent source of infection + (a) catheter colonisation + positive catheter blood or peripheral blood; (b) defervescence of symptoms after antibiotic therapy + positive catheter blood or positive peripheral blood; (c) defervescence of symptoms after antibiotic therapy and catheter removal + catheter colonisation.
Pervez *et al.*[12]	Haemodialysis	Tunnelled Cuffed	T (14): Tricitrasol (46.7%), GE (40 mg/mL)[g] C (22): H (1000 U/mL)[g]	T: (1613) C: (1311)	CRBSI T: 1 C: 4	3.0	CRBSI: Febrile episode with no other apparent source of infection + positive blood culture (not specified whether peripheral and/or catheter blood).
Saxena *et al.*[13]	Haemodialysis (patients >65 years)	Tunnelled Cuffed	T (59): CEFT (10 mg/mL), H (5000 U/mL)[a] C (60): H (5000 U/mL)[a]	T: (21 535) C: (21 900)	CRBSI T: 36 C: 79	3	CRBSI: Febrile episode with no other apparent source of infection + positive blood culture (not specified whether peripheral and/or catheter blood).
Saxena *et al.*[32]	Haemodialysis	Tunnelled Cuffed	T (51): CEFT (10 mg/mL), H (5000 U/mL)[a] C (58): H (5000 U/mL)[a]	T: (18 615) C: (21 170)	CRBSI T: 29 C: 78	3.7	CRBSI: Febrile episode with no other apparent source of infection + positive blood culture (not specified whether peripheral and/or catheter blood).
Rackoff *et al.*[23]	Predominantly oncology (children)	Tunnelled Cuffed	T (32[b]): VA (25 μg/mL), H (100 U/mL)[c] C (31[b]): H (100 U/mL)[c]	T: 137 (4378) C: 154 (4780)	BSI T: 10 C: 10	2.1	BSI: Febrile episode + positive blood culture obtained from the CVC and/or peripheral blood (low colony counts excluded). CRBSI: Febrile episode + colony count catheter blood ≥10-fold colony count peripheral blood (low colony counts excluded).
Schwartz *et al.*[24]	Oncology (children)	Tunnelled	T (24): VA (25 μg/mL), H (9.75 U/mL)[c] C (29): H (9.75 U/mL)[c]	T: 228 (4792) C: 262 (6303)	CRBSI T: 1 C: 6 BSI T: 3 C: 8	1.0 (ECRBSI) 1.3 (BSI)	Endoluminal CRBSI: Febrile episode + colony count catheter blood ≥10-fold colony count peripheral blood (with low colony counts excluded) and no local catheter infection. BSI: Febrile episode + positive blood culture obtained from the CVC and/or peripheral blood (low colony counts excluded).

AM, amikacin; C, control; CEF, cefazolin; CEFT, cefotaxime; cfu, colony-forming units; CI, ciprofloxacin; CoNS, coagulase-negative staphylococci; (CR)BSI, (catheter-related) bloodstream infection; CVC, central venous catheter; EDTA, ethylenediamine tetra-acetic acid; GE, gentamicin sulphate; H, heparin; ICVC, indwelling central venous catheter; MI, minocycline; MO, micro-organism; PICC, peripherally inserted central catheter; T, treatment; VA, vancomycin hydrochloride.

[a] Lock solution at the end of each dialysis session, and withdrawn before next dialysis session.

[b] Number of catheters not reported, number of patients presented.

[c] Flush solution daily.

[d] Lock solution.

[e] Lock solution indwelling for 1 h every two days.

[f] Lock two or three times daily for 20 or 60 min at the end of dwell time, study lock solution withdrawn.

[g] Lock solution and withdrawn before next dialysis session + catheter hub covered with a sterile bag after cleaning with povidone iodine 10%.

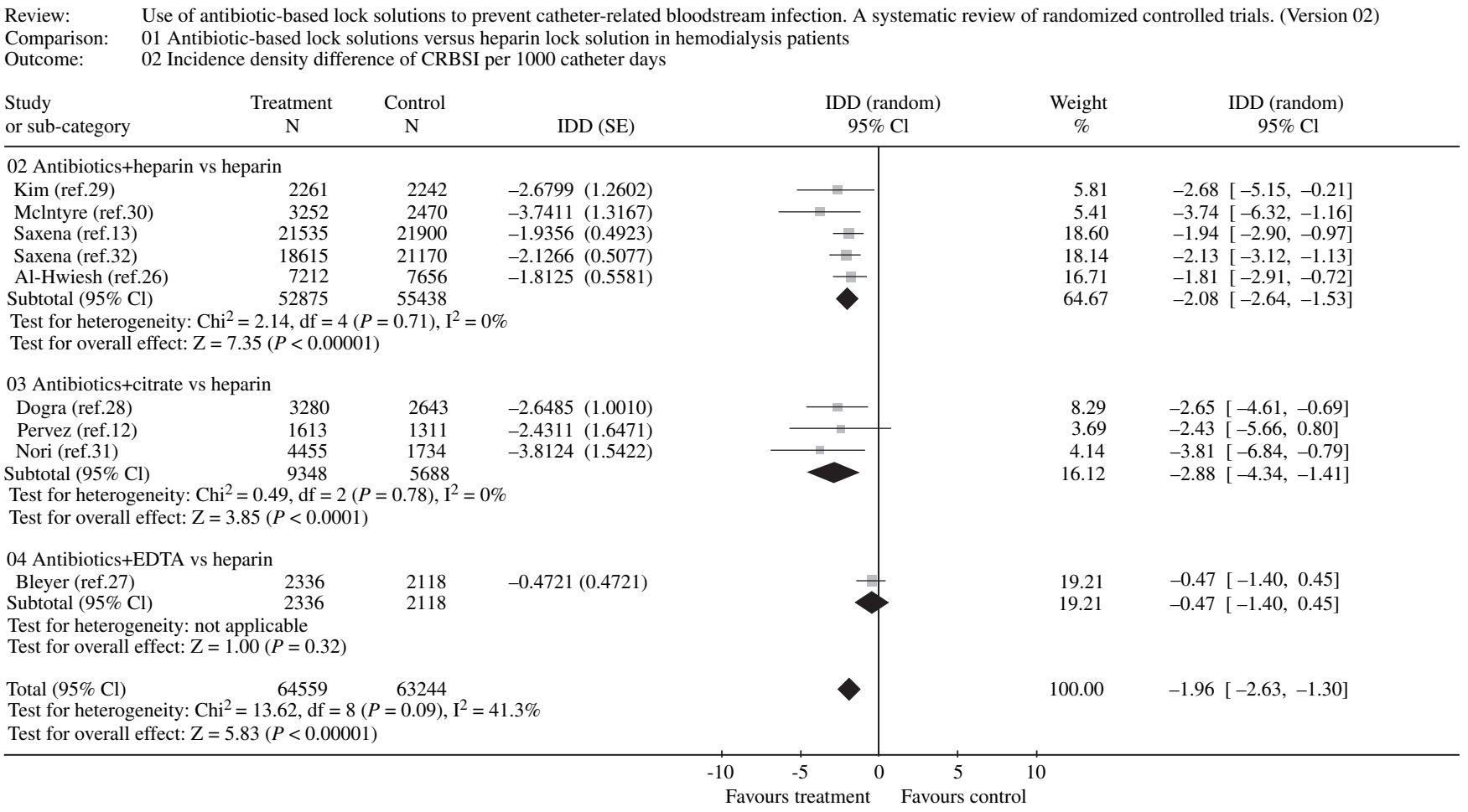

Figure 2. Analyses of association between antibiotic-based lock solutions and heparin lock solutions in haemodialysis patients expressed as incidence density difference (IDD) and 95% confidence interval (CI) using a random-effects model.

Review: Use of antibiotic-based lock solutions to prevent catheter-related bloodstream infection. A systematic review of randomized controlled trials.
Comparison: 03 Antibiotic-based lock solutions versus heparin lock solution in oncology patients
Outcome: 02 Incidence density difference of BSI per 1000 catheter days

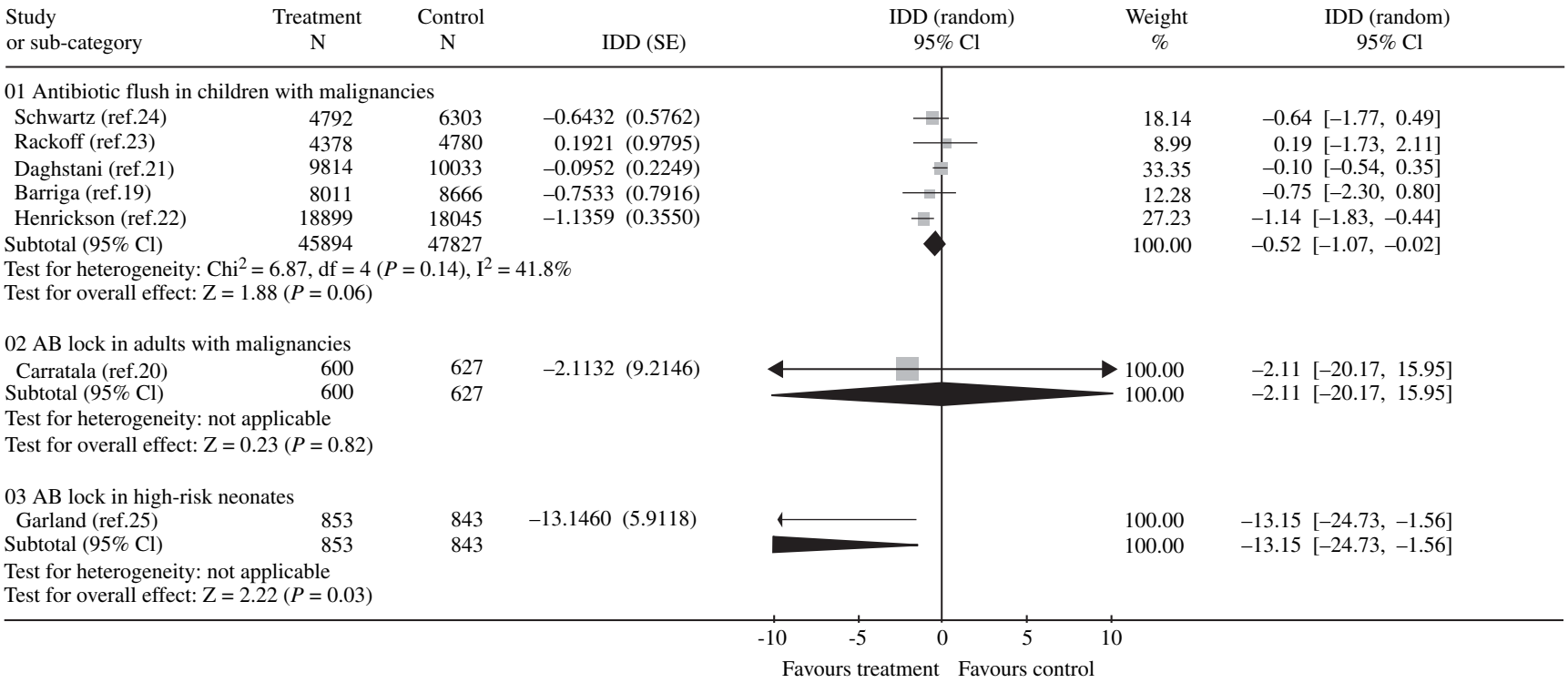

Figure 3. Analysis of association between antibiotic-based lock solutions and heparin lock solutions in oncology patients expressed as incidence density difference (IDD) and 95% confidence interval (CI) using a random-effects model.

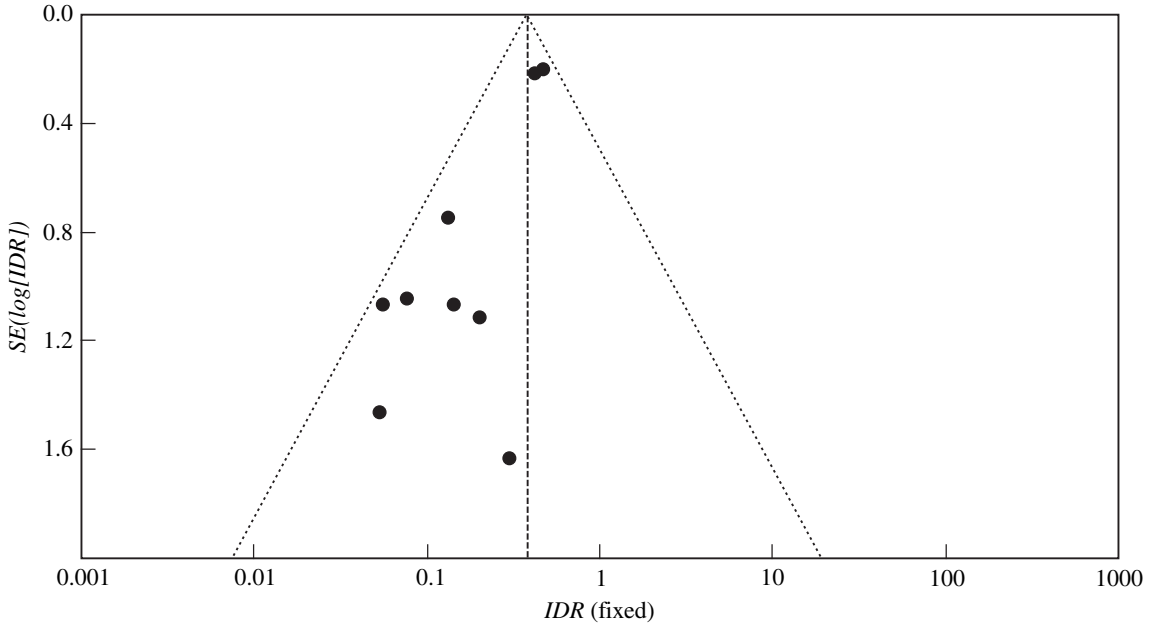

Figure 4. Funnel plot: trials studying haemodialysis patients. Publication bias assessment plot for the comparison of antibiotic-based lock solution versus heparin. Each circle represents one study, showing predominantly significant (positive) effect studies. Publication bias could not be ruled out. IDR, incidence density ratio.

from the trials is very likely to be overestimated. When a non-specific outcome is used, evidence for clinical interpretation of a preventive effect of antibiotic-based lock solutions is weak.

All included studies evaluated different preventive antibiotic and anticoagulation prescriptions. There are indications that the use of antibiotic-based lock solutions could prevent catheter-related infections. Two studies evaluated different antibiotic-based lock solutions and showed no significant effect of this comparison. Therefore it was not possible to determine which antibiotic-based lock solution is most effective.

Another concern in meta-analysis is publication bias. In trials studying haemodialysis patients, studies with fewer preventive effects and with large sample sizes are less likely to be published. The presented effect of published trials could be overestimated (Figure 4).

Against the benefits of antibiotic-based lock solutions, possible disadvantages such as development of bacterial antibiotic resistance and patient side-effects of antibiotics have to be weighed. Some studies have performed drug monitoring by measuring antibiotic levels in peripheral venous blood samples. These

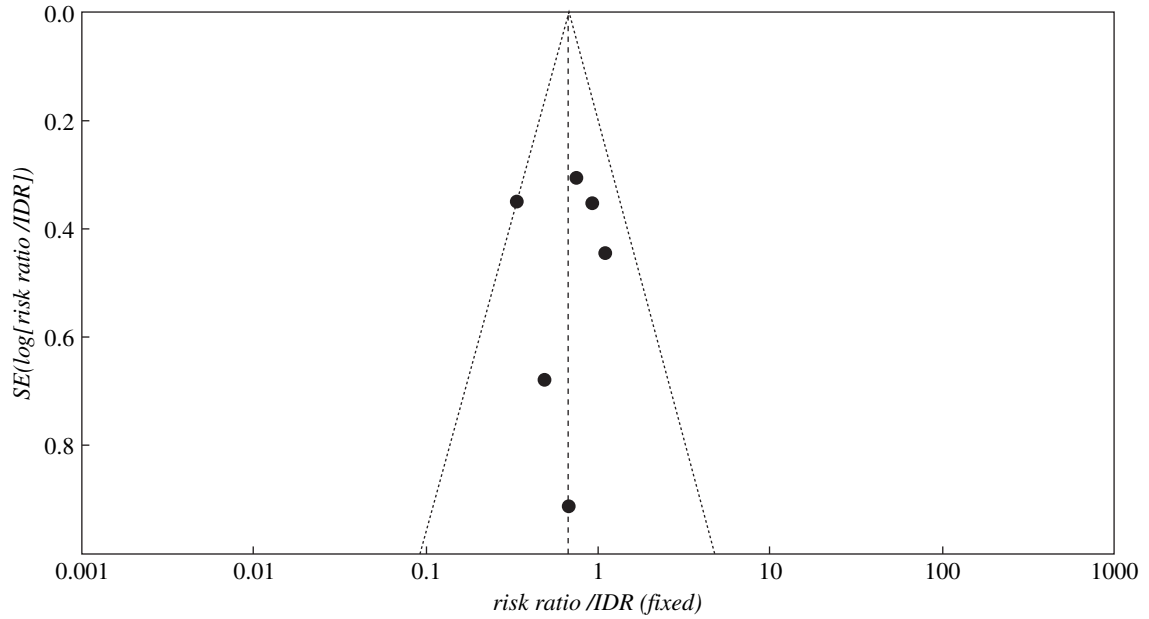

Figure 5. Funnel plot: trials studying oncology patients. Publication bias assessment plot for the comparison of antibiotic-based lock solution versus heparin. Each circle represents one study. Publication bias could not be detected. IDR, incidence density ratio.

vancomycin and gentamicin levels were not measured systematically. Although no long-term adverse effects were reported, the issue of development of antibiotic resistance still remains. It is preferable that this type of research question be addressed using long-term prospective studies.

Regarding studies comparing antibiotic–citrate locks with heparin lock solutions, it should be noted that citrate also has an antibacterial effect. After an incident with highly concentrated trisodium citrate in the USA in 2000, this agent has been banned as a catheter locking solution by the US Food and Drug Administration (FDA) until now. Whether citrate solutions, be it citrate alone or in combination with other antimicrobial and anticoagulant agents, will be FDA approved in the future has to be seen.

To determine whether routine use of antibiotic lock solutions, contrary to CDC recommendations, is to be advocated in haemodialysis patients, other factors should be borne in mind. Surely CRBSI is a complication severe enough to strive for minimisation of its occurrence. On the other hand one has to consider possible side-effects of antibiotics, such as the induction of microbial antibiotic resistance. Cost-effectiveness must also be considered before a solid recommendation on the use of antibiotic-based lock solutions can be formulated.

Conclusion

Trials studying oncology patients

Scientific proof for effectiveness of antibiotic-based lock solutions is weak, as the methodological quality has been poor, the tested antibiotics (vancomycin, amikacin, ciprofloxacin) were heterogeneous, the outcome measurement used was non-specific (sepsis and non-catheter related sepsis) and the estimated effect had marginal statistical significance.

Trials studying haemodialysis patients

Both the combination of antibiotic–heparin and of antibiotic–citrate lock solutions are superior to heparin-only lock solutions regarding risk reduction of CRBSI in haemodialysis patients. Methodological quality of underlying studies was poor to moderate, and the tested antibiotic and anticoagulant regimes (aminoglycosides, vancomycin; heparin, citrate, EDTA) were heterogeneous. There is no consistency for any of the studied regimes.

Taken together we conclude that in haemodialysis patients antibiotic catheter lock solutions are effective in preventing CRBSI. Negative side-effects on patients, micro-organism susceptibility and costs are to be considered. Finally, there are no trials comparing the antimicrobial effects of, for example, citrate locks versus antibiotic-based locks head-to-head. As these antimicrobial solutions do not induce antibiotic resistance and often are less expensive compared to antibiotics, we think a well-designed trial comparing antibiotic lock solutions to non-antibiotic antimicrobial lock solutions is warranted.

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None declared.

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