Taurolidine lock solution for catheter-related bloodstream infections in pediatric patients: A meta-analysis

Yan Sun, Guanghui Wan, Liping Liang

Zaozhuan Traditional Chinese Medicine Hospital, Zaozhuan, Shandong, P.R. China

* lianglp1234@outlook.com

Abstract

Infection is one of the most commonly described complications, and a major cause of morbidity and mortality in pediatric patients treated using central venous catheters (CVCs). Taurolidine lock solutions have been used to decrease catheter-related bloodstream infections (CRBSIs) in both adult and pediatric patients. The purpose of this study was to systematically search the literature and conduct a meta-analysis to determine the efficacy of taurolidine in reducing CRBSI in children. We conducted an electronic search of the PubMed, EMBASE, Cochrane Library, TRIP Database, CINAHL, and Google Scholar databases for articles published up to 1st November 2019. Eligible studies included randomized controlled trials (RCTs) comparing the effects of taurolidine with control for preventing CRBSI in pediatric patients. Four studies were included. Our results indicated a statistical significant reduction in the total number of CRBSI with taurolidine as compared to control (RR: 0.23; 95% CI:0.13, 0.40; I² = 0%; P<0.00001). The pooled analysis also indicated a statistical significant reduction in the incidence of CRBSI (defined as the number of CRBSI events/1000 catheter days) in the taurolidine group (MD: -1.12; 95% CI:-1.54, -0.71; I² = 1%; P<0.00001). The number of catheters removed due to infection or suspected infection was not significantly different between the two groups (RR: 0.68; 95% CI:0.22, 2.10; I² = 56%; P = 0.50) (Fig 5). The quality of the included studies was not high. The use of taurolidine as a catheter locking solution may significantly reduce CRBSI in pediatric patients. However, the quality of current evidence is not high and further high-quality large scale RCTs are needed to corroborate our results.

Introduction

Central venous catheters (CVCs) are often an inevitable part of treating adult and pediatric patients receiving antibiotic therapy, parenteral nutrition, hemodialysis, chemotherapy, or hospitalized in Intensive Care Units (ICU) [1]. However, the long-term use of CVCs carries a risk of catheter-related bloodstream infections (CRBSI) that are associated with increased morbidity and mortality rates. According to the Centre for Disease Control and Prevention, an estimated 41,000 new cases of CRBSI are diagnosed annually and the disease has a mortality...
rate of 12–15% in the general population [2]. Prevention of CRBSI is therefore pivotal to improve clinical outcomes in high-risk patients.

Intraluminal contamination, especially with Staphylococci, is considered the main cause for CRBSI, and the risk of infection further increases with long-term catheter use [3]. The most frequent mechanism of CRBSI infection is catheter hub contamination during catheter manipulation by healthcare professionals leading to endoluminal colonization and infection. CRBSI rates are high in pediatric patients (over 10 per 1000 catheter-days) and are associated with increased mortality and treatment costs [4,5].

Heparin which is routinely used to lock the catheter to prevent clotting is thought to be associated with the growth of bacteria inside the catheter hub [6]. While prophylactic antimicrobial lock solutions are beneficial in preventing CRBSI, they also increase the risk of selecting resistant microorganisms [7]. Taurolidine [bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)-methane], a derivative of the amino acid taurine, is an antimicrobial agent with a broad range of antibacterial and antifungal activity that includes both Gram-positive and Gram-negative bacteria, such as methicillin-resistant Staphylococcus aureus (MRSE), coagulase-negative Staphylococci (CoNS), and vancomycin-resistant enterococci [8]. Taurolidine has few reported side-effects, and its continued use is not associated with developing bacterial resistance [9]. Both retrospective, as well as prospective studies, have reported a reduction in the number of CRBSIs after the use of taurolidine lock in the catheter lumen [10–12].

In a systematic review and meta-analysis of six randomized controlled trials (RCTs) published in 2013, Liu et al [13] have reported a 66% reduced risk of CRBSI when taurolidine is used as a locking solution. Their review, however, included a mix of four adult and two pediatric studies. In a recent systematic review of 2017, Norris et al [13] have discussed the effectiveness and safety of prophylactic antimicrobial lock solutions in adults as well as pediatric cancer patients with CVCs. Their review was, however, not focused specifically on taurolidine and was a literature summary of all types of studies evaluating all types of antimicrobial lock solutions. To the best of our knowledge, to date, no study has pooled evidence to analyze the effectiveness of taurolidine lock in reducing CRBSI in pediatric patients. Therefore, the purpose of this study was to systematically search the literature and perform a meta-analysis to determine the efficacy of taurolidine in reducing CRBSI in pediatric patients.

Methods
Study design and literature search
This review was conducted following the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses) [14] and the Cochrane Handbook for Systematic Reviews of Intervention [15]. We conducted an electronic search of the PubMed, EMBASE, Cochrane Library, TRIP Database, CINAHL and Google Scholar databases using the MeSH or free text terms for articles published up to 1st November 2019. Google Scholar was searched for only the first 200 results for each search query. The search was restricted to studies performed on human pediatric patients (<19 years of age). No restriction on language or publication period was set. Reference lists of all included studies, as well as review articles on the subject, were manually inspected for additional relevant articles.

Search terms included “central venous catheters”, “infection”, “catheter-related infection”, “antimicrobial lock solution”, “antibiotic lock solution”, “taurolidine”, “taurolidine citrate”, “heparin”, “pediatrics”, “prevention”, and “children”. Detailed search strategy and results of the PubMed database are presented in S1 Table. Two reviewers (Y.S. & G.W.) conducted the search independently. Any disagreement with regards to inclusion/exclusion of studies were resolved by discussion with the third reviewer (L.L.).
Selection criteria
We used the PICOS (Population, Intervention, Comparison, Outcome, and Study design) model to select studies for this review. Only RCTs conducted on pediatric patients (<19 years of age) implanted with a CVC for any reason (Population), were included. Studies were to compare taurolidine lock solution (Intervention) with control (heparin or saline or no lock) (Comparator) for the reduction of CRBSI (Outcome). There was no restriction on the concentration of taurolidine or heparin used by the trials. Also, no restrictions were placed regarding language or sample size. In studies wherein both adult and pediatric patients were analyzed, the trial was included only if pediatric data was separately retrievable. Studies on adult patients, studies utilizing any other antimicrobial or alcohol lock solutions, single-arm studies, non-RCTs, abstracts, duplicates, case reports and case studies were excluded.

Data collection and analysis
Data were extracted independently by two reviewers using a pre-designed form that included the first author’s name, year of publication, study design, country of research, demographic details, sample size, catheter duration, locking protocol, use of prophylactic antibiotics, patients lost to follow-up, study outcomes, and complications. Any disagreement was resolved by discussion with the third reviewer. Missing data were requested from the original authors through electronic correspondence or mail.

The primary outcome of interest was the total number of CRBSI while secondary outcomes were incidence rate of CRBSI (defined as the number of CRBSI events/1000 catheter days) and the number of CVC removed due to infection or suspected infection. Other outcomes studied but not included in the meta-analysis involved time interval from the start of locking and infection and incidence of catheter thrombosis. Definitions of CRBSI was as per the included study.

Risk of bias in individual studies
The quality of included studies was assessed using the Cochrane Collaboration risk assessment tool for RCTs [15]. Risk of bias (low, unclear or high) was gauged for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases.

Statistical analysis
Data were analyzed on an intention-to-treat basis. Continuous data were pooled using Mean Difference (MD) and 95% confidence interval (CI). Categorical data were summarized using the Mantel-Haenszel Risk Ratio (RR) and 95% CI. The I² statistic was used to assess heterogeneity wherein values of 25–50% denoted low, 50–75% denoted medium and values of more than 75% denoted considerable heterogeneity. Considering the heterogeneity in the patient sample, the number of catheter days and other methodological variations amongst the included studies, a random-effects model was preferred for the meta-analysis. Review Manager (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014) was used for the meta-analysis. In studies reporting only 95% CI for continuous variables, standard deviations were calculated using the in-build RevMan calculator. A sensitivity analysis was carried out to assess the influence of each study on the pooled effect size. Using the one-study-out method, we evaluated whether deleting each individually would significantly change the results of the meta-analysis. Due to the limited number of included studies, publication biased was not assessed.
Results

Identification of relevant studies

The study flow chart is presented in Fig 1. Eleven articles were selected for full-text analysis. Ten studies were excluded as two were retrospective studies [16,17], one was a non-RCT [18], one was a single-arm trial [19] while six studies were carried out on adult patients [20–25]. A total of four studies [26–29] were included in this systematic review and meta-analysis.

All of the included studies followed the Declaration of Helsinki for the ethical treatment of humans in experimentation which was developed by the World Health Organization. Table 1 summarizes the characteristics of the selected studies.

All studies were RCTs carried out in European countries in a tertiary care setting. The study population consisted of cancer patients in three trials [26,27,29] while one study included patients requiring CVC during and after surgical procedures (for parenteral nutrition or drug administration) [28]. The sample of included studies ranged from 35–90 patients per group. There was a wide variation in the cumulative duration of catheter use in the included studies. The concentration of taurolidine was 1.35% with 4% sodium citrate in all studies. Three studies [26,27,29] used heparin locks in the control group while no locking solution was used in the control group of one trial [28]. Three trials used prophylactic antibiotics during the course of the study [26–28]. Duration of locking was specified in only one study wherein the mean duration was 172.6 in the taurolidine group and 187.4 days in the control group [26].

The authors' judgment of the risk of bias in the included studies is presented in Fig 2. Adequate method of randomization was utilized in only one trial [29]. None of the trials were blinded. Attrition bias was significant in one study [26]. None of the trials were pre-registered.

The definition of CRBSI in the included studies and summary of outcomes is presented in Table 2. CRBSI was studied by all four included trials. Time interval from the start of locking and first infection was reported by two trials [26,29] with no significant difference between the two groups. All included studies also did not report any significant difference between the incidence of catheter thrombosis between the two groups.

Meta-analysis

For the primary outcome of the total number of CRBSI, data of 236 patients in the taurolidine group was compared with data of 240 controls. Our results indicated a statistical significant reduction in the total number of CRBSI with taurolidine as compared to control (RR: 0.23; 95% CI:0.13, 0.40; I² = 0%; P<0.00001) (Fig 3). Data on incidence rates of CRBSI was available from three studies [26,27,29]. Pooled analysis indicated a statistical significant reduction in the incidence of CRBSI in the taurolidine group (MD: -1.12; 95% CI:-1.54, -0.71; I² = 1%; P<0.00001) (Fig 4). The number of catheters removed due to infection or suspected infection was not significantly different between the two groups (RR: 0.68; 95% CI:0.22, 2.10; I² = 56%; P = 0.50) (Fig 5). On sensitivity analysis, there was no change in the significance of the results of both primary and secondary outcomes on the exclusion of any study.

Discussion

According to the Centers for Disease Control (CDC), steps for the prevention of CRBSI should include handwashing, use of aseptic technique, site cleansing and use of impregnated catheter cuffs [2]. Regardless of these precautions, CRBSI continues to occur leading to a prolonged hospital stay, higher health-care cost as well as increased morbidity and mortality. Over the past decade, several antimicrobial catheter locking solutions have been used to reduce the incidence of CRBSI but with varying results [30]. The primary aim of this systematic review and
Fig 1. Flow diagram of the selection of studies and specific reasons for exclusion from the present meta-analysis.

https://doi.org/10.1371/journal.pone.0231110.g001
Table 1. Characteristics of the published studies included in meta-analysis.

| Author & Year          | Country    | Patient population | Setting/centers | Sample size | Age in years (Median) range | Male gender | Cumulative Catheter Duration (days) | Time of taurolidine lock | Control group protocol   | Prophylactic Antibiotics used                                                                 | Patients lost to follow up |
|------------------------|------------|--------------------|-----------------|-------------|----------------------------|-------------|--------------------------------------|--------------------------|---------------------------|---------------------------------------------------------------------------------------------|---------------------------|
| Simon et al. 2008 [27] | Switzerland | Cancer             | Tertiary care hospital | 89          | 7.2 (3.7–16.1)              | 60          | 6705                                | Once or twice a week     | 200 IU heparin lock in 2ml of normal saline | Cotrimoxazole used for prevention of Pneumocystis jirovecii pneumonia | NS                        |
| Dumichen et al. 2012 [26] | Germany    | Neoplastic Disease | Tertiary care hospital | 35          | 7.5 (4.4–18.0)              | 19          | 6576                                | NS                      | 100 IU heparin/ml of normal saline | Cotrimoxazole used for prevention of Pneumocystis jirovecii pneumonia | 10                        |
| Handrup et al. 2013 [29] | Denmark    | Cancer             | Tertiary care hospital | 64          | 6 (0–19)                    | 45          | 39127§                              | After each treatment cycle | 250 IU of heparin in 2.5 ml of normal saline | NS                                                        | 0                         |
| Lyszkowiska et al. 2019 [28] | Poland     | Surgical treatment with observation | Tertiary care hospital | 48          | <2                         | NS          | 942                                 | No locking solution       | Standard perioperative prophylaxis or for treatment of co-existing bacterial infection | 0                          |

*Combined data of study and control groups
NS, Not specified

https://doi.org/10.1371/journal.pone.0231110.t001
| Study               | 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) | Other bias |
|---------------------|---------------------------------------------|------------------------------------------|----------------------------------------------------------|-------------------------------------------------|----------------------------------------|-------------------------------------|------------|
| Dumichen 2012       | ?                                           |                                         | ?                                                        | ?                                               | -                                      | ?                                   | ?          |
| Handrup 2013        | +                                           | ?                                        | -                                                        | -                                               | +                                     | -                                   | ?          |
| Lyszkowaska 2019    | ?                                           |                                         | ?                                                        | ?                                               | +                                     | ?                                   | ?          |
| Simon 2008          | -                                           | -                                        | -                                                        | -                                               | +                                     | ?                                   | ?          |
A meta-analysis was conducted to evaluate the effectiveness of one locking solution, taurolidine, in reducing the risk of catheter-related bloodstream infection (CRBSI) in pediatric patients. The study's results indicated that taurolidine significantly decreased the total number of CRBSI events and the incidence rate of CRBSI in the pediatric population.

![Fig 2. Risk of bias summary of included studies.](https://doi.org/10.1371/journal.pone.0231110.g002)

Table 2. Definition and outcomes in included studies.

| Author & Year | Definition of catheter related CRBSI | Total number of CRBSI | Time interval from start of locking and infection (Mean ± SD) | Incidence rate of BSI (95% CI or SD) | Number of catheter removal due to infection | Catheter thrombosis |
|--------------|--------------------------------------|-----------------------|-------------------------------------------------------------|-----------------------------------|------------------------------------------|---------------------|
| Simon et al. 2008 [27] | Clinical signs of infection plus at least two positive blood cultures for coagulase-negative staphylococci (CoNS) or methicillin resistant staphylococci (MRSE) taken from a CVC, and no evidence of another primary focus of infection | 3 | 14 | NS | NS | 0.45 (0.09–1.31) | 3 | 4 | 0 | 0 |
| Dumichen et al. 2012 [26] | Patient with CVC has a recognized pathogen cultured from one or more blood cultures, and the organism cultured from blood is not related to an infection at another site | 2 | 9 | 35.6±31.8 | 41.2±49.4 | 0.3 (1.2) | 1.3 (2.5) | 5 | 2 | 3 | 2 |
| Handrup et al. 2013 [29] | Patient with CVC has a recognized pathogen cultured from one or more blood cultures; or a common skin contaminant cultured from two or more blood cultures, both drawn at separate occasions. In both cases, the cultured organism must not be related to pathogens identified at other infection sites | 7 | 26 | 300 ± NR | 156 ± NR | 0.4 (0.17–0.78) | 1.4 (0.93–2.01) | 5 | 7 | 0 | 0 |
| Lyszkowska et al. 2019 [28] | Deterioration of the patient’s condition, an increase or decrease in the number of white blood cells, thrombocytopenia, anaemia, positive blood culture and exclusion of other sources of infection. | 1 | 14 | NS | NS | 1.06 (0.096–4.96) | 14.3 (8.18–23.35) | 1 | 11 | 1 | 1 |

CVC, Central venous catheter; CRBSI, catheter-related bloodstream infection; SD, standard deviation; NR, Not reported; NS, Not studied; CI, Confidence intervals

[https://doi.org/10.1371/journal.pone.0231110.t002](https://doi.org/10.1371/journal.pone.0231110.t002)
The long term use of CVCs has been associated with intraluminal contamination and subsequent infection [31]. A microbial biofilm is formed in the catheter lumen from contamination either from the infusate or catheter hub, detachment of which, may lead to CRBSI [32]. Children are particularly high-risk candidates for CRBSI with incidence rates exceeding 10 per 1000 catheter days [4,5]. As biofilms are resistant to routine systemic antimicrobial therapy, the use of antimicrobial locking solutions may be beneficial in reducing the incidence of CRBSI. The advantage of the antimicrobial locking solution is that it maintains a high concentration of the agent in close contact with the catheter lumen for a prolonged period, with minimal systemic absorption [33]. Studies have reported that taurolidine is effective in reducing the microbial load of biofilms in hemodialysis patients requiring long-term catheterization [32]. A number of RCTs conducted on adult patients requiring long-term catheterization for hemodialysis [24], parenteral support [22] or cancer chemotherapy [20], have also demonstrated a reduced risk of CRBSI with the use of taurolidine lock solution. The outcomes of our analysis concur with the result of these trials.

In our review, the total number of CRBSI events were 13/236 (5.5%) in the taurolidine group and 63/240 (26.25%) in the control group, with a statistically significant 77% reduced risk of CRBSI in the taurolidine group. To account for the difference in duration of catheter use amongst the included trials, we also analyzed the incidence rate of CRBSI between the two groups. Our results indicate a statistical significant reduction of CRBSI incidence/1000 catheter days with the use of taurolidine. The results are similar to the previous meta-analysis of the taurolidine lock solution by Liu et al [13], who reported a 66% reduced risk of CRBSI. Their study was however not focused on pediatric patients. As a secondary outcome, we also analyzed the total number of catheters removed due to infection or suspected infection. Our analysis indicated no significant difference between the two groups. The non-significant results can be explained by the differences in catheter removal criteria as well as the severity and management protocol of CRBSI in the included trials. Also, CVCs were removed even in cases of suspected infection in one study. But, the subsequent culture of the catheter did not demonstrate bacterial growth in all cases [26].

The long term use of CVCs has been associated with intraluminal contamination and subsequent infection [31]. A microbial biofilm is formed in the catheter lumen from contamination either from the infusate or catheter hub, detachment of which, may lead to CRBSI [32]. Children are particularly high-risk candidates for CRBSI with incidence rates exceeding 10 per 1000 catheter days [4,5]. As biofilms are resistant to routine systemic antimicrobial therapy, the use of antimicrobial locking solutions may be beneficial in reducing the incidence of CRBSI. The advantage of the antimicrobial locking solution is that it maintains a high concentration of the agent in close contact with the catheter lumen for a prolonged period, with minimal systemic absorption [33]. Studies have reported that taurolidine is effective in reducing the microbial load of biofilms in hemodialysis patients requiring long-term catheterization [32]. A number of RCTs conducted on adult patients requiring long-term catheterization for hemodialysis [24], parenteral support [22] or cancer chemotherapy [20], have also demonstrated a reduced risk of CRBSI with the use of taurolidine lock solution. The outcomes of our analysis concur with the result of these trials.

In our review, the total number of CRBSI events were 13/236 (5.5%) in the taurolidine group and 63/240 (26.25%) in the control group, with a statistically significant 77% reduced risk of CRBSI in the taurolidine group. To account for the difference in duration of catheter use amongst the included trials, we also analyzed the incidence rate of CRBSI between the two groups. Our results indicate a statistical significant reduction of CRBSI incidence/1000 catheter days with the use of taurolidine. The results are similar to the previous meta-analysis of the taurolidine lock solution by Liu et al [13], who reported a 66% reduced risk of CRBSI. Their study was however not focused on pediatric patients. As a secondary outcome, we also analyzed the total number of catheters removed due to infection or suspected infection. Our analysis indicated no significant difference between the two groups. The non-significant results can be explained by the differences in catheter removal criteria as well as the severity and management protocol of CRBSI in the included trials. Also, CVCs were removed even in cases of suspected infection in one study. But, the subsequent culture of the catheter did not demonstrate bacterial growth in all cases [26].
On analysis of the results of individual studies, Dumichen et al [26] was the only study to report a minimal difference in the total number of CRBSI events (RR: 0.23, 95% CI: 0.05–0.98) as well as incidence rates of CRBSI between the two groups. This may partly be explained by the limited sample size of the study and the high attrition rate of the trial. The authors had recognized that their study was underpowered to detect statistical significant differences between the two groups.

Several factors can influence the risk of CRBSI in patients with CVCs. These include the patient’s medical history, duration of catheterization, frequency and duration of locking solutions, use of other antiseptic measures, prophylactic antibiotics, etc. It is assumed that the role of such confounding factors is negated by conducting a robust RCT in a single center to maintain homogeneity of the protocol. However, when a meta-analysis combines the results of multiple RCTs, inter-study heterogeneity can influence the study results. In the four RCTs combined in our analysis, one study assessed the efficacy of taurolidine lock solutions only in surgical patients. Data on the frequency and total duration of locking were not provided by all included trials. Also, there were differences in the cumulative duration of catheterization in the included studies. While the total duration of catheterization was less than 1000 days in the study of Lyszkowaska et al [28], patients were catheterized for a significantly longer duration in the remaining trials. Included trials also differed in the use of prophylactic antibiotics in the study population. Such inter-study heterogeneity was, however, expected as absolute similarities between RCTs conducted at different time points and different centers are not plausible. In our opinion, the included studies had sufficient similarities for the conduct of a meta-analysis, like analysis of the pediatric population with long-term central venous catheterization, use of similar concentration of taurolidine locking solution and more or less similar definition of outcomes.

The results of our study should be interpreted with the following limitations. Firstly, the strength of any meta-analysis depends upon the quality of the included studies. The results of our study should be interpreted with caution as the overall quality of studies was not high. The absence of adequate methods of randomization and the absence of blinding may have skewed the study results limiting the strength of the current evidence. Secondly, as discussed earlier, there was significant inter-study heterogeneity which may also have influenced outcomes. Thirdly, only four trials were available for analysis in our review. One of the studies included was underpowered [26]. Fourthly, the study population in the included studies was restricted to cancer and surgical patients. The efficacy of taurolidine lock solution in other patient populations is not completely known. Lastly, all included trials were conducted in European countries. There may be differences in CVC protocol in Europe vs other countries and the findings of this review cannot be generalized at this point.

Nevertheless, our review is the first meta-analysis on the efficacy of taurolidine lock solution in pediatric patients. Our results were synthesized only from RCTs to provide the highest level
of evidence on the subject. The stability of our results on sensitivity analysis lends some credibility to our conclusions.

Within the limitations of our review, our study indicates that the use of taurolidine as a catheter locking solution may significantly reduce CRBSI in pediatric patients. Strong conclusions cannot be drawn due to the limited quality of the included studies. Further high-quality large scale RCTs are needed to corroborate our results.

Supporting information

S1 Checklist.
(DOC)

S1 Table. Search strategy of the review.
(DOCX)

Author Contributions

Conceptualization: Yan Sun.
Data curation: Yan Sun, Liping Liang.
Formal analysis: Yan Sun, Guanghui Wan, Liping Liang.
Investigation: Yan Sun, Liping Liang.
Methodology: Yan Sun, Guanghui Wan, Liping Liang.
Resources: Yan Sun, Guanghui Wan, Liping Liang.
Software: Guanghui Wan.
Supervision: Liping Liang.
Validation: Yan Sun, Guanghui Wan, Liping Liang.
Visualization: Yan Sun, Guanghui Wan, Liping Liang.
Writing – original draft: Yan Sun.
Writing – review & editing: Liping Liang.

References

1. Castagnola E, Ginocchio F. Rescue therapy of difficult-to-treat indwelling central venous catheter-related bacteremias in cancer patients: a review for practical purposes. Expert Rev Anti Infect Ther. 2013; 11: 179–86. https://doi.org/10.1586/eri.12.160 PMID: 23409823

2. Centers for Disease Control and Prevention (CDC). Vital signs: central line-associated blood stream infections—United States, 2001, 2008, and 2009. MMWR Morb Mortal Wkly Rep. 2011; 60: 243–8. Available: http://www.ncbi.nlm.nih.gov/pubmed/21368740 PMID: 21368740

3. Mermel LA, Allon M, Bouza E, Craven DE, Flynn P, O’Grady NP, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009; 49: 1–45. https://doi.org/10.1086/599376 PMID: 19489710

4. Sanderson E, Yeo KT, Wang AY, Callander I, Bajuk B, Bolisetty S, et al. Dwell time and risk of central-line-associated bloodstream infection in neonates. J Hosp Infect. 2017; 97: 267–274. https://doi.org/10.1016/j.jhin.2017.06.023 PMID: 28651859

5. Mobley RE, Bizzarro MJ. Central line-associated bloodstream infections in the NICU: Successes and controversies in the quest for zero. Semin Perinatol. 2017; 41: 166–174. https://doi.org/10.1053/j.semperi.2017.03.006 PMID: 28411947
6. Shankis RMQ, Donegan NP, Graber ML, Buckingham SE, Zegans ME, Cheung AL, et al. Heparin stimulates Staphylococcus aureus biofilm formation. Infect Immun. 2005; 73: 4596–606. https://doi.org/10.1128/IAI.73.8.4596-4606.2005 PMID: 16040971

7. van de Wetering MD, van Woensel JBM. Prophylactic antibiotics for preventing early central venous catheter Gram positive infections in oncology patients. Cochrane database Syst Rev. 2007; CD003295. https://doi.org/10.1002/14651858.CD003295.pub2 PMID: 17253487

8. Torres-Viera C, Thauvin-Eliopoulos C, Souli M, DeGirolami P, Farris MG, Wennersten CB, et al. Activities of taurolidine in vitro and in experimental enterococcal endocarditis. Antimicrob Agents Chemother. 2000; 44: 1720–4. https://doi.org/10.1128/aac.44.6.1720-1724.2000 PMID: 10817739

9. Shah CB, Mittelman MW, Costerton JW, Parenteau S, Pelak M, Arsenault R, et al. Antimicrobial activity of a novel catheter lock solution. Antimicrob Agents Chemother. 2002; 46: 1674–9. https://doi.org/10.1128/AAC.46.6.1674-1679.2002 PMID: 12019075

10. Al-Amin AH, Sarveswaran J, Wood JM, Burke DA, Donnellan CF. Efficacy of taurolidine on the prevention of catheter-related bloodstream infections in patients on home parenteral nutrition. J Vasc Access. 2013; 14: 379–82. https://doi.org/10.5301/jva.5000168 PMID: 23817948

11. Olthof ED, Versleijen MW, Huisman-de Waal G, Feuth T, Kievit W, Wanten GJA. Taurolidine lock is superior to heparin lock in the prevention of catheter-related bloodstream infections and occlusions. PLoS One. 2014; 9: e111216. https://doi.org/10.1371/journal.pone.0111216 PMID: 25379871

12. Tribler S, Brandt CF, Petersen AH, Petersen JH, Fuglsang KA, Staun M, et al. Taurolidine-citrate-heparin lock reduces catheter-related bloodstream infections in intestinal failure patients dependent on home parenteral support: a randomized, placebo-controlled trial. Am J Clin Nutr. 2017; 106: 839–848. https://doi.org/10.1093/ajcn.1128/AAC.46.6.1674-1679.2002 PMID: 10817739

13. Liu Y, Zhang A-Q, Cao L, Xia H-T, Ma J-J. Taurolidine lock solutions for the prevention of catheter-related bloodstream infections: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2013; 8: e79417. https://doi.org/10.1371/journal.pone.0079417 PMID: 24278133

14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009; 6: e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

15. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systemic Reviews of Interventions. Version 6. Cochrane; 2019. Available: www.training.cochrane.org/handbook

16. Hulshof EC, Hanff LM, Olieman J, de Vette S, Driessen G-J, Meeussen C, et al. Taurolidine in Pediatric Home Parenteral Nutrition Patients. Pediatr Infect Dis J. 2017; 36: 233–235. https://doi.org/10.1097/INF.0000000000001404 PMID: 27846059

17. Trivić I, Mišak Z, Kerman V, Prlić H, Kolaček S, Hojsak I. Central Catheter Related Bloodstream Infection Rates In Children on Home Parenteral Nutrition. J Pediatr Gastroenterol Nutr. 2019 [cited 21 Feb 2020]. https://doi.org/10.1097/MPG.0000000000002559 PMID: 31738292

18. Lambe C, Poisson C, Talbotec C, Goulet O. Strategies to Reduce Catheter-Related Bloodstream Infections in Pediatric Patients Receiving Home Parenteral Nutrition: The Efficacy of Taurolidine-Citrate Prophylactic-Locking. JPEN J Parenter Enteral Nutr. 2018; 42: 1017–1025. https://doi.org/10.1002/jpen.1043 PMID: 29385236

19. Clark JE, Graham N, Kleidon T, Ullman A. Taurolidine-Citrate Line Locks Prevent Recurrent Central Line-Associated Bloodstream Infection in Pediatric Patients. Pediatr Infect Dis J. 2019; 38: e16–e18. https://doi.org/10.1097/INF.0000000000002191 PMID: 30204661

20. Longo R, Llorens M, Goetz C, Platini C, Eid N, Sellies J, et al. Taurolidine/Citrate Lock Therapy for Primary Prevention of Catheter-Related Infections in Cancer Patients: Results of a Prospective, Randomized, Phase IV Trial (ATAPAC). Oncology. 2017; 93: 99–105. https://doi.org/10.1002/jpco.20179 PMID: 28463827

21. Betjes MGH, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate-taurolidine-containing lock solution. Nephrol Dial Transplant. 2004; 19: 1546–51. https://doi.org/10.1093/ndt/gfh014 PMID: 14993498

22. Tribler S, Brandt CF, Petersen AH, Petersen JH, Fuglsang KA, Staun M, et al. Taurolidine-citrate-heparin lock reduces catheter-related bloodstream infections in intestinal failure patients dependent on home parenteral support: a randomized, placebo-controlled trial. Am J Clin Nutr. 2017; 106: 839–848. https://doi.org/10.1093/ajcn.1128/AAC.46.6.1674-1679.2002 PMID: 12019075

23. Bonkain F, Van Hulle F, Janssens P, Catalano C, Allamani M, Stolarek J-C, et al. Urokinase-containing locking solution in the prevention of dialysis catheter dysfunction: a double blind randomized controlled trial. J Vasc Access. 2017; 18: 436–442. https://doi.org/10.5301/jva.5000737 PMID: 28623638

24. Winnicki W, Herkner H, Lorenz M, Handsisurya A, Kikić Ž, Bielesz B, et al. Taurolidine-based catheter lock regimen significantly reduces overall costs, infection, and dysfunction rates of tunneled...
hemodialysis catheters. Kidney Int. 2018; 93: 753–760. https://doi.org/10.1016/j.kint.2017.06.026 PMID: 28890326

25. Al-Ali F, Hamdy AF, Hamad A, Elsayed M, Zafar Iqbal Z, Elsayed A, et al. Safety and efficacy of tauri-
dine/urokinase versus tauridine/heparin as a tunneled catheter lock solution in hemodialysis patients: a prospective, randomized, controlled study. Nephrol Dial Transplant. 2018; 33: 619–626. https://doi. org/10.1093/ndt/gfx187 PMID: 29106676

26. Dümmichen MJ, Seeger K, Lode HN, Kühl JS, Ebell W, Degenhardt P, et al. Randomized controlled trial of tauridine citrate versus heparin as catheter lock solution in paediatric patients with haematological malignancies. J Hosp Infect. 2012; 80: 304–9. https://doi.org/10.1016/j.jhin.2012.01.003 PMID: 22342714

27. Simon A, Ammann RA, Wiszniewsky G, Bode U, Fleischhack G, Besuden MM. Tauridine-citrate lock solution (TauroLock) significantly reduces CVAD-associated grampositive infections in pediatric cancer patients. BMC Infect Dis. 2008; 8: 102. https://doi.org/10.1186/1471-2334-8-102 PMID: 18664278

28. Lyszkowska M, Kowalewski G, Szymczak M, Polnik D, Mikołajczyk A, Kalicinski P. Effects of prophylactic use of tauridine-citrate lock on the number of catheter-related infections in children under 2 years of age undergoing surgery. J Hosp Infect. 2019; 103: 223–226. https://doi.org/10.1016/j.jhin.2019.04.022 PMID: 31054935

29. Handrup MM, Møller JK, Schreder H. Central venous catheters and catheter locks in children with cancer: a prospective randomized trial of tauridine versus heparin. Pediatr Blood Cancer. 2013; 60: 1292–8. https://doi.org/10.1002/pbc.24482 PMID: 23417891

30. Norris LB, Kablaoui F, Brilhart MK, Bookstaver PB. Systematic review of antimicrobial lock therapy for prevention of central-line-associated bloodstream infections in adult and pediatric cancer patients. Int J Antimicrob Agents. 2017; 50: 308–317. https://doi.org/10.1016/j.ijantimicag.2017.06.013 PMID: 28889878

31. Milstone AM, Reich NG, Advani S, Yuan G, Bryant K, Coffin SE, et al. Catheter dwell time and CLABSIIs in neonates with PICCs: a multicenter cohort study. Pediatrics. 2013; 132: e1609–15. https://doi.org/10.1542/peds.2013-1646 PMID: 24218474

32. Zwiech R, Adelt M, Churi S. A Tauridine-Citrate-Heparin Lock Solution Effectively Eradicates Pathogens From the Catheter Biofilm in Hemodialysis Patients. Am J Ther. 2016; 23: e363–8. https://doi.org/10.1097/MTJ.0000000000000460 PMID: 23665885

33. Bookstaver PB, Williamson JC, Tucker BK, Raad II, Sherertz RJ. Activity of novel antibiotic lock solutions in a model against isolates of catheter-related bloodstream infections. Ann Pharmacother. 2009; 43: 210–8. https://doi.org/10.1345/aph.1L145 PMID: 19193593