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Antimicrobial lock solutions for the prevention of catheter-related infection in patients undergoing haemodialysis: study protocol for network meta-analysis of randomized controlled trials

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Keywords: antimicrobial lock solution; haemodialysis; catheter-related infection; central venous catheters; network meta-analysis

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ABSTRACT

Introduction:

Catheter-related infection (CRI) is a difficult clinical problem in renal medicine with blood stream infections occurring in up to 40% of patients with haemodialysis (HD) catheters, conferring significant rates of morbidity and mortality. Several approaches have been assessed as a means to prevent CRI. Currently an intervention that is the source of much discussion is the use of antimicrobial lock solutions (ALS). A number of past conventional meta-analysis has compared different ALS with heparin. However, there is no a consensus recommendation regarding which type of ALS is best. The purpose of our study is to carry out a network meta-analysis comparing the efficacy of different ALS for prevention of CRI in HD patients and ranking these ALS for practical consideration.

Methods and analysis:

We will search 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 HD patients either head-to-head or against control interventions using non-ALS. Study selection and data collection will be performed by two reviewers independently. The Cochrane Risk of Bias Tool will be used to assess the quality of included studies. The primary outcome of efficacy will be catheter-related bloodstream infection (CRBSI). We will perform a Bayesian network meta-analysis to compare the relative efficacy of different ALS by WinBUGS (Version 1.4.3) and STATA (Version 13.0). The quality of evidence will be assessed by GRADE.

Ethic and dissemination:

Ethical approval is not required given that this study includes no confidential personal data and interventions on the patients. The results of this study will be submitted to a peer-review journal for publication.

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

This is the first comprehensive review comparing the efficacy of different antimicrobial lock solutions through network meta-analysis.

This Bayesian network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons to estimate the interrelations across all treatments.

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.

This study will provide evidence for clinical decision makers to formulate better prevention of catheter-related infection.

This study is inherently retrospective and based on the published randomized controlled trials only.

Our study's work team includes clinical nursing experts and methodologists who have experience with conducting and reporting systematic and meta-analysis.

INTRODUCTION

Central venous catheters (CVCs) remain a common form of vascular access for chronic haemodialysis (HD) patients despite recommendations by several national and international guidelines to minimize their usage as much as possible. [1,2] It has been estimated that almost 30% to 40% of chronic HD patients are dependent on CVCs for their vascular access.[1,2,3] Widespread application of CVCs exposes patients to an enhanced risk for catheter-related infection (CRI), which includes catheter-related bloodstream infection (CRBSI) and exit-site infection. The incidence of CRI varies per dialysis unit, site of insertion, and type of catheter inserted. Generally, the incidence of episodes of CRBSI ranges between 2.5 and 5.5 cases/1000 catheter days for tunneled catheters, and between 3.8 and 12.8 cases/1000 catheter days for non-tunneled catheters. [4,5] Episodes of exit site infection vary from 0.35 to 8.3 cases /1000 catheter days and 8.2 to 16.75 cases /1000 catheter days for tunneled and non-tunneled catheters respectively. [6,7,8]

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, [9] and the leading cause of catheter removal and morbidity in dialysis patients. [10,11] Data from non-tunneled catheters used in intensive care units (ICU) indicate an average 3% per annum mortality rate.[12] Besides, the costs to the health care system are also substantial. It has been estimated that the cost per infection is an estimated $34,508-$56,000, [13,14] and the annual cost of caring for patients with CVC-associated BSIs ranges from $296 million to $2.3 billion. Therefore, it is a real clinical challenge to prevent CRI.

CRI are a consequence of colonization of the catheter hub or surrounding skin followed by intraluminal or extraluminal spread. [15] Prevention strategies are directed at decreasing growth and/or adherence of pathogens to the catheter hub and surface. Currently several modalities have been assessed as a means to prevent CRI, which suggested confusion regarding best practice in this area. A recent promising technique has been used to instillate an antimicrobial solution into the lumen(s) of the catheter between HD sessions in order to prevent intraluminal colonization and the development of a biofilm. The rationale for the use of antimicrobial lock solutions (ALS) is the high intraluminal concentration achieved, with subsequent elimination of the internal biofilm. The biofilm constitutes a permanent source of bacteraemia, as well as a key factor favouring bacterial resistance.[16]

Over recent years, the growing number of research projects investigating this approach attests to the benefits of ALS in preventing CRI. Efforts to evaluate and compare the efficacy of ALS for the prevention of CRI have also been performed in almost ten meta-analysis with conventional methodologies. Jaffer et al meta analyzed seven RCTs in HD patients, revealing antibiotic lock solutions reduced the frequency of CRI without significant side effects.[17] Another meta-analysis of the use of ALS for HD patients concluded that antibiotic lock solutions reduced CRBSI.[18] Similarly, other six meta-analysis confirmed the positive impact of ALS in reducing CRI.[19-24] These available antibiotic lock solutions include gentamicin, vancomycin, cefotaxime and cefazolin. In addition, Liu et al's meta-analysis results found that

taurolidine-citrate catheter lock solutions reduced the risk of CRI, [25] and another meta-analysis showed that subjects assigned to the ethanol locks had the lower CRBSI-rate per 1000 catheter days in comparison to heparin locks.[26] In a word, results from this relevant literature indicated that ALS had a positive effect on the reduction of CRI.

However, due to head-to-head trials of different ALS are scarce, these systematic reviews and meta-analysis have not focused on any head-to-head comparisons of different ALS. Besides, the main drawback of the current state of the art is that meta-analysis focuses on comparing only two alternatives, while decision-makers need to know the relative ranking of a set of alternative options and not only whether option A is better than B. That is, there is no consensus recommendation regarding which ALS is best.

Thus, the evidence for the efficacy of these ALS in prevention of CRI has never been assessed in the comprehensive setting of a systematic review and meta-analysis. For these reasons, a better-designed approach utilizing Bayesian network meta-analysis is urgently needed in this area, integrating direct evidence (from studies directly comparing interventions) with indirect evidence (information about two interventions derived via a common comparator) from multiple intervention comparisons to estimate the interrelations across all interventions.[27,28]

The purpose of our study is to carry out a network meta-analysis comparing the efficacy of different ALS for prevention of CRI for HD patients based on existing RCT and ranking these ALS for practical consideration. This study is expected to begin in September 2015 and conclude in February 2016.

OBJECTIVE

The objective of this study is to explore the efficacy of ALS to prevent CRI for patients undergoing HD using a network meta-analysis.

METHODS

Design

Bayesian network meta-analysis. This protocol of network meta-analysis will be conducted and reported mainly according to the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P)[29] and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis.[30]

Inclusion Criteria

1. Type of study

Any relevant RCTs will be included. Quasi-randomised trials will be excluded.

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 tunneled or non-tunneled CVC as vascular access, regardless of the type of kidney failure (acute or chronic), whatever the cause and duration of use of the catheter.

3. Type of interventions

RCTs of ALS used to prevent CRI in HD patients will be included, regardless of whether the antimicrobials were tested between themselves (head-to-head) or against placebo/control intervention such as heparin. For antimicrobials, antibiotic, citrate, taurolidine and alcohol will be included regardless of their concentration**.** All ALS could be given with anticoagulants (e.g., heparin, citrate or EDTA).

4. Outcomes of interest

The primary outcome will be CRBSI. The Centers for Disease Control (CDC) definitions for CRBSI will be used.[31] Only RCTs that used this definition, or RCTs whose results were detailed enough to be re-adjudicated according to the aforementioned definition, will be included. In cases when a study separately reported definite, probable, and possible CRBSI, we will choose not to include "possible" blood stream infection (defined as the absence of laboratory confirmation of blood stream infection).

The secondary outcomes will be exit site infection (defined as the development of a purulent exudates or redness around the site not resulting from residual stitches) and all-cause mortality.

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 are (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.

Data sources and Search

We will systematically perform 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 will search 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 will also search 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 will be identified and bibliographies will be scrutinise for further relevant trials, as well as those of RCTs included in the review. The search strategy will be developed by Zhang Jun and Tian JinHui (more than 10 years experience as information specialist). The search method will include 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 Item S1.

Selection of literature

Literature search results will be imported into ENDNOTE X6 literature management software. Two authors (Li Rongke and Chen KeXin) will independently review the literature searches from the title, abstract or descriptors and will exclude the study that clearly does not meet the inclusion criteria. After excluding the duplicated and apparently irrelevant studies, the remaining studies will be review in full text to assess eligibility for inclusion. Any disagreements will be resolved by discussion or by seeking an independent third opinion (Tian JinHui). Excluded trials and the reason for their exclusion were listed and examined by a third reviewer (Tian JinHui). Selection process of relevant studies retrieved from databases will be shown in a PRISMA-compliant flow chart (figure 1).

Data extraction

Two authors (Zhang Jun and Ge Long) will independently extract 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 interventions, number of catheter days), outcome variables (e.g., number of episodes) and any additional prophylactic measures used that may have affected outcomes. Outcomes will be extracted preferentially by intention to treat (ITT) at the end of interventions. Quantitative data will be extracted to calculate effect sizes. Data on effect size that could not be obtained directly will be recalculated, when possible. Any discrepancy will be resolved by consensus. If necessary, we will try to contact the corresponding authors for more information.

Methodological quality assessment

Two authors (Zhang Jun and Ge Long) will independently evaluate the methodological quality of the included studies for major potential sources of bias by using the Cochrane Collaboration's risk of bias tool, [32] which including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other sources of bias. We will evaluate methodological quality of each study on each criterion as low, high, or unclear risk of bias. Any disagreements will be resolved through discussion, if need be, with another reviewer (Tian JinHui).

Statistical analysis

We will perform a Baysian network meta-analysis to assess the relative outcomes of different ALS and control conditions with each other from all direct and indirect comparisons. Dichotomous outcomes will be analyzed on ITT basis.

Network meta-analysis

Bayesian network meta-analysis will be performed by using the Markov chain Monte Carlo method in WinBUGS 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml). The other analyses will be performed and presented by the STATA 13.0 using the mvmeta command. The results of dichotomous outcomes will be reported as posterior medians of RR with 95% credible intervasl (CrIs). The fixed and random effect models with vague priors for multi-arm trials will be used. The choices between fixed and random effect models will be made by comparing the deviance information criteria (DIC) for each model. The model with the lowest DIC will be preferred (differences >3 are considered meaningful). [33] Three Markov chains will be run simultaneously with different arbitrarily chosen initial values. To ensure convergence, trace plots and Brooks-Gelman-Rubin plots will be assessed.[34] Convergence will be found to be adequate after running 20 000 samples for three chains. These samples will be then discarded as "burn-in", and posterior summaries will be based on 100 000 subsequent simulations. When a loop connected three treatments, it will be possible to evaluate the inconsistency between direct and in direct evidence. The node splitting method will be used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence. [35]

We will estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain a treatment hierarchy using the probability of being the best treatment by using the surface under the cumulative ranking curve (SUCRA). The larger the SUCRA value, the better the rank of the treatment with a SUCRA of 1.0 if an intervention always ranks first and 0.0 if it always ranks last. [36]

Investigation and Treatment of Heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. Statistical heterogeneity among the studies and in the entire network will be assessed on the bias of the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from network meta-analysis models using R 3.2.2 software (https://cran.r-project.org/src/base/R-3/). Network meta-regression or subgroup analysis will be used to explore possible sources of heterogeneity. Network meta-regression will be conducted using random effects network meta-regression models to examine potential effect moderators such as patients' gender, site of catheter insertion, type of catheter, sample size, and study quality. If we include enough trials per comparison, a sensitivity analysis will be conducted. We will conduct a sensitivity analysis base on the type of the catheter (e.g., tunneled catheters and non- tunneled catheters). And we will conduct another sensitivity analysis excluding trials with a total sample size of less than 50 randomized patients.

Funnel plot analysis

Publication bias will be examined with the Begg's[37] and Egge's[38] funnel plot method. And the contour-enhanced funnel plot will be used as an aid to distinguish asymmetry

due to publication bias from that due to other factors.

Quality of evidence

The quality of evidence will be assess by GRADE four step approach for rating the quality of treatment effect estimates from network meta-analysis [39]:①Present direct and indirect treatment estimates for each comparison of the evidence network. ② Rate the quality of each direct and indirect effect estimate. ③Present the network meta-analysis estimate for each comparison of the evidence network. ④Rate the quality of each network meta-analysis effect estimate. The quality of evidence will be classified by the GRADE group into four levels: high quality, moderate quality, low quality and very low quality. The quality rating of RCT may be rated down by -1 (serious concern) or -2 (very serious concern) for the following reasons: risk of bias, inconsistency, indirectness, imprecision and publication bias. This process will performed using GRADE pro 3.6 software (http://www.gradeworkinggroup.org/).

ETHICS AND DISSEMINATION

Ethical issues

As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required.

Publication plan

This network meta-analysis will be submitted to a peer-reviewed journal. It will be disseminated electronically and in print.

Conflicts of Interest

None

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

ZJ and TJH participated in the conception and design of the study, including search strategy development. ZJ and CKX tested the feasibility of the study. All authors drafted and critically reviewed this manuscript and approved the final version.

REFERENCES

1. Rayner HC, Besarab A, Brown WW, et al. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): performance against Kidney Diseases Outcomes Quality Initiative (KDOQI) Clinical ractice Guidelines. *Am J Kidney Dis* 2004;44:22-6.
2. Mendelssohn DC, Ethier J, Elder SJ, et al. Haemodialysis vascular access problems in Canada: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS II). *Nephrol Dial Transplant* 2006;21:721-8.
3. Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: results from the DOPPS. *Kidney* Int 2002;61:305-16.
4. Kairaitis LK, Gottlieb T. Outcome and complications of temporary haemodialysis catheters. *Nephrol Dial Transplant* 1999;14:1710-4.
5. Oliver MJ, Callery SM, Thorpe KE, et al. Risk of bacteremia from temporary HD catheters by site of insertion and duration of use: a prospective study. *Kidney Int* 2000;58:2543-5.
6. Develter W, De Cubber A, Van Biesen W, et al. Survival and complications of indwelling venous catheters for permanent use in hemodialysis patients. *Artif Organs* 2005;29:399-405.
7. Stevenson KB, Adcox MJ, Mallea MC, et al. Standardized surveillance of hemodialysis vascular access infections: 18-month experience at an outpatient, multifacility hemodialysis center. *Infect Control Hosp Epidemiol* 2000;21:200-3.
8. Weijmere MC, Vervloet MG, ter Wee PM. Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. *Nephrol Dial Transplantation* 2004;19:670–7.
9. Rabindranath KS, Bansal T, Adams J, et al. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. *Nephrol Dial Transplant* 2009;24: 3763–74
10. Marr KA, Sexton DJ, Conlon PJ, et al. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med* 1997;127:275-80.
11. Butterly DW, Schwab SJ. Dialysis access infections. *Curr Opin Nephrol Hypertens* 2000;9: 631-5.
12. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132: 391-402.
13. Rello J, Ochagavia A, Sabanes E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. *Am J Respir Crit Care Med* 2000;162:1027-30.
14. Dimick JB, Pelz RK, Consunji R, et al. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. Arch Surg 2001;136: 229-34.
15. Pearson ML. Guideline for prevention of intravascular devicerelated infections. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;17:438-73.
16. Donlan RM. Biofilm formation: a clinically relevant microbiologic process. *Clin Infect Dis* 2001;33:1387-92.
17. Jaffer Y, Selby NM, Taal MW, et al. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. *Am J Kidney Dis* 2008;51:233-41.
18. Yahav D, Rozen-Zvi B, Gafter-Gvili A, et al. Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2008;47: 83-93.

19. Labriola L, Crott R, Jadoul M. Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials. *Nephrol Dial Transplant* 2008;23:1666-72.
20. Rabindranath KS, Bansal T, Adams J, et al. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. *Nephrol Dial Transplant* 2009;24: 3763-74.
21. Snaterse M, Rüger W, Scholte Op Reimer WJ, et al. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. *J Hosp Infect* 2010;75:1-11.
22. O'Horo JC, Silva GL, Safdar N. Anti-Infective Locks for Treatment of Central Line-Associated Bloodstream Infection: A Systematic Review and Meta-Analysis. *Am J Nephrol* 2011;34:415-22.
23. Wang AY, Ivany JN, Perkovic V, et al. Anticoagulant therapies for the prevention of intravascular catheters malfunction in patients undergoing haemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Nephrol Dial Transplant* 2013;28:2875-88.
24. Zacharioudakis IM, F Zervou FN, Arvanitis M, et al. Antimicrobial Lock Solutions as a Method to Prevent Central Line-Associated Bloodstream Infections: A Meta-analysis of Randomized Controlled Trials. *Clin Infect Dis* 2014;59:1741-9.
25. Liu H, Liu H, Deng J, et al. Preventing Catheter-Related Bacteremia with Taurolidine-Citrate Catheter Locks: A Systematic Review and Meta-Analysis. *Blood Purif* 2014;37:179-87.
26. Oliveira C, Nasr A, Brindle M, et al. Ethanol Locks to Prevent Catheter-Related Bloodstream Infections in Parenteral Nutrition: A Meta-Analysis. *Pediatrics* 2012;129:318-29.
27. Jansen JP, Crawford B, Bergman G, et al. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. *Value Health* 2008;11:956-64.
28. Salanti G, Higgins JP, Ades AE, et al. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17:279-301.
29. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
30. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med* 2015;162:777-84.
31. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2002;51:1-29.
32. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
33. Spiegelhalter DJ, Best NG, Carlin BP, et al. Bayesian measures of model complexity and fit. *J Royal Statistical Soc (B)* 2002;64:583-639.
34. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;7:434-45.
35. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-3124.
36. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:

163-71.

37. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.

38. Egger M, Davery Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

39. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.

Figure 1 Flow chart of the study selection

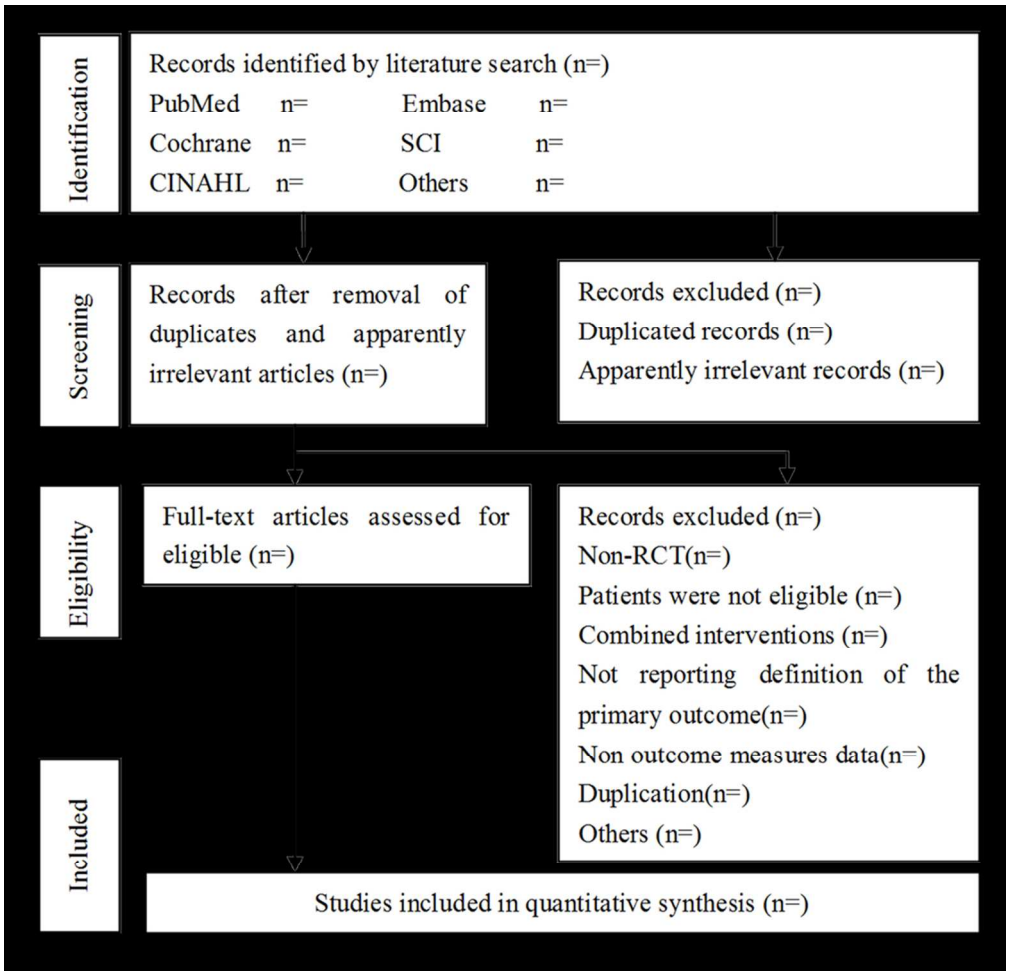

Figure 1 Flow chart of the study selection
102x98mm (300 x 300 DPI)

PubMed:

#1 “Renal Dialysis”[Mesh]

#2 dialysis[Title/Abstract] OR dialyses[Title/Abstract] OR hemodialysis[Title/Abstract] OR hemodialyses[Title/Abstract] OR haemodialysis[Title/Abstract] OR haemodialyses[Title/Abstract] OR hemofiltration[Title/Abstract] OR haemofiltration[Title/Abstract] OR haemodiafiltration[Title/Abstract] OR hemodiafiltration[Title/Abstract]

#3 #1 OR #2

#4 “Infection” [Mesh]

#5 infection*[Title/Abstract] OR bacteremia*[Title/Abstract] OR bacteraemia*[Title/Abstract] OR sepsis[Title/Abstract] OR fungemia*[Title/Abstract] OR pyemia*[Title/Abstract] OR pyohemia*[Title/Abstract] OR pyaemia*[Title/Abstract] OR septicemia*[Title/Abstract] OR "blood poisoning"[Title/Abstract] OR "blood poisonings"[Title/Abstract] OR CRB[Title/Abstract] OR CRI[Title/Abstract] OR CRBSI[Title/Abstract]

#6 #4 OR #5

#7 “Catheters, Indwelling” [Mesh]

#8 “Central Venous Catheter” [Mesh]

#9 “Catheterization, Central Venous” [Mesh]

#10 catheter*[Title/Abstract] OR "central venous line"[Title/Abstract] OR "central line"[Title/Abstract] OR "central venous lines"[Title/Abstract] OR "central lines"[Title/Abstract]

#11 #7 OR #8 OR #9 OR #10

#12 random*[Title/Abstract]

#13 "randomized controlled trial*"[All Fields]

#14 "randomized trial*"[All Fields]

#15 “Randomized Controlled Trial”[Publication Type]

#16 “Randomized Controlled Trial as Topic” [Mesh]

#17 #12 OR #13 OR #14 OR #15 OR #16

#18 #3 AND #6 AND #11 AND #17

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary File

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7,8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan021):g7647.

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Antimicrobial lock solutions for the prevention of catheter-related infection in patients undergoing haemodialysis: study protocol for network meta-analysis of randomized controlled trials

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Antimicrobial lock solutions for the prevention of catheter-related infection in patients undergoing haemodialysis: study protocol for network meta-analysis of randomized controlled trials

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ABSTRACT

Introduction:

Catheter-related infection (CRI) is a difficult clinical problem in renal medicine with blood stream infections occurring in up to 40% of patients with haemodialysis (HD) catheters, conferring significant rates of morbidity and mortality. Several approaches have been assessed as a means to prevent CRI. Currently an intervention that is the source of much discussion is the use of antimicrobial lock solutions (ALS). A number of past conventional meta-analysis has compared different ALS with heparin. However, there is no a consensus recommendation regarding which type of ALS is best. The purpose of our study is to carry out a network meta-analysis comparing the efficacy of different ALS for prevention of CRI in HD patients and ranking these ALS for practical consideration.

Methods and analysis:

We will search 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 HD patients either head-to-head or against control interventions using non-ALS. Study selection and data collection will be performed by two reviewers independently. The Cochrane Risk of Bias Tool will be used to assess the quality of included studies. The primary outcome of efficacy will be catheter-related bloodstream infection (CRBSI). We will perform a Bayesian network meta-analysis to compare the relative efficacy of different ALS by WinBUGS (Version 1.4.3) and STATA (Version 13.0). The quality of evidence will be assessed by GRADE.

Ethic and dissemination:

Ethical approval is not required given that this study includes no confidential personal data and interventions on the patients. The results of this study will be submitted to a peer-review journal for publication.

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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is the first comprehensive review comparing the efficacy of different antimicrobial lock solutions through network meta-analysis.
- This Bayesian network meta-analysis can integrate direct evidence with indirect evidence from multiple treatment comparisons to estimate the interrelations across all treatments.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence.
- This study will provide evidence for clinical decision makers to formulate better prevention of catheter-related infection.
- This study is inherently retrospective and based on the published randomized controlled trials only.
- A possible and anticipated weakness may be the quantity and quality of the trials we identify.
- Our study's work team includes clinical nursing experts and methodologists who have experience with conducting and reporting systematic and meta-analysis.

INTRODUCTION

Central venous catheters (CVCs) remain a common form of vascular access for chronic haemodialysis (HD) patients despite recommendations by several national and international guidelines to minimize their usage as much as possible. [1,2] It has been estimated that almost 30% to 40% of chronic HD patients are dependent on CVCs for their vascular access.[1,2,3] Widespread application of CVCs exposes patients to an enhanced risk for catheter-related infection (CRI), which includes catheter-related bloodstream infection (CRBSI) and exit-site infection. The incidence of CRI varies per dialysis unit, site of insertion, type of catheter inserted and adequacy of catheter care. Generally, the incidence of episodes of CRBSI ranges between 2.5 and 5.5 cases/1000 catheter days for tunneled catheters, and between 3.8 and 12.8 cases/1000 catheter days for non-tunneled catheters. [4,5] Episodes of exit site infection vary from 0.35 to 8.3 cases /1000 catheter days and 8.2 to 16.75 cases /1000 catheter days for tunneled and non-tunneled catheters respectively. [6,7,8]

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, [9] and the leading cause of catheter removal and morbidity in dialysis patients. [10,11] Data from non-tunneled catheters used in intensive care units (ICU) indicate an average 3% per annum mortality rate.[12] Besides, the costs to the health care system are also substantial. It has been estimated that the cost per infection is an estimated $34,508-$56,000, [13,14] and the annual cost of caring for patients with CVC-associated BSIs ranges from $296 million to $2.3 billion. Therefore, it is a real clinical challenge to prevent CRI.

CRI results from migration of skin organisms along the catheter into the bloodstream or contamination and colonization of catheter lumens. Prevention strategies are directed at decreasing growth and/or adherence of pathogens to the catheter hub and surface. Currently several modalities including intraluminal and extraluminal approaches have been assessed as a means to prevent CRI, which suggested confusion regarding best practice in this area. A recent promising technique has been used to instillate an antimicrobial solution into the lumen(s) of the catheter between HD sessions in order to address intraluminal sources of infection. It is known from in vitro studies that solutions containing antimicrobials can prevent biofilm formation [15]. The biofilm constitutes a permanent source of bacteraemia, as well as a key factor favouring bacterial resistance.[16] At the same time, there have been concerns about the real effect and toxicity of ALS in case of overfills, especially at high concentrations.

Over recent years, the growing number of clinical research projects investigating this approach attests to the benefits of ALS in preventing CRI. Efforts to evaluate and compare the efficacy of ALS for the prevention of CRI have also been performed in almost ten meta-analysis with conventional methodologies. Jaffer et al meta analyzed seven RCTs in HD patients, revealing antibiotic lock solutions reduced the frequency of CRI without significant side effects.[17] Another meta-analysis of the use of ALS for HD patients concluded that antibiotic lock solutions reduced CRBSI.[18] Similarly, other six meta-analysis confirmed the positive impact of ALS in reducing CRI.[19-24]

These available antibiotic lock solutions include gentamicin, vancomycin, cefotaxime and cefazolin. In addition, Liu et al's meta-analysis results found that taurolidine-citrate catheter lock solutions reduced the risk of CRI, [25] and another meta-analysis showed that subjects assigned to the ethanol locks had the lower CRBSI-rate per 1000 catheter days in comparison to heparin locks.[26] In a word, results from this relevant literature indicated that ALS had a positive effect on the reduction of CRI.

However, due to head-to-head trials of different ALS are scarce, these systematic reviews and meta-analysis have not focused on any head-to-head comparisons of different ALS. Besides, the main drawback of the current state of the art is that meta-analysis focuses on comparing only two alternatives, while decision-makers need to know the relative ranking of a set of alternative options and not only whether option A is better than B. That is, there is no consensus recommendation regarding which ALS is best.

Thus, the evidence for the efficacy of these ALS in prevention of CRI has never been assessed in the comprehensive setting of a systematic review and meta-analysis. For these reasons, a better-designed approach utilizing Bayesian network meta-analysis is urgently needed in this area, integrating direct evidence (from studies directly comparing interventions) with indirect evidence (information about two interventions derived via a common comparator) from multiple intervention comparisons to estimate the interrelations across all interventions.[27,28]

The purpose of our study is to carry out a network meta-analysis comparing the efficacy of different ALS for prevention of CRI for HD patients based on existing RCT and ranking these ALS for practical consideration. This study is expected to begin in September 2015 and conclude in February 2016.

OBJECTIVE

The objective of this study is to explore the efficacy of ALS to prevent CRI for patients undergoing HD using a network meta-analysis.

METHODS

Design

Bayesian network meta-analysis. This protocol of network meta-analysis will be conducted and reported mainly according to the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P)[29] and the PRISMA extension statement for reporting of systematic reviews incorporating network meta-analysis.[30]

Inclusion Criteria

1. Type of study

Any relevant RCTs will be included. Quasi-randomised trials will be excluded.

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 tunneled or

non-tunneled CVC as vascular access, regardless of the type of kidney failure (acute or chronic), whatever the cause and duration of use of the catheter.

3. Type of interventions

RCTs of ALS used to prevent CRI in HD patients will be included, regardless of whether the antimicrobials were tested between themselves (head-to-head) or against placebo/control intervention such as heparin. For antimicrobials, antibiotic, citrate, taurolidine and alcohol will be included regardless of their concentration**.** All ALS could be given with anticoagulants (e.g., heparin, citrate or EDTA).

4. Outcomes of interest

The primary outcome will be CRBSI. The Centers for Disease Control (CDC) definitions for CRBSI will be used. [31] Only RCTs that used this definition, or RCTs whose results were detailed enough to be re-adjudicated according to the aforementioned definition, will be included. In cases when a study separately reported definite, probable, and possible CRBSI, we will choose not to include "possible" blood stream infection (defined as the absence of laboratory confirmation of blood stream infection).

The secondary outcomes will be 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 author.

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 are (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.

Data sources and Search

We will systematically perform 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 will search 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 will also search 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 will be identified and bibliographies will be scrutinise for further relevant trials, as well as those of RCTs included in the review. The search strategy will be developed by Zhang Jun and Tian JinHui (more than 10 years experience as information specialist). The search method will include 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 Item Supplementary File S1.

Selection of literature

Literature search results will be imported into ENDNOTE X6 literature management software. Two authors (Li Rongke and Chen KeXin) will independently review the literature searches from the title, abstract or descriptors and will exclude the study that clearly does not meet the inclusion criteria. After excluding the duplicated and apparently irrelevant studies, the remaining studies will be review in full text to assess eligibility for inclusion. Any disagreements will be resolved by discussion or by seeking an independent third opinion (Tian JinHui). Excluded trials and the reason for their exclusion were listed and examined by a third reviewer (Tian JinHui). Selection process of relevant studies retrieved from databases will be shown in a PRISMA-compliant flow chart (figure 1).

Data extraction

Two authors (Zhang Jun and Ge Long) will independently extract 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 will be extracted preferentially by intention to treat (ITT) at the end of interventions. Quantitative data will be extracted to calculate effect sizes. Data on effect size that could not be obtained directly will be recalculated, when possible. Any discrepancy will be resolved by consensus. If necessary, we will try to contact the corresponding authors for more information.

Methodological quality assessment

Two authors (Zhang Jun and Ge Long) will independently evaluate the methodological quality of the included studies for major potential sources of bias by using the Cochrane Collaboration's risk of bias tool, [32] which including method of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (detection bias), selective reporting (detection bias), and other sources of bias. We will evaluate methodological quality of each study on each criterion as low, high, or unclear risk of bias. Any disagreements will be resolved through discussion, if need be, with another reviewer (Tian JinHui).

Statistical analysis

We will perform a Baysian network meta-analysis to assess the relative outcomes of different ALS and control conditions with each other from all direct and indirect

comparisons. Dichotomous outcomes will be analyzed on ITT basis.

Network meta-analysis

Bayesian network meta-analysis will be performed by using the Markov chain Monte Carlo method in WinBUGS 1.4.3 (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml). The other analyses will be performed and presented by the STATA 13.0 using the mvmeta command. The results of dichotomous outcomes will be reported as posterior medians of RR with 95% credible intervasl (CrIs). The fixed and random effect models with vague priors for multi-arm trials will be used. The choices between fixed and random effect models will be made by comparing the deviance information criteria (DIC) for each model. The model with the lowest DIC will be preferred (differences >3 are considered meaningful). [33] Three Markov chains will be run simultaneously with different arbitrarily chosen initial values. To ensure convergence, trace plots and Brooks-Gelman-Rubin plots will be assessed.[34] Convergence will be found to be adequate after running 20 000 samples for three chains. These samples will be then discarded as "burn-in", and posterior summaries will be based on 100 000 subsequent simulations. When a loop connected three treatments, it will be possible to evaluate the inconsistency between direct and in direct evidence. The node splitting method will be used to calculate the inconsistency of the model, which separated evidence on a particular comparison into direct and indirect evidence. [35]

We will estimate the ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain a treatment hierarchy using the probability of being the best treatment by using the surface under the cumulative ranking curve (SUCRA). The larger the SUCRA value, the better the rank of the treatment with a SUCRA of 1.0 if an intervention always ranks first and 0.0 if it always ranks last. [36]

Investigation and Treatment of Heterogeneity

We will assess clinical and methodological heterogeneity by carefully examining the characteristics and design of included trials. Statistical heterogeneity among the studies and in the entire network will be assessed on the bias of the magnitude of heterogeneity variance parameter (I^2 or τ^2) estimated from network meta-analysis models using R 3.2.2 software (https://cran.r-project.org/src/base/R-3/). Network meta-regression or subgroup analysis will be used to explore possible sources of heterogeneity. Network meta-regression will be conducted using random effects network meta-regression models to examine potential effect moderators such as age of participants, site of catheter insertion, type of catheter, duration of hemodialysis, sample size and study quality. Where possible, we will perform the subgroup analysis according to the concentration of ALS.

If we include enough trials per comparison, a sensitivity analysis will be conducted. We will conduct a sensitivity analysis by excluding trials that the criterion of CRBSI diagnosis does not meet the Infectious Diseases Society of America (IDSA) guidelines. And we will conduct another sensitivity analysis excluding trials with a

total sample size of less than 50 randomized patients.

Funnel plot analysis

Publication bias will be examined with the Begg's[37] and Egge's[38] funnel plot method. And the contour-enhanced funnel plot will be used as an aid to distinguish asymmetry due to publication bias from that due to other factors.

Quality of evidence

The quality of evidence will be assess by GRADE four step approach for rating the quality of treatment effect estimates from network meta-analysis [39]:①Present direct and indirect treatment estimates for each comparison of the evidence network. ② Rate the quality of each direct and indirect effect estimate. ③Present the network meta-analysis estimate for each comparison of the evidence network. ④Rate the quality of each network meta-analysis effect estimate. The quality of evidence will be classified by the GRADE group into four levels: high quality, moderate quality, low quality and very low quality. The quality rating of RCT may be rated down by -1 (serious concern) or -2 (very serious concern) for the following reasons: risk of bias, inconsistency, indirectness, imprecision and publication bias. This process will performed using GRADE pro 3.6 software (http://www.gradeworkinggroup.org/).

ETHICS AND DISSEMINATION

Ethical issues

As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required.

Publication plan

This network meta-analysis will be submitted to a peer-reviewed journal. It will be disseminated electronically and in print.

Conflicts of Interest

No, there are no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Authors' contributions

ZJ and TJH participated in the conception and design of the study, including search strategy development. ZJ and CKX tested the feasibility of the study. All authors drafted and critically reviewed this manuscript and approved the final version.

REFERENCES

1. Rayner HC, Besarab A, Brown WW, et al. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): performance against Kidney Diseases Outcomes Quality Initiative (KDOQI) Clinical ractice Guidelines. *Am J Kidney Dis* 2004;44:22-6.
2. Mendelssohn DC, Ethier J, Elder SJ, et al. Haemodialysis vascular access problems in Canada: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS II). *Nephrol Dial Transplant* 2006;21:721-8.
3. Pisoni RL, Young EW, Dykstra DM, et al. Vascular access use in Europe and the United States: results from the DOPPS. *Kidney* Int 2002;61:305-16.
4. Kairaitis LK, Gottlieb T. Outcome and complications of temporary haemodialysis catheters. *Nephrol Dial Transplant* 1999;14:1710-4.
5. Oliver MJ, Callery SM, Thorpe KE, et al. Risk of bacteremia from temporary HD catheters by site of insertion and duration of use: a prospective study. *Kidney Int* 2000;58:2543-5.
6. Develter W, De Cubber A, Van Biesen W, et al. Survival and complications of indwelling venous catheters for permanent use in hemodialysis patients. *Artif Organs* 2005;29:399-405.
7. Stevenson KB, Adcox MJ, Mallea MC, et al. Standardized surveillance of hemodialysis vascular access infections: 18-month experience at an outpatient, multifacility hemodialysis center. *Infect Control Hosp Epidemiol* 2000;21:200-3.
8. Weijmere MC, Vervloet MG, ter Wee PM. Compared to tunnelled cuffed haemodialysis catheters, temporary untunnelled catheters are associated with more complications already within 2 weeks of use. *Nephrol Dial Transplantation* 2004;19:670–7.
9. Rabindranath KS, Bansal T, Adams J, et al. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. *Nephrol Dial Transplant* 2009;24: 3763–74
10. Marr KA, Sexton DJ, Conlon PJ, et al. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med* 1997;127:275-80.
11. Butterly DW, Schwab SJ. Dialysis access infections. *Curr Opin Nephrol Hypertens* 2000;9: 631-5.
12. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med* 2000;132: 391-402.
13. Rello J, Ochagavia A, Sabanes E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. *Am J Respir Crit Care Med* 2000;162:1027-30.
14. Dimick JB, Pelz RK, Consunji R, et al. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. *Arch Surg* 2001;136: 229-34.
15. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. *Science* 1999; 284:1318-22.
16. Donlan RM. Biofilm formation: a clinically relevant microbiologic process. *Clin Infect Dis* 2001;33:1387-92.
17. Jaffer Y, Selby NM, Taal MW, et al. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. *Am J Kidney Dis* 2008;51:233-41.
18. Yahav D, Rozen-Zvi B, Gafter-Gvili A, et al. Antimicrobial lock solutions for the prevention of infections associated with intravascular catheters in patients undergoing hemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2008;47: 83-93.

19. Labriola L, Crott R, Jadoul M. Preventing haemodialysis catheter-related bacteraemia with an antimicrobial lock solution: a meta-analysis of prospective randomized trials. *Nephrol Dial Transplant* 2008;23:1666-72.
20. Rabindranath KS, Bansal T, Adams J, et al. Systematic review of antimicrobials for the prevention of haemodialysis catheter-related infections. *Nephrol Dial Transplant* 2009;24: 3763-74.
21. Snaterse M, Rüger W, Scholte Op Reimer WJ, et al. Antibiotic-based catheter lock solutions for prevention of catheter-related bloodstream infection: a systematic review of randomised controlled trials. *J Hosp Infect* 2010;75:1-11.
22. O'Horo JC, Silva GL, Safdar N. Anti-Infective Locks for Treatment of Central Line-Associated Bloodstream Infection: A Systematic Review and Meta-Analysis. *Am J Nephrol* 2011;34:415-22.
23. Wang AY, Ivany JN, Perkovic V, et al. Anticoagulant therapies for the prevention of intravascular catheters malfunction in patients undergoing haemodialysis: systematic review and meta-analysis of randomized, controlled trials. *Nephrol Dial Transplant* 2013;28:2875-88.
24. Zacharioudakis IM, F Zervou FN, Arvanitis M, et al. Antimicrobial Lock Solutions as a Method to Prevent Central Line-Associated Bloodstream Infections: A Meta-analysis of Randomized Controlled Trials. *Clin Infect Dis* 2014;59:1741-9.
25. Liu H, Liu H, Deng J, et al. Preventing Catheter-Related Bacteremia with Taurolidine-Citrate Catheter Locks: A Systematic Review and Meta-Analysis. *Blood Purif* 2014;37:179-87.
26. Oliveira C, Nasr A, Brindle M, et al. Ethanol Locks to Prevent Catheter-Related Bloodstream Infections in Parenteral Nutrition: A Meta-Analysis. *Pediatrics* 2012;129:318-29.
27. Jansen JP, Crawford B, Bergman G, et al. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. *Value Health* 2008;11:956-64.
28. Salanti G, Higgins JP, Ades AE, et al. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17:279-301.
29. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
30. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations. *Ann Intern Med* 2015;162:777-84.
31. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2002;51:1-29.
32. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
33. Spiegelhalter DJ, Best NG, Carlin BP, et al. Bayesian measures of model complexity and fit. *J Royal Statistical Soc (B)* 2002;64:583-639.
34. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;7:434-45.
35. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;23:3105-3124.
36. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:

163-71.

37. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.

38. Egger M, Davery Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

39. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:g5630.

Figure 1 Flow chart of the study selection

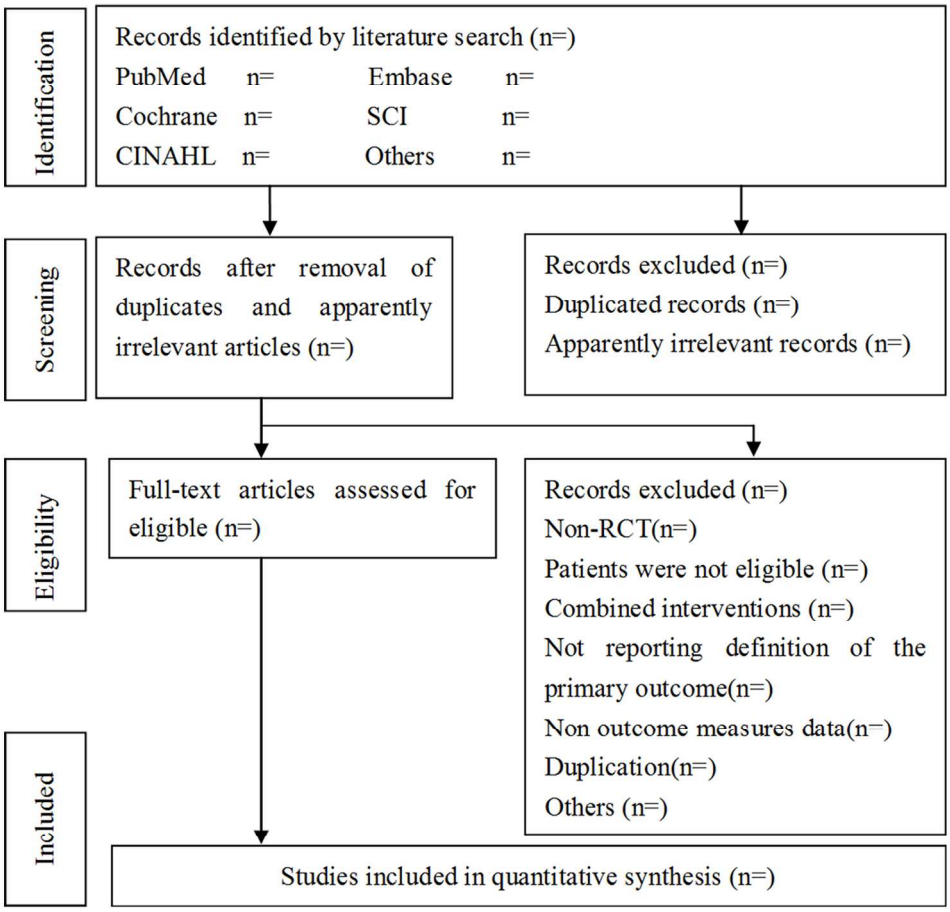

Figure 1 Flow chart of the study selection
250x240mm (300 x 300 DPI)

PubMed:

#1 “Renal Dialysis”[Mesh]

#2 dialysis[Title/Abstract] OR dialyses[Title/Abstract] OR hemodialysis[Title/Abstract] OR hemodialyses[Title/Abstract] OR haemodialysis[Title/Abstract] OR haemodialyses[Title/Abstract] OR hemofiltration[Title/Abstract] OR haemofiltration[Title/Abstract] OR haemodiafiltration[Title/Abstract] OR hemodiafiltration[Title/Abstract]

#3 #1 OR #2

#4 “Infection” [Mesh]

#5 infection*[Title/Abstract] OR bacteremia*[Title/Abstract] OR bacteraemia*[Title/Abstract] OR sepsis[Title/Abstract] OR fungemia*[Title/Abstract] OR pyemia*[Title/Abstract] OR pyohemia*[Title/Abstract] OR pyaemia*[Title/Abstract] OR septicemia*[Title/Abstract] OR "blood poisoning"[Title/Abstract] OR "blood poisonings"[Title/Abstract] OR CRB[Title/Abstract] OR CRI[Title/Abstract] OR CRBSI[Title/Abstract]

#6 #4 OR #5

#7 “Catheters, Indwelling” [Mesh]

#8 “Central Venous Catheter” [Mesh]

#9 “Catheterization, Central Venous” [Mesh]

#10 catheter*[Title/Abstract] OR "central venous line"[Title/Abstract] OR "central line"[Title/Abstract] OR "central venous lines"[Title/Abstract] OR "central lines"[Title/Abstract]

#11 #7 OR #8 OR #9 OR #10

#12 random*[Title/Abstract]

#13 "randomized controlled trial*"[All Fields]

#14 "randomized trial*"[All Fields]

#15 “Randomized Controlled Trial”[Publication Type]

#16 “Randomized Controlled Trial as Topic” [Mesh]

#17 #12 OR #13 OR #14 OR #15 OR #16

#18 #3 AND #6 AND #11 AND #17

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary File

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7,8
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	8
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	8
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	9

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan021):g7647.