Ethanol locks for the prevention of catheter-related bloodstream infection: a meta-analysis of randomized control trials

Peng Zhang, Jun-Hao Lei, Xin-Jun Su* and Xing-Huan Wang*

Abstract

Background: Current evidence regarding the efficacy of ethanol locks in preventing catheter-related bloodstream infection (CRBI) is inconclusive.

Methods: Electronic databases, including PubMed, Web of Science, Embase, and the Cochrane Library (until April 2018), were systematically searched for relevant studies. Two reviewers independently screened the retrieved records and identified RCTs that met the inclusion criteria. Relevant data were extracted for pooled analyses using Review Manager 5.3 software. Subgroup analysis was performed according to the study quality, duration of the ethanol lock, disease type and CRBI definition. Eggs’ method was applied to detect publication bias. Sensitivity analysis was conducted to check the stability of the meta-analysis results.

Results: Ten RCTs involving 2,760 patients were included in the analysis. The overall pooled result indicated that ethanol locks significantly reduced the incidence of CRBI (RR 0.66, 95% CI 0.51–0.86). Subgroup analysis suggested that an ethanol lock significantly decreased the incidence of CRBI in patients with hematological diseases (RR 0.50, 95% CI 0.31–0.80). An ethanol lock significantly reduced the incidence of CRBI in a 2-hour ethanol lock group (RR 0.49, 95% CI 0.33–0.73). The meta-analysis showed that an ethanol lock significantly reduced the incidence of CRBI according to high-(RR 0.66, 95% CI 0.47–0.94) or low-(RR 0.66, 95% CI 0.46–0.95) quality studies. Meta-analysis of studies with a strict CRBI definition showed that an ethanol lock can significantly prevent CRBI (RR 0.61, 95% CI 0.42–0.89). The results of sensitivity analysis suggested that the pooled result was stable. Meta-analysis of adverse events showed that an ethanol lock did not increase the incidence of thrombosis (RR 1.05, 95% CI 0.51–2.18) or mortality (RR 0.99, 95% CI 0.90–1.08) but did result in increased nausea (RR 1.54, 95% CI 1.01–2.35), dizziness (RR 4.21, 95% CI 2.40–7.39), elevated blushing rates (RR 3.27, 95% CI 2.05–5.22) and altered taste rates (RR 2.61, 95% CI 1.93–3.54).

Conclusions: An ethanol lock may play a role in the prevention of CRBI, especially in immunocompromised patients with hematological diseases.

Keywords: Catheter-related bloodstream infection, Ethanol lock, Meta-analysis
Background
Tunneled central venous catheters (CVCs) are widely used for long-term venous access to deliver blood and its products, chemotherapy and parenteral nutrition [1]. However, despite improved international guidelines on CVC placement and catheter care, the use of CVCs carries a high risk of developing catheter-related bloodstream infection (CRBI) [2]. Furthermore, CRBIs are related to increased healthcare costs, morbidity, hospitalization and death [3].

There are many ways to reduce CRBIs, including antimicrobial lock solutions, catheter care procedures, and agents that reduce nasal colonization of *Staphylococcus aureus*, and one meta-analysis showed that antimicrobial lock solutions significantly reduce the risk of CRBI [4]. Overall, ethanol locks are considered a promising lock solutions because they are inexpensive, universally available, and effective against a broad spectrum of bacteria and fungi [5]. Nevertheless, study results to date on ethanol locks are controversial.

For example, Bertrand Souweine et al. observed that a 2-min ethanol lock does not decrease the frequency of infection of dialysis catheters (DCs) in intensive care unit (ICU) patients [6]. A randomized pilot study showed that a 30% ethanol/4% sodium citrate appears to prevent CRBI and may improve catheter survival compared to heparin [7], and a randomized controlled multi-center trial showed that ethanol locks can prevent CRBI in pediatric oncology patients [8]. However, ethanol lock therapy has not been observed to affect patients after major heart surgery (MHS) [9].

Here, we present the results of a meta-analysis to investigate the association between ethanol locks and CRBI.

Methods
This study was performed according to the preferred reporting items of the systematic review and meta-analysis (PRISMA) guidelines.

Systematic search strategy
We conducted an electronic search of the PubMed (1966 to April 2018), Embase (1974 to April 2018), Science Citation Index (1974 to April 2018) and Cochrane (April 2018) databases for relevant studies on the efficacy of ethanol locks in preventing CRBI.

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Fig. 1 PRISMA flow diagram
| NO. | Country | Sample size(T/C) | Gender(T/C, %) | Inclusion criteria | Exclusion criteria | Intervention | Control | Diagnosis of CRBSI | Catheter types | Follow up |
|-----|---------|------------------|----------------|-------------------|------------------|--------------|---------|-------------------|---------------|----------|
| Bradley R.S. 2017 [12] | USA | 18/20 M(33/30) | 49/52 | Adult patients providing consent, non-medicare insurance, or medicare in suance with a sup plementary insurance, anticipated duration on home parenteral nutrition(HPN) > 3 m not previously on HPN at Mayo Clinic, or elsewhere, patients with single lumen, sili cone Hickman ® cath eters, and no known alcohol addiction | Failure to provide consent, medicare insurance without supplemental private insurance, patients with a catheter type other than a single lumen Hickman ®, patients who were anticipated to be on HPN for less than three months, pregnant patients, patients who have previously proven addiction and/or dependence to alcohol | 3 ml 70% ethanol lock until next PN infusion | Heparin lock plus saline infusion | (1)Bacteremia or fungemia in a patient who had an intravascular device and > 1 positive blood culture result obtained from the peripheral vein; (2)Clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and no apparent source for blood steam infection other than the central venous catheter. | Single lumen, silicone Hickman ® catheters | NA |
| Lavern MV. 2016 [7] | Canada | 20/19 M(60/47) | 63/62.3 | Eligible participants were 18 years of age or older with end-stage renal disease and planned vascular access with a catheter or current hemodialysis patients requiring exchange of an existing catheter | (1) they were critically ill in the ICU setting, (2) had acute kidney injury and were unlikely to require prolonged vascular access, (3) had a maturing or planned arteriovenous fistula/ graft creation within 2 months, or (4) planned antibiotic treatment courses lasting longer than 4 weeks from the date of the new catheter insertion. | 2.5 ml 30% ethanol/4% sodium citrate for a 6-month period | Heparin 1000 units/ mL | Two or more positive blood cultures of the same organism (species, antibiogram) from any source (peripheral or intravascular device cultures) from a patient with clinical and microbiologic data suggesting no other source for the bacteremia except the intravascular device. | Inserted dual-lumen tunneled, cuffed catheters made of carbothane, an alcohol-resistant polymer with silicone extensions (Tal Palin drome, Tyco Health care Kendall/Covi dien, Mansfield, MA, USA) | If an outcome occurred, an additional 30 days for safety was added |
| Bertrand 2015 [6] | France | 730/730 M(60.8/ 61.1) | 65/66 | Patients required insertion of DGs with an expected duration of use longer than 48 h in ICU | Ethanol intolerance and pregnancy | 60% wt/wt EL locks for 2 min | 0.9% saline lock | In patients with one or more blood cultures positive for coagulase-negative staphylococci, identity of pulse-field gel electrophoresis patterns in the catheter tip and blood cultures was required for a diagnosis of CRBS | A nontunneled, nonantimicrobial- impregnated double- lumen dialysis catheters (DC) | Until death or 48 h after ICU discharge |
| Reineke A 2015 [8] | Netherlands | 153/154 M(58/56) | 9.8/7.8 | Paediatric oncology patients (1–18 years) with a newly inserted, tunnelled central venous catheters (CVC) | At least one of the following criteria: (1) recognised pathogen cultured from ≥1 blood cultures, not | 70% ethanol locks for 2 h | 100 IU/ml heparin locks | Tunnelled CVC(port-a-cath (PAC) or Broviac) | Time to CABSI or death due to CABSI, during a maximum |
| NO. | Country | Sample size (T/C | Gender (T/C, %) | Age (T/C) | Inclusion criteria | Exclusion criteria | Intervention | Control | Diagnosis of CRBSI | Catheter types | Follow up |
|-----|---------|-----------------|----------------|-----------|-------------------|-------------------|--------------|---------|-------------------|--------------|-----------|
| L.J. Worth 2014 [16] | Australia | 42/43 | M (28/24) | 47.0/48.1 | Patients with haematological malignancy or planned BMT were eligible for enrolment at time of insertion of a dual lumen, non-antibiotic-impregnated, tunnelled, cuffed intravascular catheter (Hickman catheter) into subclavian or internal jugular veins, where the intended period of catheterization was 30 days. | Related to an infection at another site (2) Clinical manifestations of infection and a common skin microorganism (such as coagulase-negative staphylococci (CoNS), diphtheroids, Bacillus spp., or micrococci) cultured from >2 blood cultures drawn on separate occasions | 70% ethanol locks for 2 h | Heparinized saline | NA | Double lumen, non-antibiotic-impregnated, tunnelled, cuffed, intravascular catheter (Hickman catheter) | Until a device-related bloodstream infection occurred, or planned study end-date |
| Suhir 2014 [15] | India | 35/35 | NA | NA | Hemodialysis population | NA | 70% ethanol lock for 20 min | Heparin lock (1000 U/mL) | NA | Double lumen polyurethane hemodialysis catheter | NA |
| Mara 2014 [14] | Spain | 113/87 | M (55/54) | 67/65 | Recent MHS admission with Central Vascular Catheters (CVC) inserted >48 h; Age > 18 years; No evidence or suspicion of CRBSI at enrolment; No signs of infection neither general nor at catheter site entrance | Allergy or intolerance to ethanol or chronic liver disease; Pregnancy | 70% ethanol lock for 20 min | Conventional catheter-care | Microbiologically proven CRBSI considered when the same microorganism was recovered from blood and a catheter tip within less than 8 days. | Conventional catheter | Enrolled patients were prospectively followed for the occurrence of CRBSI until catheter withdrawal, hospital discharge or death |
| Jennifer K 2012 [13] | Australia | 25/24 | M (52/46) | 52/64 | Adults > 18 years, the presence of a tunnelled intravenous catheter and the ability to give informed consent | Pregnancy or breast feeding, religious or personal objection to the use of ethanol, intolerance of ethanol, and a history of an exit site, tunnel or blood stream | 70% ethanol for 48 h | Thrice weekly standard heparin locks (heparin sodium 5000 U/mL) | Microbiologically proven CRBSI considered when the same microorganism was recovered from blood and a catheter tip within less than 8 days. | A tunnelled central venous catheter | NA |
| No. | Country          | Sample size (T/C) | Gender (T/C, %) | Age (T/C) | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Intervention | Control | Diagnosis of CRBSI | Catheter types | Follow up |
|-----|-----------------|-------------------|-----------------|-----------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------|---------|-------------------|---------------|-----------|
|     |                 |                   |                 |           |                                                                                   | infection associated with the current catheter.                                 |              |         |                   |               |           |
| 1   | Lennert Solbbe  | Netherlands       | 226/222         | M (57.5/56.3) | 51.7/49.8                                                                            | Eligible study-participants were all consecutive adult (age > 17 years) hematology patients with a tunnelled silicone CVC, inserted in the preceding 72 h before study entry | Patients with an alcohol-intolerance or concomitant treatment with metronidazole | 70% ethanol lock for 15 min per day | 0.9% NaCl | A positive central or peripheral blood culture; For (coagulase-negative staphylococci) or other skin-colonizers, 2 blood cultures had to be positive when no peripheral cultures were available [19] | A tunnelled silicone CVC | NA        |
| 2   | Sanders         | New Zealand       | 32/28           | M (53/57) | 52.4/47.2                                                                            | An age > 18 years or older and admission as an inpatient to receive intensive chemotherapy likely to produce neutropenia (< 0.5 x 10^9 L) for the treatment of haematological disease, including haematopoietic stem cell transplantation. | Abnormal liver function tests or a history of alcohol abuse | 70% ethanol for 2 h | Control | The culture of a recognized pathogen from one or more blood cultures, unrelated to infection at another site [18]. | Identical dual lumen Hickman central venous catheters | The study period ended with either diagnosis of CAPS, removal or failure of catheter, discharge from hospital, death or end of study period after an arbitrary 30 days. |
The two keywords used to search the above electronic databases were ‘ethanol lock’ and ‘infection.’ All reference sections of eligible studies were hand-reviewed for potential inclusion, and no limits on language were imposed.

Eligibility criteria
We included studies if they met the following criteria: (1) study participants were patients with indwelling central venous catheters, (2) the intervention group received ethanol locks and the control group heparin/NaCl locks, and (3) the studies were randomized controlled trials (RCTs).

Study selection and data extraction
Two reviewers independently screened and assessed titles and abstracts to confirm whether the inclusion criteria were met. Data, including study characteristics (title, publication time, and sample size), detailed information in the PICOS approach (participant, intervention, comparison, outcomes, and study design), and other characteristics, were extracted by two authors using standard data extraction forms. Where necessary, the authors of the original studies were contacted for missing information.

Methodological quality assessment
The Cochrane Collaboration tool for assessing the risk of bias was used to evaluate the methodological quality of each included RCT. There were seven items for assessing bias including 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 (attrition bias), selective reporting (reporting bias) and other biases. Each item was categorized as a low risk of bias, an “unclear” (either lack of information or uncertainty about the potential for bias) risk of bias, or a high risk of bias under the guidelines in the Cochrane Handbook.

Data synthesis and analysis
The meta-analysis was performed using Review Manager 5.3 software based on PRISMA guidelines. Heterogeneity was assessed by examining the clinical characteristics of the included studies and by formal statistical $\chi^2$ and $I^2$ tests. For main outcomes (incidence of CRBI), Mantel-Haenszel estimates with a random-effects analytical model (due to the considered between-trial heterogeneity) were used to calculate relative risks (RRs) and their 95% confidence intervals (CIs). The funnel plot methods of Egger’s test were used to assess publication bias. We performed subgroup analysis according to study quality, duration of the ethanol lock, disease type and CRBI definition. Sensitivity analysis was conducted to determine the stability of the meta-analysis results using Stata 12.0 software.

Results
Characteristics of the included studies
The initial results of databases searching produced 461 records and 10 studies [6–8, 10–16] that met the inclusion criteria and were ultimately included after screening and reviewing by the authors. The selection flowchart is shown in Fig. 1. Reasons for the exclusion of 36 studies in the literature screening process are presented in Additional file 1.

The characteristics of the 10 included trials are listed in Table 1. A total of 2760 patients were
included in the meta-analysis, among whom 1396 received intervention with ethanol locks. Three studies [10, 11, 16] included only patients with hematological diseases, and 4 included hemodialysis patients [6, 7, 13, 15]. Pediatric oncology patients were included only in one study [8], and the remaining two studies involved home parenteral nutrition patients [12] or those after major heart surgery [9].

**Risk of bias**

There were seven studies [6–8, 10–13] that were considered to have a low risk of bias for “Random sequence generation” and “Allocation concealment.” “Blinding of participants and personnel” was judged to have a low risk of bias in five studies [6, 8, 10–12] and a high risk in two studies [7, 13]. There was only one study that was deemed to have a low risk of bias for the item “Blinding of outcome assessment” [11]. For “Incomplete outcome data”, six studies had a low risk of bias [6, 7, 10–13] and three a high risk [8, 14, 16]. There were seven studies [7, 8, 10, 11, 13, 14, 16] that could be judged as having a low risk of bias in the item “selective reporting.” The risk of bias assessment results are shown in Fig. 2.

**CRBI**

Definitions of CRBI among the included studies are shown in the Table 1, and a positive blood culture was necessary to diagnose CRBI [17, 18]. All included studies reported the incidence of CRBI. The total pooled results showed that there was a significant difference between ethanol locks and conventional catheter-care (RR 0.66, 95% CI 0.51 to 0.86), without
| Table 2: The pathogens involved in the infections |
|-----------------------------------------------|
| **NO.** | **Ethanol lock(n)**                                                                 | **Control(n)**                                |
| Bradley R.S. 2017 [12] | Candida species(2), Staphylococcus species(1); Escherichia coli plus Klebsiella species plus Pseudomonas(1). | Unidentified gram positive cocci              |
| Lavern M.V. 2016 [7]  | NA                                                                                         | Klebsiella                                    |
| Bertrand 2015 [6]  | Staphylococcus epidermidis(20)                                                             | Staphylococcus epidermidis(9)                 |
|           | Staphylococcus aureus(2)                                                                   | Staphylococcus aureus(0)                      |
|           | Enterococcus species (0)                                                                   | Enterococcus species (1)                      |
|           | Other coagulase negative Staphylococci(31)                                               | Other coagulase negative Staphylococci(27)    |
|           | Other Gram-positive (5)                                                                    | Other Gram-positive (6)                       |
|           | Escherichia coli (2)                                                                       | Escherichia coli (1)                          |
|           | Proteus species (0)                                                                       | Proteus species (2)                           |
|           | Pseudomonas aeruginosa (10)                                                                | Pseudomonas aeruginosa (9)                    |
|           | Enterobacteriaceae (2)                                                                    | Enterobacteriaceae (2)                       |
|           | Other Gram-negative (2)                                                                    | Other Gram-negative (3)                       |
|           | Fungi(5)                                                                                    | Fungi(3)                                      |
|           | Polymicrobial(20)                                                                         | Polymicrobial(17)                             |
| Reineke A 2015 [8] | Staphylococcus epidermidis(2)                                                             | Staphylococcus epidermidis(1)                 |
|           | Other coagulase-negative Staphylococcus(4)                                                | Other coagulase-negative Staphylococcus(8)    |
|           | Staphylococcus aureus(0)                                                                   | Staphylococcus aureus(2)                      |
|           | Streptococcus parasanguis(1)                                                               | Streptococcus parasanguis(0)                  |
|           | Other alpha-haemolytic streptococci (1)                                                   | Other alpha-haemolytic streptococci (0)       |
|           | Enterococcus faecalis(0)                                                                   | Enterococcus faecalis(1)                      |
|           | Bacillus sp.(0)                                                                            | Bacillus sp.(2)                               |
|           | Streptomyces sp.(0)                                                                       | Streptomyces sp.(1)                           |
|           | Escherichia coli(1)                                                                        | Escherichia coli(3)                           |
|           | Citrobacter freundii(1)                                                                    | Citrobacter freundii(0)                       |
|           | Brevundimonas vesicularis(1)                                                               | Brevundimonas vesicularis(0)                  |
|           | Gram-negative rod (1)                                                                      | Gram-negative rod (0)                         |
|           | Polymicrobial(3)                                                                           | Polymicrobial(0)                              |
|           | Candida sp.(1)                                                                             | Candida sp.(2)                                |
| L.J. Worth 2014 [16] | Coagulate-negative Staphylococcus spp. (3), Staphylococcus aureus (1), Listeria monocytogenes (1), Klebsiella pneumoniae (2), Escherichia coli (1), Pseudomonas aeruginosa (1), E. coli (2) and C. glabrata (1). | Coagulate-negative Staphylococcus spp. (7), Staphylococcus aureus (1), Enterococcus faecium (1), Klebsiella pneumoniae (2), Escherichia coli (1), Pseudomonas aeruginosa (1), Enterobacter cloacae(1), E. coli and E. faecium (1), and Candida parapsilosis (1). |
| Sishir 2014 [15]  | NA                                                                                         | NA                                           |
| Mara 2014 [14]  | Gram positive cocci(0)                                                                     | Gram positive cocci(1)                        |
|           | Enterobacteriaceae(2)                                                                      | Enterobacteriaceae(2)                         |
|           | Gram negative non-fermenting rods(0)                                                       | Gram negative non-fermenting rods(1)          |
|           | Fungi(0)                                                                                   | Fungi(0)                                      |
| Jennifer K 2012 [13] | Staphylococcus aureus(1)                                                                  | Staphylococcus aureus(1)                      |
|           |                                                                                        | Enterobacter cloacae(1)                       |
|           |                                                                                        | Staphylococcus hominis (1)                    |
| Lennert Solbbe 2010 [11] | n = episodes Coagulate-negative staphylococci(49), Other skin colonizers(2), Staphylococcus aureus(2), Other gram-positive cocci(12), Gram-negatives(4), Polymicrobial(20), Yeasts(2) | n = episodes Coagulate-negative staphylococci(57), Other skin colonizers(2), Staphylococcus aureus(3), Other gram-positive cocci(10), Gram-negatives(5), Polymicrobial(13), Yeasts(1) |
| Sanders 2008 [10]  | n = episodes A-haemolytic Streptococcus(1), Streptococcus group B (agalactiae)(0), S. epidermidis(0), Staphylococcus aureus(0), Stomatococcus rothia mucilaginosa(1), Escherichia coli(1), Pseudomonas aeruginosa(0), Klebsiella pneumoniae(0), non-specified Gram-negative bacilli(0). | n = episodes A-haemolytic Streptococcus(1), Streptococcus group B (agalactiae)(1), S. epidermidis(3), Staphylococcus aureus(1), Stomatococcus rothia mucilaginosa(0), Escherichia coli(4), Pseudomonas aeruginosa(1), Klebsiella pneumoniae(1), non-specified Gram-negative bacilli(1). |
significant heterogeneity ($I^2 = 16\%$, Fig. 3). The pathogens involved in the reported infections are shown in Table 2.

Subgroup analysis showed that an ethanol lock can reduce the incidence of CRBI in patients with hematological diseases (RR 0.50, 95% CI 0.31 to 0.80, $I^2 = 0\%$, Fig. 3). There was no significant difference between ethanol lock and conventional catheter care groups (RR 0.87, 95% CI 0.59 to 1.27) among hemodialysis patients, without significant heterogeneity ($I^2 = 0\%$, Fig. 3). In addition, an ethanol lock was more effective than traditional controls at preventing CRBI in pediatric oncology patients (RR 0.56, 95% CI 0.31 to 0.98, Fig. 3). Meta-analysis of high-quality studies (random sequence generation, allocation concealment and binding of participants and personnel in the study can be evaluated as low risk) showed that an ethanol lock significantly reduced CRBI in patients with central venous catheters (RR 0.66, 95% CI 0.47 to 0.94), and meta-analysis of low-quality studies also suggested a significant difference in the incidence of CRBI between ethanol lock and control groups (RR 0.66, 95% CI 0.46 to 0.95) (Fig. 4). Subgroup analysis indicated that there was a significant difference between 2-h ethanol lock and conventional catheter care groups (RR 0.49, 95% CI 0.33 to 0.73), without significant heterogeneity ($I^2 = 0\%$, Fig. 5). There was no significant difference between less than 20-min ethanol lock and conventional catheter care groups (RR 0.84, 95% CI 0.59 to 1.19), again without significant heterogeneity ($I^2 = 0\%$, Fig. 5), or 48-hour ethanol lock and conventional catheter care groups (RR 1.29, 95% CI 0.37 to 4.47). Meta-analysis of studies with a strict CRBI definition revealed that an ethanol lock can significantly prevent CRBI (RR 0.61, 95% CI 0.42–0.89), though pooled analysis of studies with a less strict CRBI definition suggested no significant change in the incidence of CRBI between ethanol lock and control lock groups (RR 0.65, 95% CI 0.39–1.07) (Fig. 6).

Sensitivity analysis results showed that the results were relatively consistent (Fig. 7), and no obvious publication bias was detected, as based on Eggers' funnel plots (Fig. 8).

Adverse events

The results of meta-analysis involving adverse events are depicted in Fig. 7. An ethanol lock did not significantly increase the incidence of a thrombus (RR 1.05, 95% CI 0.51 to 2.18) or mortality (RR 0.99, 95% CI 0.90 to 1.08) but did increase nausea (RR 1.54, 95% CI 1.01 to 2.35), dizziness (RR 4.21, 95% CI 2.40 to 7.39), and blushing (RR 3.27, 95% CI 2.05 to 5.22) and altered taste (RR 2.61, 95% CI 1.93 to 3.54) (Fig. 9).

![Fig. 4 Forest plot for subgroup analysis of the incidence of CRBI according to different study quality (RR, relative risk; CI, confidence interval)](image-url)
Discussion

Our meta-analysis first identified the efficacy of ethanol locks in preventing CRBIs. We found that ethanol locks significantly reduced the incidence of CRBI (RR 0.66, 95% CI 0.51–0.86). Subgroup analysis suggested that an ethanol lock significantly decreased CRBI incidence in patients with hematological diseases (RR 0.50, 95% CI 0.31–0.80), and a meta-analysis that only included high-quality studies showed that an ethanol lock significantly reduced CRBI incidence (RR 0.64, 95% CI 0.46–0.91). A 2-h ethanol lock diminished the frequency of CRBI, but a shorter (less than 20 min) ethanol lock did not decrease infection risk. Additionally, a meta-analysis of studies with strict CRBI definitions showed that an ethanol lock can significantly prevent a CRBI. Although an ethanol lock did not significantly increase thrombus and mortality rates, it did increase certain adverse reactions, such as nausea, dizziness, blushing and altered taste, in patients.

Tunneled CVCs are used for long-term venous access to deliver blood and blood products, chemotherapy and parenteral nutrition. The prevalence of CRBI is high in patients with indwelling CVCs, which also leads to a severe result [19], and internal colonization in long-term tunneled CVCs more frequently contributes to bacteremia [20, 21]. Many methods have been employed to prevent catheter-related sepsis, including the use of cutaneous antisepsis at the time of insertion, catheter tunneling, intraluminal antibiotic locks, antiseptic hubs and anti-microbial coating of catheters [22, 23]. However, these methods may fail to decrease the risk of infection and may instead increase the risk of hypersensitivity and development of anti-microbial resistance. Ethanol-based catheter locks may provide a
better alternative because ethanol is a widely used antiseptic with no known acquired resistance [24]. A meta-analysis of observational studies found that ethanol locks are effective alternatives to heparin locks for preventing CRBI in pediatric patients with intestinal failure [25], with the ethanol lock dwell time ranging from more than 2 h per day to 4 h 3 days per week.

To the best of our knowledge, this report describes the first meta-analysis of RCTs to investigate the efficacy of ethanol locks in the prevention of CRBI. Ten RCTs were included in our meta-analysis, and the high quality of the included studies enhances current evidence. Moreover, we performed subgroup analysis based on differences in study quality, duration of the ethanol lock and disease type.
Three studies reported the incidence of CRBI in patients with hematological diseases whose immune system was suppressed, and pooled analysis of these three studies suggested that an ethanol lock significantly reduces CRBI in immunosuppressed patients. Despite no significant difference according to the subgroup analysis in CRBI in hemodialysis patients, immune status or homeostasis may have an effect on the incidence of CRBI with an ethanol lock, which can result in bias among studies. In addition, to exclude bias by differences in study quality, subgroup analysis of relative high-quality or low-quality studies was performed, and the results suggested that an ethanol lock can significantly reduce CRBI risk. However, our definition of high-quality study was different from the Cochran high-quality trial definition; the latter requires all seven domains of the risk of bias assessment tool to be at "low risk of bias". Consequently, our subgroup analysis results regarding study quality are not very accurate. More high-quality studies that meet the Cochran definition are needed.

Three studies reported that the CVCs were locked with ethanol for 2 min, 15 min, and 20 min. The incidences of CRBI in these studies were determined by pooled analysis, though the short time frame for the ethanol lock did not effectively prevent CRBIs. In addition, the follow-up times were only 48 h, or shorter in the study by Bertrand et al., who used a 2-min ethanol lock. In combination with the low incidence of CRBI in that study, this situation might have contributed to the low efficiency in calculating a difference. In the remaining two studies, ethanol locks exhibited a tendency to prevent CRBIs, though without statistical significance. Interestingly, our findings showed that a 2-h ethanol lock (2-h duration of the lock) significantly decreased the frequency of CRBI. The preferable baseline similarity in the included four studies with a 2-h ethanol lock also enhanced the reliability of our meta-analysis results. Raad et al. found that prolonged exposure to lock solutions containing 25% ethanol in ethylenediaminetetraacetic acid (EDTA) can effectively enhance antibacterial activity in the silicone disk biofilm colonization model [26]. We did not find that a 48-h or 6-month lock can effectively prevent CRBI in our meta-analysis, and this may be due to their smaller size.

The strict definition of CRBI is such that clinical symptoms are not included and only blood culture results are used. Interestingly, meta-analysis of the studies with a strict CRBI definition showed that an ethanol lock can significantly prevent CRBI; however, this was not the result of pooled analysis of studies with a less strict CRBI definition. This finding may be the reason why a less strict CRBI definition reduced the sample weight. Because there was one study that included pediatric patients, the subgroup analysis on age was achieved by sensitivity analysis. Sensitivity analysis showed the results of pooled analysis were relatively stable. Statistical significance was lost when the trial by Reineke et al. was removed, which was due to the large sample size (307) of the study, resulting in its larger weight in the pooled result. It is noteworthy that an ethanol lock did not reduce the incidence of mortality, but there was a notable lack of mortality data in most of the trials. No obvious publication bias was detected, enhancing the value of the meta-analysis results. In addition, based on data of the pathogens involved in the infections, we determined that *Staphylococcus* has an important role as a cause of CRBI.
Fig. 9 Forest plot for adverse events including thrombus (a), nausea (b), dizziness (c), blushing (d), altered taste (e) and mortality (f)
There were also several limitations to our meta-analysis. First, we included only the abstract of studies for which we could not find the full text. Second, although a significant difference was detected in CRBI between ethanol lock and control lock groups according to subgroup analysis, the analyzable number of studies was low, which can result in bias risk. Third, very small differences in catheter type, such as dialysis catheter, and inserting catheters for parenteral nutrition may also lead to bias risk. Fourth, we did not find a significant difference in the incidence of CRBI between ethanol locks and control locks in hemodialysis patients, which was according to meta-analysis results of four studies, and the incidence of CRBI can be influenced by disturbed homeostasis. Sixth, the inclusion of the pediatric population of one study with a large sample might represent a small bias (adult and pediatric populations are different). Finally, patients with an ethanol lock may have certain adverse reactions, such as nausea, dizziness, blushing and altered taste, which might becaused by the ethanol lock solution entering into the bloodstream during catheter use.

Conclusions
Ethanol locks may play a role in preventing CRBI, though the strength of evidence is limited by the number of studies in the analysis.

Additional file

Additional file 1: Reasons for the exclusion of 36 studies in the literature screening process. (DOCX 67 kb)

Abbreviations
CI: Confidence interval; CRBI: Catheter-related bloodstream infection; CVC: Central venous catheters; DCs: Dialysis catheters; MHS: Major Heart Surgery; PRISMA: Preferred reporting items of the systematic review and meta-analyses; RCTs: Randomized controlled trials; RR: Relative risk.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
PZ and JHL participated in the project development, literature search, statistical analysis, and manuscript writing; XI-S and XH-W did the project development. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not Applicable as our manuscript is a meta-analysis.

Competing interests
The authors declare that they have no competing interests.

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Received: 20 January 2018 Accepted: 24 June 2018
Published online: 24 July 2018

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