

Does antimicrobial lock solution reduce catheter-related infections in hemodialysis patients with central venous catheters? A Bayesian network meta-analysis

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Abstract

Purpose The purpose of our study is to carry out a Bayesian network meta-analysis comparing the efficacy of different antimicrobial lock solutions (ALS) for prevention of catheter-related infections (CRI) in patients with hemodialysis (HD) and ranking these ALS for practical consideration.

Methods We searched six electronic databases, earlier relevant meta-analysis and reference lists of included studies for randomized controlled trials (RCTs) that compared

ALS for preventing episodes of CRI in patients with HD either head-to-head or against control interventions using non-ALS. Two authors independently assessed the methodological quality of included studies using the Cochrane risk of bias tool and extracted relevant information according to a predesigned extraction form. Data were analysed using the WinBUGS (V.1.4.3) and the Stata (V.13.0).

Results Finally, 18 studies involving 2395 patients and evaluating 9 ALS strategies were included. Network meta-analysis showed that gentamicin plus citrate (OR 0.07, 95% CrI 0.00–0.48) and gentamicin plus heparin (OR 0.04, 95% CrI 0.00–0.23) were statistically superior to heparin alone in terms of reducing CRBSI. For exit site infection and all-cause mortality, no significant difference in the intervention effect ($p > 0.05$) was detected for all included ALS when compared to heparin. Moreover, all ALS were similar in efficacy ($p > 0.05$) from each other for CRBSI, exit site infection and all-cause mortality.

Conclusions Our findings indicated that gentamicin plus heparin may be selected for the prophylaxis of CRI in patients undergoing HD with CVCs. Whether this strategy will lead to antimicrobial resistance remains unclear in view of the relatively short duration of included studies. More attentions should be made regarding head-to-head comparisons of the most commonly used ALS in this field.

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Keywords Antimicrobial lock solution · Catheter-related infections · Central venous catheters · Network meta-analysis · Renal dialysis

Introduction

For chronic hemodialysis (HD) treatment, a functioning arteriovenous fistula or synthetic graft is preferred for

vascular access [1, 2]. However, in current practice, central venous catheters (CVCs) remain a common form of access for many patients [3, 4]. They are temporarily used in acute kidney injury and in a substantial proportion of incident and prevalent HD patients until their permanent vascular access becomes available. However, CVCs are prone to catheter malfunction and catheter-related infection (CRI), which includes catheter-related bloodstream infection (CRBSI) and exit site infection. It has been estimated that the relative risk (RR) for infection in HD catheters when compared with native arteriovenous fistulae is 15.5 and 25.5 [5].

CRI is associated with a substantial morbidity and mortality. According to the US Renal Data System, infection is the second leading cause of death in patients with end-stage renal disease, and the leading cause of catheter removal and morbidity in dialysis patients [6–8]. Besides, the costs to the health care system are also substantial [9]. Therefore, the prevention and management of CRI remains a significant clinical challenge in the management of this form of vascular access.

Over recent years, interest has focused on the use of antimicrobial lock solutions (ALS) of the catheters between each HD session. It is known from *in vitro* studies that solutions containing antimicrobials can prevent biofilm formation [10]. The biofilm constitutes a permanent source of bacteraemia, as well as a key factor favouring bacterial resistance [11, 12]. Also there were some clinical researches reports that ALS is significantly more effective in reducing the occurrence of CRI when used in HD patients [13–15]. These available antimicrobials include gentamicin, taurolidine, minocycline and so on. Similarly, several recent meta-analyses confirmed that prophylactic antimicrobial locks are effective in preventing such infections when compared to heparin locks [16–20].

However, the most appropriate antimicrobial agent has not been determined to date, as few head-to-head comparisons among different ALS have been published and the traditional meta-analysis only focuses on comparing two alternatives. In this situation, a network meta-analysis is urgently needed in this area. Network meta-analysis methods enabled us to simultaneously compare more than two interventions in the same analysis; provided relative effect estimates for all intervention comparisons, even those in which there was no direct evidence available; enabled the estimation of the probability that each intervention is best; and reduced the uncertainty in the intervention effect estimates [21–23]. Thus, we carried out this network meta-analysis to compare the efficacy of different ALS for prevention of CRI for HD patients based on existing RCT and ranking these ALS for practical consideration.

Subjects and methods

Protocol and registration

This protocol has been registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>) under registration number CRD42015027010.

Eligibility criteria

1. Type of study

Any relevant RCTs were included.

2. Participants

The participants must be adults, aged at least 18 years, who had or were about to commence either short-term or maintenance hemodialysis using tunnelled or non-tunnelled CVC as vascular access.

3. Type of interventions

RCTs of ALS used to prevent CRI in HD patients were included, regardless of whether the antimicrobials were tested between themselves (head-to-head) or against placebo/control intervention such as heparin.

4. Outcomes of interest

The primary outcome was CRBSI. The Centers for Disease Control (CDC) definitions for CRBSI were used [24]. Only RCTs that used this definition, or RCTs whose results were detailed enough to be re-adjudicated according to the aforementioned definition, were included. In cases when a study separately reported definite, probable and possible CRBSI, we chose not to include ‘possible’ blood stream infection (defined as the absence of laboratory confirmation of blood stream infection).

The secondary outcomes were exit site infection (defined as the development of a purulent exudates or redness around the site not resulting from residual stitches), all-cause mortality and adverse events as reported by study authors.

5. Other criteria

Other inclusion criteria: the RCTs must report sufficient data for calculating the risks of CRBSI in the intervention and control group. Other exclusion criteria were (1) duplicated or redundant studies, (2) combined interventions with multiple antimicrobial solutions and (3) studies dealing with the treatment of CRI rather than with prophylaxis.

Information sources and search

We systematically performed an electronic search of PubMed, Cochrane Library, Embase (via Embase.com platform), Sciences Citation Index (via Web of knowledge platform), CINAHL (via EBSCO platform) and Chinese Biomedical Literature Database from their inception to September 2015 with no language restrictions. In addition, we searched unpublished theses and dissertations via Conference Proceedings Citation Index, China Proceeding of Conference Full-text Database, China Doctoral Dissertation Full-text Database, China Master's Theses Full-text Database and the System for Information on Gray Literature database in Europe (SIGLE). We also searched the World Health Organization International Clinical Trials Registry Platform Search Portal (www.who.int/trialsearch/) for ongoing trial registers. Relevant systematic reviews and meta-analyses from these databases were identified and bibliographies were scrutinised for further relevant trials, as well as those of RCTs included in the review. The search method included relevant text words and medical subject headings related to HD, infection, CVC and RCT. The exact search strategy used in the PubMed database is provided as an example in Online Resource 1.

Study selection

Literature search results were imported into ENDNOTE X7 literature management software. Two authors independently reviewed the literature searches from the title, abstract or descriptors and excluded the study that clearly does not meet the inclusion criteria. After excluding the duplicated and apparently irrelevant studies, the remaining studies were reviewed in full text to assess eligibility for inclusion. Any disagreements were resolved by discussion or by seeking an independent third opinion. Excluded trials and the reason for their exclusion were listed and examined by a third reviewer.

Data collection process and data items

Two authors independently extracted the data from each study using a standardized data extraction checklist, which include study characteristics (e.g. first author's name, publication year, journal, country where the study was conducted), characteristics of study subjects (e.g. number of participants, age, gender distribution), characteristics of catheter (e.g. type of catheters, number of catheters), interventions details (e.g. type and concentration of lock solutions, patient involvement, duration of hemodialysis, number of catheter days), outcome variables (e.g. number of episodes) and any additional prophylactic measures used that may have affected outcomes (e.g. catheter care).

Outcomes were extracted preferentially by intention to treat (ITT) at the end of follow-up. Quantitative data were extracted to calculate effect sizes. Data on effect size that could not be obtained directly were recalculated, when possible. Any discrepancy was resolved by consensus.

Risk of bias within individual studies

Two authors independently evaluated the methodological quality of the included studies for major potential sources of bias by using the Cochrane Collaboration's risk of bias tool [25], which include method of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data selective reporting, and other sources of bias. We evaluated methodological quality of each study on each criterion as low, high or unclear risk of bias. Any disagreements was resolved through discussion, if need be, with another reviewer.

Statistical analysis

Bayesian network meta-analysis was performed by using the Markov chain Monte Carlo method in WinBUGS 1.4.3. The other analyses were performed and presented by the Stata 13.0 using the `mvmeta` command. Treatment effects of dichotomous outcomes were reported as posterior means of odds ratio (OR) with corresponding 95% credible intervals (CrI), which can be interpreted similarly to conventional 95% confidence intervals (CI). Both random effects and fixed effects models with vague priors for multiarm trials were used. The main difference between these two types of model is that the former takes into account the between-study variance, thereby producing wider credible intervals. Model fit was determined based on the deviance information criteria (DIC) for each outcome measure [26]. Three Markov chains were run simultaneously with different arbitrarily chosen initial values. To ensure convergence, Brooks–Gelman–Rubin method was assessed [27]. By this process, a potential scale reduction factor (PSRF) was calculated by comparing within-chain and between-chain variance. A PSRF very close to 1 was considered to indicate an approximate convergence. Convergence were found to be adequate after running 20,000 samples for three chains. These samples were then discarded as 'burn-in', and posterior summaries were based on 100,000 subsequent simulations. When a loop connected three treatments, it was possible to evaluate the inconsistency between direct and indirect evidence. The node-splitting method was used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence. Significant inconsistency was indicated if node-splitting analysis derived $p < 0.05$.

The ranking probabilities of all interventions were used to calculate a summary numerical value: the surface under the cumulative ranking curve (SUCRA). SUCRA values are expressed as percentages; if an intervention is certainly the best, its SUCRA value would be 100%, and if an intervention is certainly the worst, its SUCRA value would be 0%.

We assessed clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. The I^2 statistic was used to assess heterogeneity among the studies and in the entire network and considered values over 50% to represent high heterogeneity. We conducted a sensitivity analysis by excluding trials with a total sample size of less than 50 randomized patients. A comparison-adjusted funnel plot was used to assess whether smaller studies produced larger treatment effects.

Results

Study selection

Figure 1 presents a flow diagram illustrating the studies selection process. The electronic searches identified 1467 studies, of which 572 duplicates were excluded by Endnote software and 793 articles were clearly not relevant after the first screening. 102 were retrieved in full text for in-depth consideration, and then 84 were excluded. Finally, 18 studies [13–15, 28–42] were included in our analysis. References cited in published original and review papers were examined until no further studies were found.

Characteristics of included studies

The characteristics of studies included in the network meta-analysis are presented in Table 1.

Of these included studies, four [33, 34, 38, 42] were performed in China, three [15, 31, 40] in the USA, two [37, 41] in Greece, two [28, 35] in the United Kingdom, two [13, 39] in Australia, two [14, 30] in Netherlands, one [32] in Canada, one [29] in Saudi Arabia and one [36] in Brazil. The combined sample size across 18 included studies [13–15, 28–42] was 2395 participants with a total of 2548 catheters. The interventions used in studies were highly variable. The antimicrobials assessed were gentamicin in 8 trials [13, 28, 31, 33, 34, 37, 38, 40], taurolidine in 3 trials [14, 35, 37], minocycline-EDTA in 3 trials [15, 31, 36], citrate in 2 trials [30, 32], cefotaxime in 1 trial [29], vancomycin in 1 trial [41], cefazolin in 1 trial [42] and ethanol in 1 trial [39]. Nori et al. [31] and Sofroniadou et al. [41] used two active comparator groups in their studies in addition to the control group. Of note, we were unable to include in our analysis the linezolid arm of the study conducted by

Sofroniadou et al. [41] because of missing data for patients in this group. Comparison treatments were somewhat less varied with most trials using heparin as controls. There was the only one study in which both study groups included an antimicrobial agent. The concentration of antimicrobial lock solutions and heparin used in individual studies were presented in Online Resource 2. Not all studies used the same type of catheter. Nine [13, 28, 31–35, 39, 40] assessed tunnelled catheters only, 2 [29, 41] assessed non-tunnelled catheters only, 4 [14, 15, 30, 36] assessed both types of catheters and the remainders [37, 38] were unclear in the reported paper. Catheter care is of crucial importance to patients using intravascular catheters. Fourteen studies [13, 14, 28–30, 32, 34–41] described catheter care procedures. Cleaning the catheter site with iodine or chlorhexidine solutions and changing of dressing after each dialysis session appeared to be the most common catheter care. All trials evaluated the incidence of CRBSI and some of them assessed the incidence of exit site infection. All-cause mortality at the end of follow-up was reported in 7 trials [30–34, 40, 41].

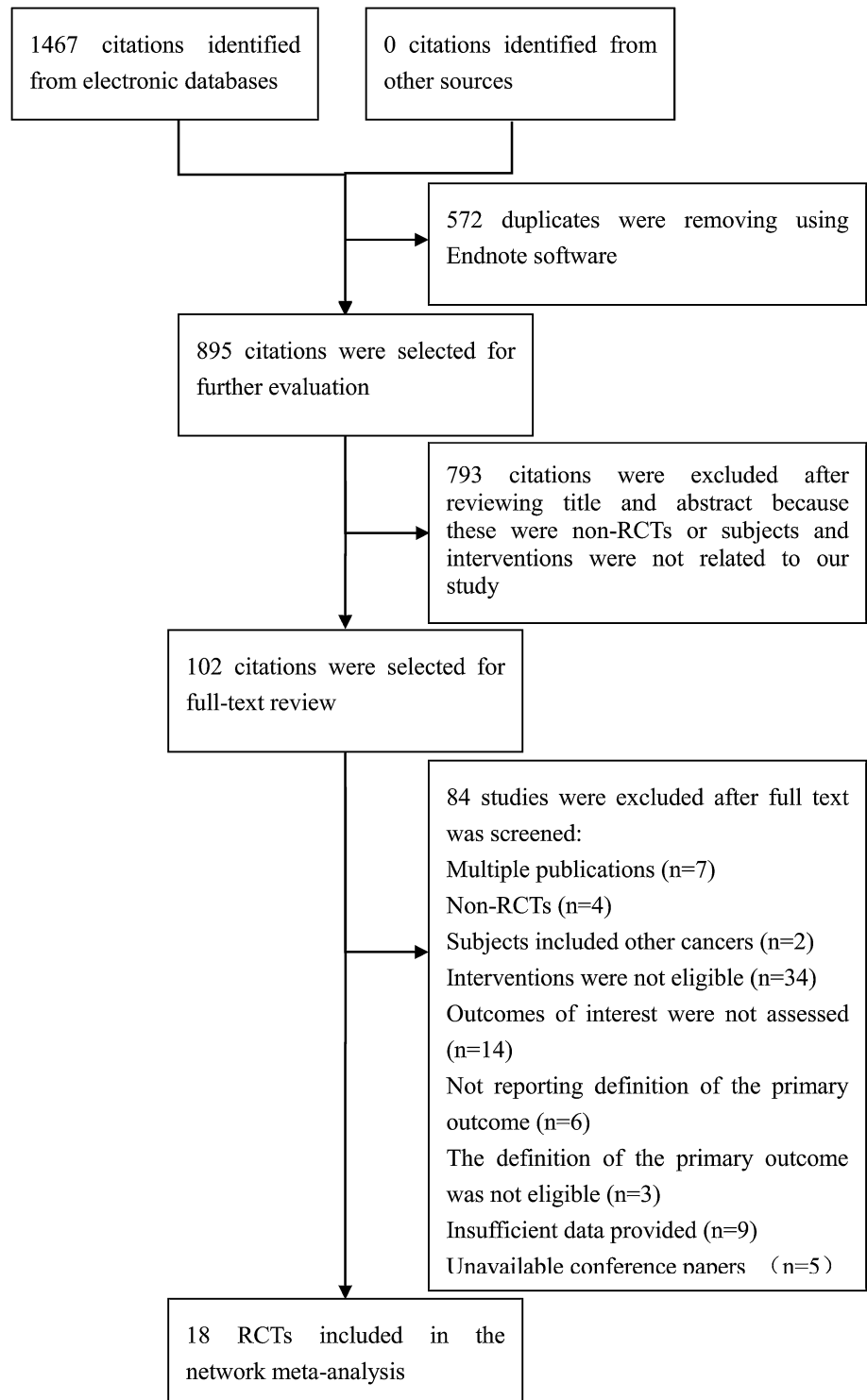
Methodological quality of included studies

Table 2 shows the quality assessment of the studies in this network meta-analysis. All included studies were stated to be randomized, but based on the Cochrane Collaboration tool, only 10 [13, 14, 29, 30, 34, 35, 37, 39–41] specified the method of randomization and 7 [13, 28–30, 35, 36, 39] had a clearly defined method to conceal allocation of patients. Three trials [13, 29, 30] had blinding of patient, personnel and outcome assessors. The patients and personnel providers alone were blinded in 4 trials [15, 34, 35, 41], and one trial [40] had blinding of patients alone. Seven trials [14, 28, 31, 32, 36, 37, 39] were open-label trials. Description of drop-outs was adequate in 14 trials [13–15, 28, 30–33, 35–39, 41], and the remainders were unclear in the reported paper [29, 34, 40, 42].

The results of the network meta-analysis

We performed a Bayesian network meta-analysis to assess the relative outcomes of different ALS and control conditions with each other from all direct and indirect comparisons. The random effects model was used for CRBSI because the DIC for this outcome measure favoured this model over the fixed effects model. So, the analysis of CRBSI was based on the results generated by the former. For exit site infection and all-cause mortality, the fixed effects model showed a better fit than the random-effect one.

Figure 2 showed the network structure of the comparisons among the different interventions for the outcomes. The lines between interventions nodes indicate the direct

Fig. 1 Flow diagram of included and excluded studies

comparisons made within randomized trials. The width of the lines is proportional to the number of trials comparing each pair of interventions, and the size of each node is proportional to the number of randomly assigned participants.

All these network plots have a star geometry, with heparin acting as the common comparator. The missing links between active interventions reflect the scarcity of direct comparisons.

Table 1 Characteristic of included studies

First Author, Year	Country	No. of patients (Exp/control)	No. of catheters (Exp/control)	Tunnelled or non-tunnelled catheter	Site of catheter insertion	No. of catheter days (Exp/control)	Intervention		Outcomes
							Exp	Control	
Dogra 2002 [13]	Australia	42/37	53/55	Tunnelled	Jugular vein	3280/2643	Gentamicin + citrate	Heparin	a, b
Beijes 2004 [14]	Netherlands	58	37/39	Both	Jugular, subclavian and femoral vein	1519/1885	Taurolidine + citrate	Heparin	a, b
Mcintyre 2004 [28]	UK	25/25	25/25	Tunnelled	Jugular and subclavian vein	3252/2470	Gentamicin + heparin	Heparin	a
Bleyer 2005 [15]	USA	30/30	30/30	Both	Unclear	2336/2118	Minocycline-EDTA	Heparin	a
Saxena 2005 [29]	Saudi Arabia	159/49	159/49	Non-tunnelled	Jugular, subclavian and femoral vein	58035/17885	Cefotaxime + heparin	Heparin	a, b
Weijmer 2005 [30]	Netherlands	148/143	148/143	Both	Jugular, subclavian and femoral vein	8431/8116	Citrate	Heparin	a, b, c
Nori 2006 [31]	USA	Exp1: 20; Exp2: 21/21	Exp1: 20; Exp2: 21/21	Tunnelled	Jugular vein	Exp1: 2002; Exp2: 2453/1734	Exp1: Gentamicin + citrate; Exp2: Minocycline-EDTA	Heparin	a, c
MacRae 2008 [32]	Canada	32/29	32/29	Tunnelled	Jugular and subclavian vein	2273/1818	Citrate	Heparin	a, b, c
Tan 2008 [33]	China	70/69	70/69	Tunnelled	Jugular vein	17606/16213	Gentamicin + heparin	Heparin	a, c
Zhang 2009 [34]	China	71/69	71/69	Tunnelled	Jugular vein	17781/16299	Gentamicin + heparin	Heparin	a, b, c
Solomon 2010 [35]	UK	55/55	56/58	Tunnelled	Jugular and subclavian vein	8129/9642	Taurolidine + citrate	Heparin	a, b
Campos 2011 [36]	Brazil	150	102/102	Both	Jugular and subclavian vein	4371/4376	Minocycline-EDTA	Heparin	a, b
Filiopoulos 2011 [37]	Greece	60/59	74/76	Unclear	Jugular and subclavian vein	2190/2180	Gentamicin + heparin	Taurolidine + citrate	a
Lu 2011 [38]	China	180/176	180/176	Unclear	Jugular and femoral vein	10224/9648	Gentamicin + heparin	Heparin	a, b
Broom 2012 [39]	Australia	25/24	25/24	Tunnelled	Jugular vein	3614/1834	Ethanol	Heparin	a
Moran 2012 [40]	USA	155/148	155/148	Tunnelled	Jugular, subclavian and femoral vein	39827/32933	Gentamicin + citrate	Heparin	a, b, c

Table 1 continued

First Author, Year	Country	No. of patients (Exp/control)	No. of catheters (Exp/control)	Tunnelled or non-tunnelled catheter	Site of catheter insertion	No. of catheter days (Exp/control)	Intervention		Outcomes
							Exp	Control	
Sofroniadou 2012 [41]	Greece	135	Exp1: 49; Exp2: 52/51	Non-tunnelled	Jugular, subclavian and femoral vein	Exp1: 1653; Exp2: unclear/1642	Exp1: vancomycin + heparin; Exp2: linezolid + heparin	Heparin	a, b, c
Hu 2013 [42]	China	13/12	13/12	Unclear	Jugular vein	2353/2183	Cefazolin + citrate	Heparin	a

Exp experimental group, Control control group, a CRBSI, b exit site infection, c all-cause mortality

Effects on CRBSI

The results of network meta-analysis about 10 interventions (including the control group) comparing with each other were reported in Fig. 3. A total of 18 trials [13–15, 28–42] (2395 participants, 2496 catheters) contributed to the analysis of CRBSI. It indicated that only gentamicin plus citrate (OR 0.07, 95% CrI 0.00–0.48) and gentamicin plus heparin (OR 0.04, 95% CrI 0.00–0.23) were statistically significantly more effective in terms of reducing CRBSI when compared to heparin alone. Besides that, there was no difference in effects between active interventions.

The results of the evaluation of heterogeneity showed a moderate to high level of statistical heterogeneity for many of the pair-wise comparisons (Online Resource 3), as well as across all studies as a whole ($I^2 = 50%$). However, given the low number of eligible studies for the majority of comparisons, we didn't perform meaningful subgroup analysis, which is important given the heterogeneity of the study.

Table 3 shows which ALS had the greatest possibility of being the most efficacious intervention based on an analysis of the area under the SUCRA curve, which was drawn according to the cumulative probabilities, with the percentage of the area under each curve shown (larger area signifying a better result). Based on SUCRA, gentamicin plus heparin ranked the first, the second was vancomycin plus heparin and the last was heparin alone. As shown in Figure S1, the inspection of the 'comparison-adjusted' funnel plot did not show small study bias (Online Resource 4).

Effects on exit site infection

Figure 4 summarizes the overall efficacy to reduce exit site infection of the included antimicrobial categories. A total of 11 trials [13, 14, 29, 30, 32, 34–36, 38, 40, 41] (1891 participants, 1961 catheters) contributed to this analysis. The results showed that none of the intervention arms were found to be statistically significantly different when compared with each other. According to SUCRA values (Table 3), vancomycin plus heparin got the highest probability (69.0%) and taurolidine plus citrate got the second highest (66.8%) among all the eight treatments. No significant evidence of heterogeneity was observed in the evaluation of heterogeneity on this outcome ($I^2 = 0%$) (Online Resource 3); therefore, we did not perform subgroup analyses in relation to heterogeneity. As shown in Figure S2, the inspection of the 'comparison-adjusted' funnel plot did not show small study bias (Online Resource 4).

Effects on all-cause mortality

Seven trials [30–34, 40, 41] (1131 participants, 1096 catheters) provided data for the analysis of all-cause mortality.

Table 2 Methodological quality of included studies

First Author, Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other source of bias
Dogra 2002 [13]	Random number table	Pharmacists	Low risk	Low risk	Low risk	Unclear	Unclear
Betjes 2004 [14]	Computer-generated	Unclear	High risk	High risk	Low risk	Unclear	Unclear
Mcintyre 2004 [28]	Unclear	Sealed envelope	High risk	High risk	Low risk	Unclear	Unclear
Bleyer 2005 [15]	Unclear	Unclear	Low risk	Unclear	Low risk	Low risk	Unclear
Saxena 2005 [29]	Random number table	Pharmacists	Low risk	Low risk	Unclear	Unclear	Unclear
Weijimer 2005 [30]	Computer-generated	Pharmacy	Low risk	Low risk	Low risk	Unclear	Unclear
Nori 2006 [31]	Unclear	Unclear	High risk	High risk	Low risk	Unclear	Unclear
MacRae 2008 [32]	High risk	High risk	High risk	High risk	High risk	Unclear	Unclear
Tan 2008 [33]	Unclear	Unclear	Unclear	Unclear	High risk	Unclear	Unclear
Zhang 2009 [34]	Random number table	Unclear	Low risk	High risk	Unclear	Unclear	Unclear
Solomon 2010 [35]	Computer-generated	Pharmacists	Low risk	Unclear	Low risk	Unclear	Unclear
Campos 2011 [36]	Unclear	Sealed envelope	High risk	High risk	Low risk	Unclear	Unclear
Filiopoulos 2011 [37]	Computer-generated	Unclear	High risk	High risk	Low risk	Unclear	Unclear
Lu 2011 [38]	Unclear	Unclear	Unclear	Unclear	Low risk	Unclear	Unclear
Broom 2012 [39]	Computer-generated	Calling a centralized number	High risk	High risk	Low risk	Low risk	Unclear
Moran 2012 [40]	Computer-generated	Unclear	Participants alone	Unclear	Unclear	Unclear	Unclear
Sofroniadou 2012 [41]	Random number table	Unclear	Low risk	Unclear	Low risk	Unclear	Unclear
Hu 2013 [42]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

The analysis results suggested that there was no difference in reducing all-cause mortality between included interventions (Fig. 5). Similarly, substantial heterogeneity was not present, therefore we did not perform subgroup analyses ($I^2 = 0\%$) (Online Resource 3). In the rank probability test (Table 3), gentamicin plus citrate had the highest rank (74.7%), followed by heparin (69.2%). As shown in Figure S3, the inspection of the ‘comparison-adjusted’ funnel plot did not show small study bias (Online Resource 4).

Adverse events

A summary of adverse events reported in the included trials is presented in Table 4. A total of eleven trials [13, 14, 28, 30, 33, 34, 37–39, 41, 42] reported adverse effects in their results. Five [14, 28, 37, 38, 41] of them claimed

no adverse effects related to taurolidine plus citrate, gentamicin plus heparin and vancomycin plus heparin, respectively. However, two other studies [33, 34] reported adverse effect of tinnitus related to gentamicin plus heparin. One trial [30] reported a higher frequency of adverse events, mainly bleeding, in the heparin group, and 1 trial [30] reported a higher rate of paraesthesia with citrate compared with heparin. In Broom’s study [39], in the ethanol group there was 1 patient who complained of stinging at the catheter exit site and another patient complained of dry lips and being thirsty.

Sensitivity analysis

In order to assess the robustness of results, we conducted a sensitivity analysis by excluding trials with a total

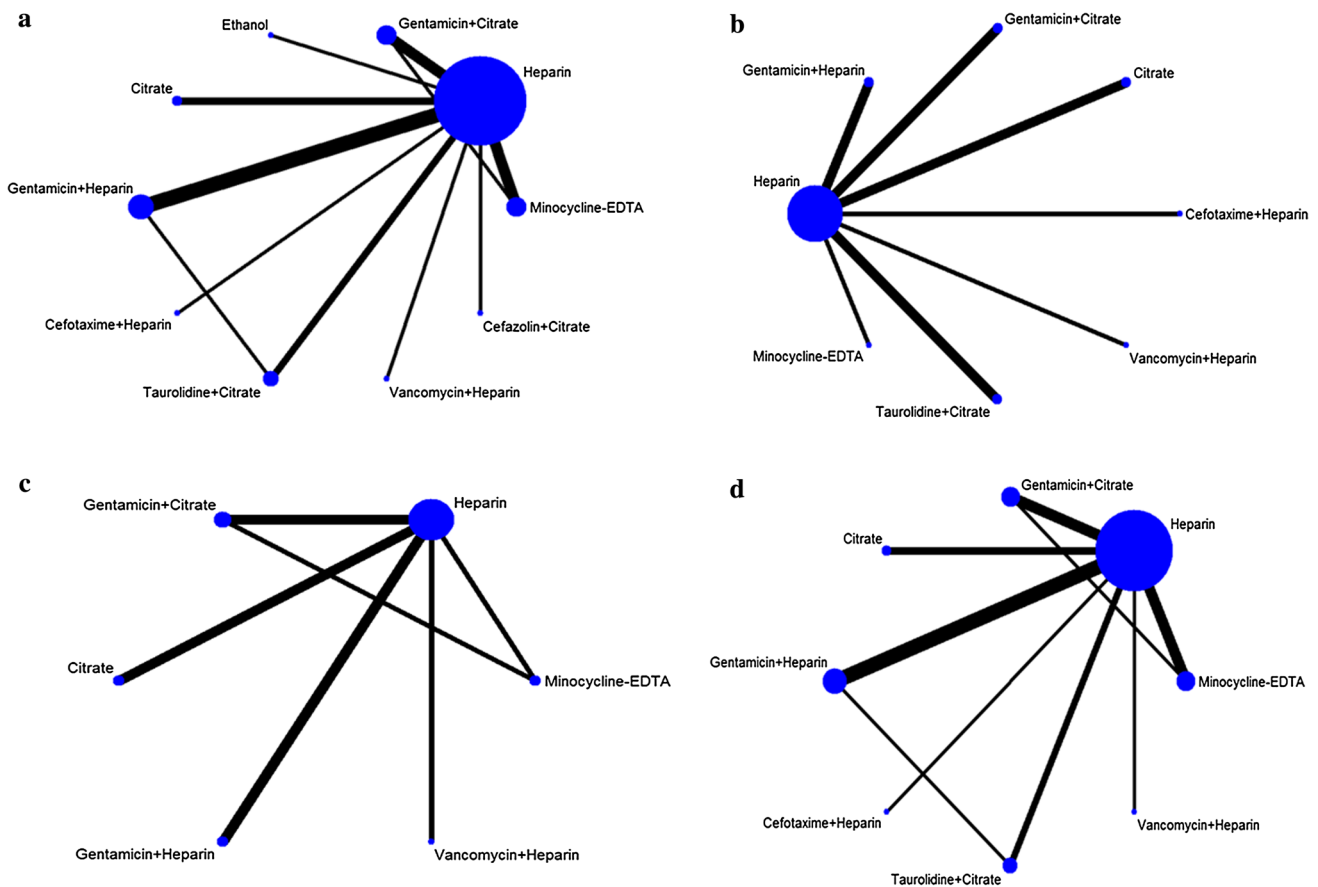


Fig. 2 Network plot of evidence for CRBSI (a), exit site infection (b), all-cause mortality (c) and the sensitive analysis for CRBSI (d)

sample size of less than 50 randomized patients. A total of 16 trials [13–15, 28–38, 40, 41] (2321 participants, 2422 catheters) contributed to the analysis. The results of the sensitivity analysis did not show a major influence on the primary outcome (Fig. 6; Table 3). We were not able to recalculate effect sizes for the other two outcomes due to the small number of studies that were examined. Similarly, given the low number of eligible studies, we did not perform another meaningful sensitivity analysis by excluding trials that the criterion of CRBSI diagnosis does not meet the Infectious Diseases Society of America (IDSA) guidelines.

Inconsistency and convergence

In network (a) and network (d), 2 triangle loops (gentamicin + heparin vs heparin vs taurolidine + citrate and gentamicin + citrate vs heparin vs minocycline-EDTA) were found. In network (c), 1 triangle loop (gentamicin + citrate vs heparin vs minocycline-EDTA) was found. There was no loop in networks (b). In these 3 loops, the direct comparisons and indirect comparisons did not show any major inconsistency. That is, all the *p* values of

node-splitting analysis were not statistically significant at the 5% significance level (Online Resource 5).

The PSRFs of parameters were all unlimitedly close to 1 without exception, which represented good convergence.

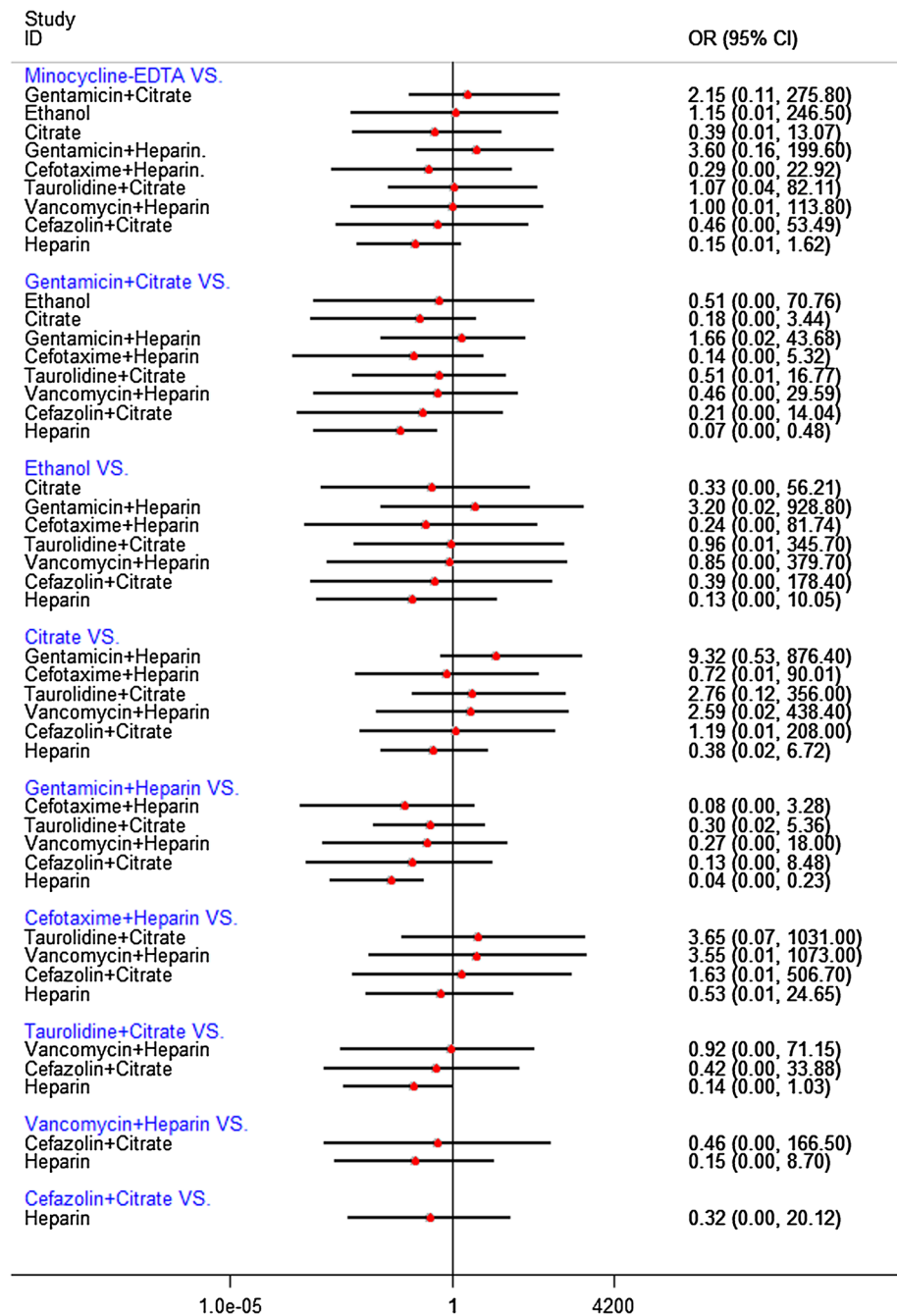
Discussion

The objective of this study was to compare the efficacy of different kinds of ALS in terms of CRBSI, exit site infection, all-cause mortality and adverse events among HD patients. This is the first systematic review that has included almost all ALS categories for hemodialysis in the same analysis using a network meta-analysis method that includes indirect comparisons.

Summary of the results

In terms of reducing the occurrences of CRBSI, gentamicin plus citrate and gentamicin plus heparin had a positive effect in comparison with heparin alone. However, after conducting the rank probability test, the effectiveness of vancomycin plus heparin and ethanol appeared to be better

Fig. 3 Network meta-analysis of intervention effects on CRBSI



than gentamicin plus citrate in this outcome measure. Sensitivity analysis was conducted to assess the robustness of results by excluding trials with a total sample size of less than 50 randomized patients. The results of the sensitivity analyses showed broad agreement with the main analyses, and the rank probability for sensitive analysis was also consistent with the previous probability. Overall, gentamicin plus heparin is most likely (highest probability) to be the best intervention option among the nine ALS in preventing CRBSI for HD patients. These findings barely changed in sensitivity analysis. In this network meta-analysis, no

significant difference in the intervention effect was detected with respect to either the exit site infection or the all-cause mortality for all included ALS. Based on the rank probability, vancomycin plus heparin was associated with lowest exit site infection and gentamicin plus citrate was associated with lowest all-cause mortality.

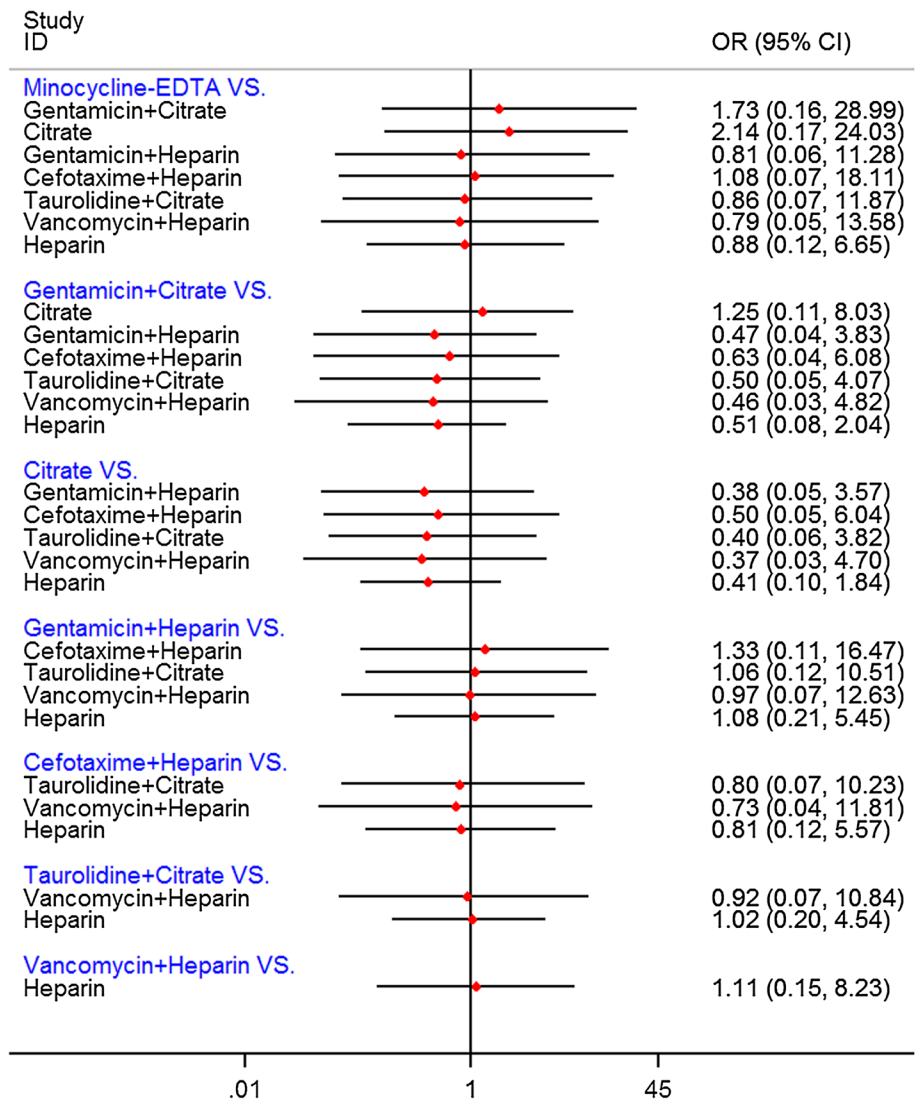
In the past few years, some pair-wise meta-analyses regarding these techniques have been published [16, 18, 43]. From these studies, it is concluded that ALS reduces the risk of CRBSI for HD patients with CVCs. However, it is notable that these studies did not distinguish the types of

Table 3 SUCRA values for each outcome (%)

Interventions	CRBSI	Exit site infection	All-cause mortality	Sensitive analysis for CRBSI
Gentamicin + heparin	84.7	65.2	36.3	87.8
Vancomycin + heparin	66.8	69.0	38.4	66.2
Ethanol	64.3	NA	NA	NA
Gentamicin + citrate	63.2	29.3	74.7	65.9
Minocycline-EDTA	59.8	54.1	43.8	62.2
Taurolidine + citrate	47.0	66.8	NA	47.6
Citrate	40.3	6.7	37.5	40.5
Cefazolin + citrate	41.5	NA	NA	NA
Cefotaxime + heparin	28.3	44.4	NA	27.6
Heparin	4.2	64.4	69.2	2.3

NA not applicable (the intervention was not included in the outcome measure)

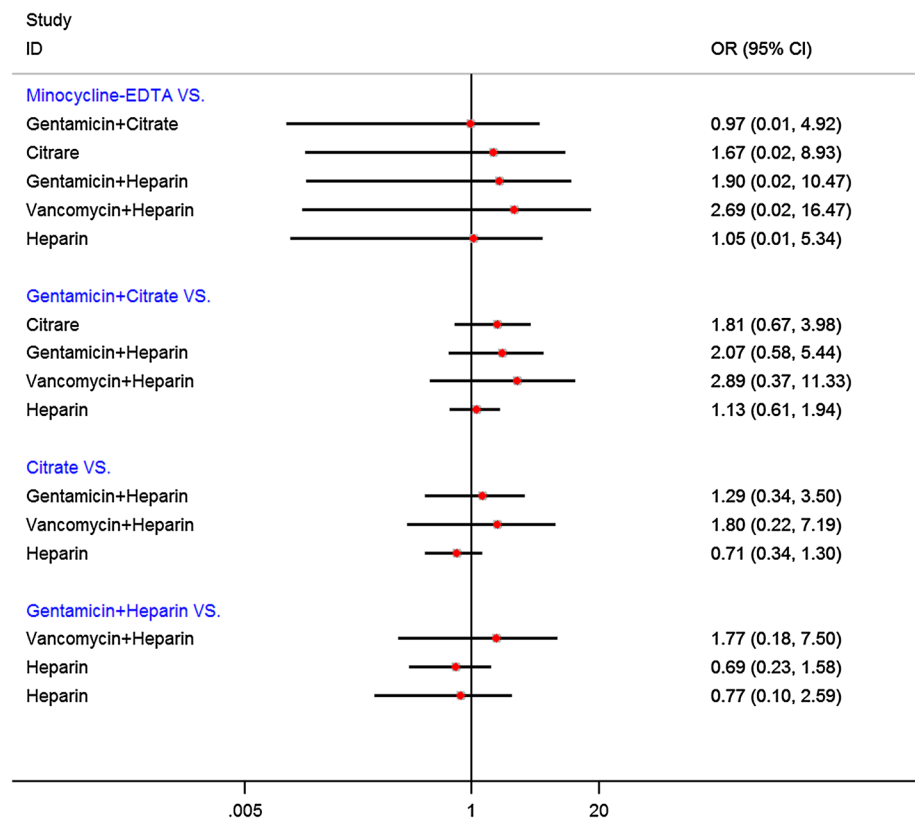
Fig. 4 Network meta-analysis of intervention effects on exit site infection



antimicrobials analysed by each domain. Thus, it is unclear from these meta-analyses whether particular antimicrobial agent or certain combinations of antimicrobial agents may

have been responsible for the observed treatment effects. Besides, no evidence focused on the efficacy of these ALS when compared to each other due to few RCT compared

Fig. 5 Network meta-analysis of intervention effects on all-cause mortality



them directly. In this case, our study adds to these previous efforts by providing a more complete understanding of the current body of evidence on comparative effectiveness of ALS for the prevention of CRBSI.

Exit site infections are an additional cause of morbidity in patients with CVCs, and these infections may contribute to the pathogenesis of CRBSI [44]. Pooled analysis from eleven trials in our network meta-analysis indicated that all included ALS did not significantly reduce the exit site infections when compared to heparin alone and also no significant difference was observed among them. But results from Zacharioudakis et al.'s [43] and Rabindranath et al.'s [17] studies suggested that ALS have a significant effect in reducing the risk of these infections. In these two meta-analyses [17, 43], pooling data on exit site infections were provided by 12 included RCTs. Based on the results of these individual RCTs presented, we found that none of the ALS was significantly superior to heparin except for citrate in Weijmer's study [30]. However, Zhao et al.'s meta-analysis [20] showed no statistical significance between citrate and heparin in the prevention of exit site infection.

Seven RCTs [30–34, 40, 41] involving 5 different ALS provided a measure of all-cause mortality. In these, no statistically significant difference was observed. Results from the previous meta-analyses also confirmed that prophylaxis against CRI with ALS may not reduce all-cause mortality for patients [43, 45].

It must be noted that despite the accumulation of RCTs supporting the efficacy of gentamicin prophylaxis for CRBSI, the implementation of this agent in clinical practice should be prudent due to the potential for development of bacterial antibiotic resistance. Admittedly, gentamicin-resistant CRIs have been observed among HD patients who are receiving gentamicin lock therapy [46]. However, none of the included studies in our analysis reported the emergence of drug-resistant bacterial isolates. The major reason may be the relatively short duration of follow-up of the included studies. It is preferable that this type of research question be addressed using long-term prospective studies.

Besides, a decision regarding use of the gentamicin-containing lock solutions should be based on potential adverse events. It is known that gentamicin has been linked to ototoxicity. In the studies using gentamicin in our analysis, the formal audiology testing of ototoxicity was not performed. Dogra et al. [13] reported deafness in almost 10% of patients in the study arm using high-concentration gentamicin plus citrate in the context of a significant increase in serum gentamicin levels. Moreover, there was 1 patient who complained of mild tinnitus that might be attributable to gentamicin, respectively, in Tan's [33] and Zhang et al.'s studies [34]. However, this adverse effect was not seen in 5 other studies [28, 31, 37, 38, 40], which also used a low concentration of gentamicin.

Table 4 Adverse events reported in the included trials

First Author, Year	Adverse events	
	Exp	Control
Dogra 2002 [13]	Intermittent nonspecific dizziness without vertigo, deafness or ataxia ($n = 4$)	No adverse events
Betjes 2004 [14]	No adverse events	
Mcintyre 2004 [28]	No adverse events	
Bleyer 2005 [15]	No reporting	
Saxena 2005 [29]	No reporting	
Weijmer 2005 [30]	Paraesthesia, tingling, metallic taste ($n = 9$); major bleedings ($n = 5$); persistent bleeding after insertion ($n = 6$); unexplained thrombocytopenia ($n = 2$)	Paraesthesia, tingling, metallic taste ($n = 2$); major bleedings ($n = 16$); persistent bleeding after insertion ($n = 19$); unexplained thrombocytopenia ($n = 4$)
Nori 2006 [31]	No reporting	
MacRae 2008 [32]	No reporting	
Tan 2008 [33]	Tinnitus ($n = 1$)	Dizziness, fatigue ($n = 1$)
Zhang 2009 [34]	Tinnitus ($n = 1$); pruritus ($n = 1$)	Bleeding ($n = 1$)
Solomon 2010 [35]	No reporting	
Campos 2011 [36]	No reporting	
Filiopoulos 2011 [37]	No adverse events	
Lu 2011 [38]	No adverse events	
Broom 2012 [39]	Stinging at the catheter exit site ($n = 1$), dry lips and thirst ($n = 1$)	No adverse events
Moran 2012 [40]	No reporting	
Sofroniadou 2012 [41]	No adverse events	
Hu 2013 [42]	Lips numbing ($n = 3$); gastrointestinal intolerance ($n = 1$)	No adverse events

Exp experimental group, *Control* control group

Therefore, low-dose gentamicin appears safe. If possible, we proposed further studies should monitor serum gentamicin levels with the detailed documentation of safety parameters.

Limitation

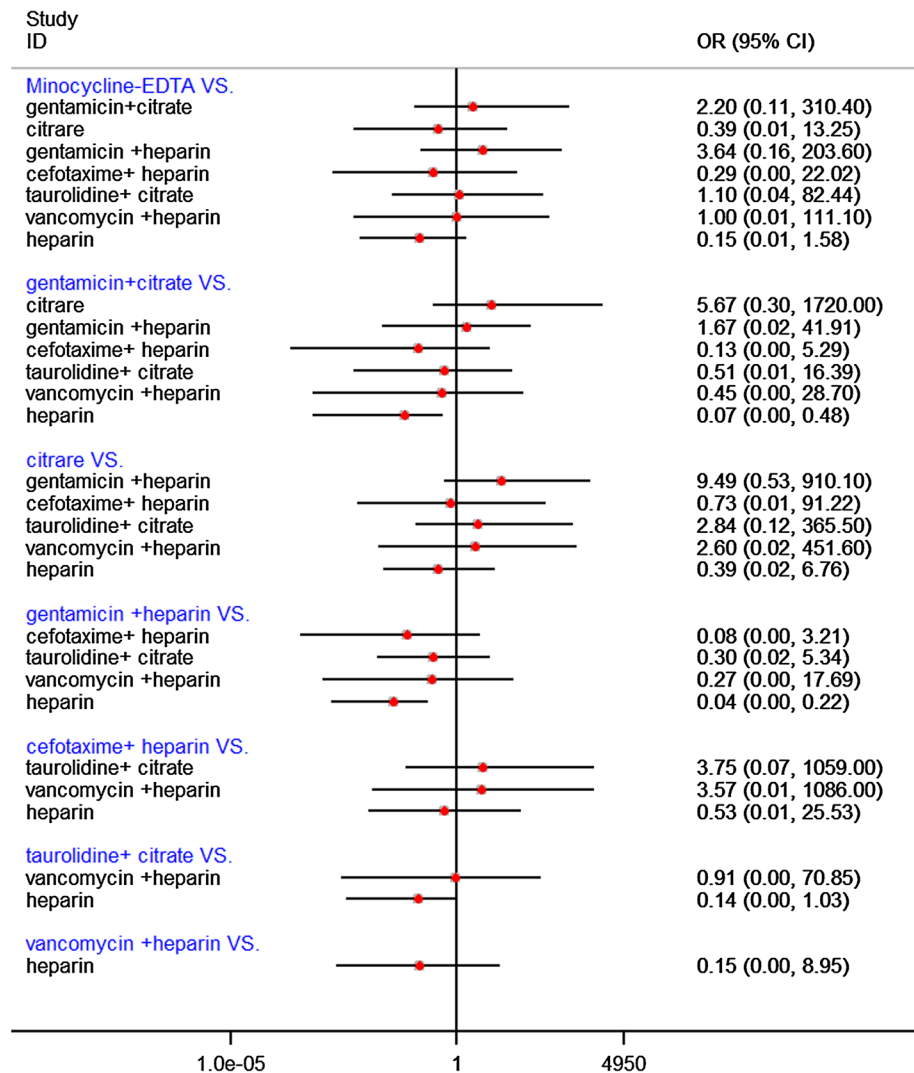
In this study, a comprehensive literature search with several databases and sources was performed to cover as many eligible trials as possible. In order to minimize possible concerns about heterogeneity and transitivity, we selected all relevant studies strictly according to the pre-specified inclusion criteria. The review was conducted according to modern methodological standards. But, as is the case with all systematic reviews, several important limitations of this study should be noted.

First, reporting of the included studies themselves was incomplete. The majority of trials were failed to specify the method of randomization, use appropriate allocation concealment procedures and ensure blinding of relevant personnel, representing significant methodological limitations that may have biased the results.

Second, both the number of included studies and the sample size were small. Some comparisons were performed based on only 1 RCT, so the potential for bias should not be neglected. Moreover, the small number of studies that evaluated each particular pair of treatments limits performing a meaningful subgroup meta-analysis. An additional question caused by the low number of eligible studies and small sample sizes within trials was the wide CrI. Moreover, when event rates are very low, CrI around relative effects may also be wide. Wide CrI represent the high uncertainty of results. The conclusion drawn from such meta-analysis remains preliminary. More RCTs in this field are definitely needed to allow more solid conclusions about most moderating factors. However, we have confidence in the estimates of efficacy of gentamicin prophylaxis for CRBSI in our analysis. The 95% CrI excluding no effect indicates a robust effect when compared to heparin alone.

Third, we excluded trials investigating ALS with more than one antimicrobial agent, although combination intervention is common. The large number of intervention combinations and scarcity of trials comparing these

Fig. 6 Network meta-analysis of intervention effects on CRBSI (sensitive analysis)



interventions prompted us to restrict our analysis to monotherapies. The decision to exclude combination interventions was also intended to minimize heterogeneity among interventions because it was believed that combination therapies would probably vary considerably, which would preclude meaningful pooling of data.

Finally, antimicrobial resistance remains an unresolved issue in view of the relatively short duration of included studies.

Fortunately, no obvious evidence of inconsistency was observed in this network meta-analysis. Secondly, the low level of methodological quality and the limitation in sample size of some studies could be a potential threat to the validity of results. However, the stability of the results of the sensitivity analyses confirms that the main findings of this research are robust and justified.

Conclusions

We compared the most commonly used ALS for HD patients via a Bayesian network meta-analysis. The use of this method has enabled us to provide new information on the relative effectiveness of ALS for the management of CRI in HD patients. Based on the results of network meta-analysis and probability rank, gentamicin plus heparin may be the best way to prevent CRBSI, vancomycin plus heparin might lead to the lowest incidence of exit site infection and gentamicin plus citrate might had the lowest risk of all-cause mortality for HD people. However, evidence is scant, mostly indirect and often derived from small trials with an unclear risk of bias. A certain degree of caution should be taken with interpretation of these results. Our network meta-analysis therefore has implications for future research

efforts and highlights the need for properly designed RCTs and more head-to-head comparisons of the most commonly used ALS in this field.

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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