JPPT | Systematic Review and Meta-Analysis

Ethanol Lock for Prevention of CVC-Related Bloodstream Infection in Pediatric Patients: A Systematic Review and Meta-Analysis

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Ethanol lock therapy (ELT) can be used in patients with an indwelling central line to assist in the prevention of central venous catheter (CVC)–associated infections. However, its efficacy has not been consistently demonstrated in the pediatric population. The primary objective of this review and meta-analysis was to determine the efficacy and safety of ELT in prevention of central line–associated bloodstream infection (CLABSI) in the pediatric population. A search was conducted with the PubMed, CINAHL, PSCYInfo, Cochrane Library, and Academic Search Premier databases from inception through January 21, 2022. Studies were included if they reported incidence of CVC-related infections with ELT in pediatric patients. Meta-analyses used random-effects models according to the heterogeneity of all included studies. Of 736 studies, 25 met inclusion criteria for review and 10 for inclusion in the meta-analysis. Meta-analysis with pre- and post-ELT treatment showed that use of ELT significantly decreased mean CVC-related infections when compared with pre-treatment with no ELT with a mean difference of −5.79 (95% CI, −9.08 to −2.51; p < 0.001). The number of CVC infections also significantly decreased (OR, 0.42; 95% CI, 0.23–0.75; p = 0.004). Increased risk of thrombosis and increased frequency of catheter breakage, repair, and replacement were noted in several studies. Ethanol lock therapy is effective in preventing infection related to central venous catheter use in pediatric patients. Further study is warranted to determine the optimal protocol for, and incidence of, adverse events related to use of ELT.

ABBREVIATIONS BSI, bloodstream infection; CABSI, catheter-associated bloodstream infection; CLABSI, central line–associated bloodstream infection; CRBSI, catheter-related bloodstream infection; CRI, catheter-related infection; CVAD, central venous access device; CVC, central venous catheter; ELT, ethanol lock therapy; ICU, intensive care unit; LOS, length of stay

KEYWORDS catheter-related infections; central venous catheter; ethanol; pediatrics

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Introduction

Pediatric patients undergoing cancer treatment, who have intestinal failure, or who are critically ill may require central venous catheters (CVCs) for long-term administration of blood products, parenteral nutrition, chemotherapy, fluids, or other medications. Significant morbidity and mortality can arise from CVC infections[1] and they can have high associated institutional costs.[1,2] Incidence of CVC infections varies in the literature.[3,4] One systematic review concluded that 25% of central venous access devices (CVADs) fail (including CVAD-associated bloodstream infection, thrombosis, occlusion, blockage, dislodgement, or breakage) before completion of therapy.[5]

Several studies have examined use of antibiotic lock solutions to decrease rates of CVC infections.[6,7] However, concerns have been raised about antibiotic lock therapy possibly increasing bacterial resistance[8] as well as the challenge of penetrating biofilms created by many bacteria that cause catheter-related infections (CRIs).[9,10] Ethanol has been considered as an alternative lock solution because it penetrates these biofilms.[11,12]

Literature in adults indicate that ethanol locks decrease the number of CRIs.[13–15] The ethanol lock dwell time plays an important role, as adult intensive care unit (ICU) patients receiving only a 2-minute catheter lock with either 60% ethanol or normal saline had no difference in CRIs (3.83 vs 2.64 per 1000 catheter days; 95% CI, 0.83–2.87).[16] However, no literature comparing dwell times *in vitro* is available. In pediatric patients, several studies examine the efficacy of ethanol locks, frequently in patients with malignancy or intestinal failure requiring long-term CVC access. In a study of pediatric patients with a catheter instilled for hemodialysis, 25 patients received an antibiotic lock with clindamycin and heparin for 6 months followed by receipt of an ethanol lock for an additional 6 months. The rate of infection during the ethanol lock period was significantly lower (12% vs 44%, $p < 0.05$) than during the antibiotic lock period.[17]

A challenge with much of the literature regarding ethanol locks is the lack of consistent study design and data capture across studies, thereby limiting comparisons. Some studies use comparator solutions such as heparin or a combination of taurolidine and heparin to evaluate the efficacy of ethanol lock therapy in preventing CVC-related infection.[18,19] Other studies use a pre-post analysis, with the same patient cohort serving as their own control.[17] Similarly, studies use different endpoints, from catheter-related infections to length of stay (LOS) to catheter salvage. This review and meta-analysis is a comprehensive assessment of all comparative studies using ethanol locks in pediatric patients, independent of underlying disease state and comparator solution, and was undertaken to investigate the prevention of CVC infection and safety of ethanol locks in pediatric patients.

Methods

A systematic literature review was performed in Public/Publisher MEDLINE (PubMed; 359 studies retrieved), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 132 studies retrieved), Psychology database (PSCYInfo; 3 studies retrieved), Cochrane Library (105 studies retrieved), and Academic Search Premier (136 studies retrieved) for articles from the first available date in the database through January 21, 2022, using the following search terms: (ethanol OR ethanol lock OR lock OR locks) AND (pediatric OR child OR children OR infant) AND (catheter). Searches were limited to studies conducted in humans and published in English for which a full-text was available electronically, as well as scanned papers that were available for downloading. Studies eligible for inclusion were conducted in patients younger than 18 years with a CVAD who received ELT. Studies were excluded if they did not include pediatric patients or did not separate out data of pediatric patients from adult patients, included only neonates, or were review articles or meta-analyses. Studies with exclusively neonatal patients were excluded owing to potential for increased variability in ELT protocols as well as the variety in types of lines that are used in neonatal patients. The initial search and data extraction were conducted by 2 investigators (CMS and CR) working independently. In the event of disagreement, further discussion was conducted jointly by both investigators to resolve the conflicts. Data collected included study design, demographic data of the patients evaluated, ethanol lock protocols including ethanol concentration and dwell time, CVC-related infection rates with use of ELT, comparators against which ELT was studied, how infections were diagnosed, catheter types, adverse events documented, and effect of ELT on LOS and catheter salvage.

The 2020 PRISMA abstract checklist (BMJ 2021; 372:n71) was adhered to with the exception of conduction of a formal bias assessment. This review was not registered and no protocol was prepared. Using Review Manager 5.4, the outcomes from each study were compared by using a fixed- or random-effects model according to the heterogeneity of all included studies. If the insistency index (I^2) was >50 (indicating high heterogeneity), the random-effects model was used to interpret the results. Otherwise, the fixed-effects model was used. Funnel plots to assess publication bias were not produced because this meta-analysis involved fewer than 10 studies, which would make the funnel plots non-reliable to assess publication bias.[20] Significance was set at an alpha of 0.05.

Results

Using our search criteria, 735 studies were retrieved for review. Of these, 710 studies were excluded on the basis of the protocol's exclusion criteria: 225 did not have data pertaining to ELT, 210 were duplicates from another database, 146 studies used agents other than ethanol locks, 59 were review articles, 20 were not conducted in humans, 14 did not have outcomes related to CVC infection, 12 included data only in adults or did not delineate pediatric data, 9 were commentaries, 9 were meta-analyses, and 6 included only data on the neonatal population. This resulted in 25 studies for full-text review. Several studies were further excluded from the meta-analysis: 7 did not have a comparator group[21–27]; 4 started with patients with central line–associated bloodstream infections (CLABSIs) or catheter-associated bloodstream infection (CABSI) and assessed treatment failure[28–31]; 1 was a case series[32]; 1 examined change pre and post ELT, using data only showing median change[33]; and 2 had no measure of variation.[34,35] This left 10 studies for inclusion in the meta-analysis. Of these, 8 studies compared bloodstream infections (BSIs) pre and post initiation of ELT[36–43] and 2 compared the number of subjects with BSI on ELT against a comparator.[44,45] A flow chart illustrating the study selection process is outlined in Figure 1. Additionally, characteristics of the 10 studies included in the meta-analysis are presented in Table 1. The characteristics of the remaining 15 studies included in the review but not in the meta-analysis are presented in Table 2. Protocols for ELT for the studies included in the meta-analysis are provided in Table 3. All studies included in the meta-analysis used 70% ethanol in their protocols.

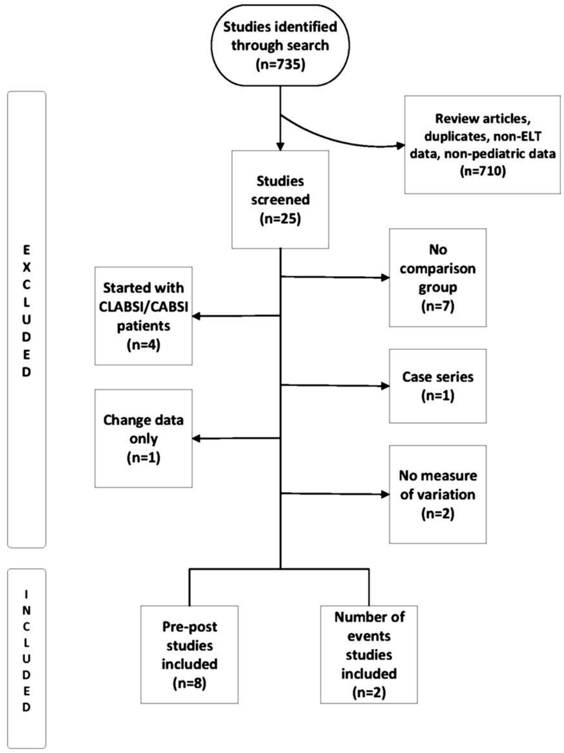
CVC Infection. Varying definitions for a BSI related to use of a central catheter were used in the studies included for review. Lopes and colleagues[45] found that ELT decreased the rate (25.86 vs 8.67 per 1000 catheter days, $p = 0.077$) and significantly decreased the number (12 vs 3, $p = 0.018$) of CLABSIs.[45] Studies by Mokha et al[41] and Jones et al[36] used an endpoint of CVC infection, finding a non–statistically significant decrease in mean CVC infections with ELT (10.39–4.59 per 1000 catheter days, p = 0.570) when compared with patients receiving heparin locks and saline flushes,[41] and a significant decrease in the rate of CVC infections after initiation of ELT (median, 9.9 [IQR, 4.4–16.0] per 1000 catheter days to 2.1 [IQR, 0.0–7.6]; p = 0.030).[36] Both Cober et al[37] and Mezoff et al[40] reported a statistically significant decrease in mean number of BSIs (8.0 ± 5.4 to 1.3 ± 3.0 per 1000 catheter days, p < 0.001 and 5.53 to 3.14 per 1000 catheter days, p < 0.015, respectively) with use of ELT compared with no ELT.

Using the endpoint of catheter-related bloodstream infections (CRBSIs), Kawano and colleagues[21] showed a nonsignificant decrease in the CRBSI rate per 1000 days after addition of prophylactic ELT (6.77 ± 2.48 vs 3.13 ± 2.80, p = 0.14) when compared with treatment with ELT alone. This is similar to the results in a study by Wales et al,[38] which demonstrated a statistically significant decrease in CRBSI rate after addition of ELT (10.2 ± 6.2 to 0.9 ± 1.8 per 1000 catheter days, p = 0.005).[38] Chiba et al[31] found that ELT prevented CRBSI in 88% of incidences; Abu-El-Haija et al[43] showed a statistically significant decrease in CRBSIs (10.3 vs 1.4 per 1000 catheter days, p = 0.02) in comparison to heparin alone. In contrast, Menkmongol and colleagues[42] showed a nonsignificant increase in CRBSI per 1000 catheter days with use of ELT (median, 5.6 vs 7; p = 0.630).

Ardura and colleagues[34] showed a statistically significant decrease in mean central catheter–associated BSI rates per 1000 catheter days (7.01 vs 0.64, p < 0.001) and per patient (2 vs 0, p = 0.004) with use of ELT compared with no ELT.[34] Pieroni et al[39] and Schoot et al[44] showed statistically significant decreases in median CABSI (9.8 vs 2.7 per 1000 catheter days, p < 0.001) and rate of CABSI with ELT compared with heparin (16 vs 29; p = 0.039; HR, 0.53; 95% CI, 0.29–0.98), respectively.

Catheter Salvage. Ardura and colleagues[34] found that, after implementation of an ELT CVC infection prevention bundle, the median number of new central catheter insertions decreased significantly (0 [range, 0–2] vs 3 [range, 0–6], p = 0.001). However, the rate of catheter repairs did not differ significantly (1 vs 1, p = 0.22). Chiba and colleagues[31] demonstrated that 84% of catheters could be salvaged with use of ELT. In a study by Jones et al,[36] catheter changes significantly decreased with use of ELT (median, 8.2 [IQR, 4.6–11.7] to 0 [IQR, 0–4.7] per 1000 catheter days; p < 0.001) compared with no ELT.[36] Wales and colleagues[38] determined that CVC replacements significantly decreased with use of ELT (5.6 ± 4.1 to 0.3 ± 0.2 per 1000 catheter days, p = 0.038); Pieroni et al[39] found a similar statistically significant decrease in CVC change rate (median, 4.3 [IQR, 0–21.7] to 1.0 [IQR, 0–8.3] per 1000 catheter days; p = 0.05). Chaudhary and colleagues[30] found a nonsignificant increased rate of catheter salvage with ELT compared with no ELT (85% vs 72%, p = 0.169). A case series by Kawano et al[21] showed a significant decrease in average rate of CVC replacements in patients receiving therapeutic vs prophylactic ELT (4.92 ± 1.30 to 1.72 ± 1.17 per 1000 catheter days, p = 0.02).[21] Mezoff et al[40] showed a statistically significant decrease in mean line perforations and breakage with use of ELT (1.8 vs 1.53, p < 0.006) as compared with patients not receiving ELT.

Figure 1. Flow chart of study process.



CABSI, catheter-associated bloodstream infection; CLABSI, central line–associated blood stream infection; ELT, ethanol lock therapy.

Contrastingly, several studies reported an increased number of catheter breakages associated with ELT. Mokha and colleagues[41] documented a statistically significantly increased mean number of breakages (4.15 vs 0.48, p = 0.006), as well as increased repairs (1.62 vs 0.27, p = 0.15) and replacements due to breakages (2.53 vs 0.37, p = 0.07) in patients receiving ELT compared with patients not receiving ELT. Lopes and colleagues[45] also reported the number of catheters broken or removed was significantly greater in patients receiving ELT (10 vs 0, p = 0.001 and 13 vs 7, p = 0.011, respectively). Cober et al[37] demonstrated a similar result, with a nonsignificant increase in mean number of repairs (5.2 ± 3.1 vs 10 ± 6.4, p = 0.200) after implementation of ELT; however, CVC replacements decreased significantly (13 vs 0, p = 0.002). Meckmongkol and colleagues[42] showed a significantly increased

Table 1. Characteristics of the 10 Full-Text Studies Included in the Meta-Analysis

Reference	Study Design	Patient Population/ Diagnosis	Age	Comparator	Sample Size	Clinical Outcome	With ELT Therapy	Without ELT Therapy	Inclusion/ Reason for Exclusion
Abu-El-Haija[43]	Retrospective review	Intestinal failure	Range, 1 day–196 mo	Pre-post	7	CRBSI per 1000 catheter days*	Median (IQR): 1.4 (0–4.3)	Median (IQR): 10.3 (6.7–24.4)	Included
Cober[37]	Retrospective review	Short-bowel syndrome or intestinal failure	Mean ± SD (range): 5.6 ± 6.9 yr (0.5–21.4)	Pre-post	15	BSI per 1000 catheter days*	Mean ± SD: 1.3 ± 3.0	Mean ± SD: 8.0 ± 5.4	Included
Jones[36]	Retrospective review	Intestinal failure	Median (IQR): 18.3 mo (11.2–31.4)	Pre-post	23	CVC infection per 1000 catheter days*	Median (IQR): 2.1 (0.0–7.6)	Median (IQR): 9.9 (4.4–16.0)	Included
Lopes[45]	Randomized clinical trial	Pediatric/neonatal ICU or pediatric surgery ward	Mean ± SD ELT: 40.4 ± 23.3 days Control: 43 ± 23.7 days	Standard protocol	ELT = 35 Non-ELT = 39	CLABSI per 1000 catheter days	8.67	25.86	Included
Meckmongkol[42]	Retrospective review	Intestinal failure	Not provided	Pre-post	19	CRBSI per 1000 catheter days	Median, 7	Median, 5.6	Included
Mezoff[40]	Retrospective review	Intestinal failure	Median (range): 6 yr (1–20)	Pre-post	22	BSI per 1000 catheter days*	Mean, 3.14	Mean, 5.53	Included
Mokha[41]	Retrospective review	Intestinal failure	Median (range): 2 yrs (2 mo–14 yr)	Pre-post	13	CVC infection per 1000 catheter days*	Mean, 4.59	Mean, 10.39	Included
Pieroni[39]	Retrospective review	Long-term parenteral nutrition	Mean (IQR): 4.3 yr (0.4–19.1)	Pre-post	14	CABSI per 1000 catheter days*	Mean, 2.7	Mean, 9.8	Included
Schoot[44]	Randomized, double-blind, multicenter	Oncology	Range: 1.0–17.9 yr	Heparin lock	ELT = 153 Non-ELT = 154	CABSI (number of events)*	16/153 (10%)	29/154 (19%)	Included
Wales[38]	Retrospective cohort	Home parenteral nutrition with at least 1 previous CRBSI	Median (IQR): 44 mo (31–129)	Pre-post	10	CRBSI per 1000 catheter days*	Mean ± SD: 0.9 ± 1.8	Mean ± SD: 10.2 ± 6.2	Included

BSI, bloodstream infection; CABSI, catheter-associated bloodstream infection; CLABSI, central line–associated bloodstream infection; CRBSI, catheter-related bloodstream infection; CVC, central venous catheter; ELT, ethanol lock therapy; ICU, intensive care unit

* Statistically significant result.

median number of catheter replacements and breakage (1 vs 0 per 1000 catheter days, p = 0.05 and 13.7 vs 0 per 1000 catheter days, p = 0.001), as well as a statistically significant increased median number of visits to the emergency room for catheter repair, with use of ELT compared with no ELT (4 vs 0, p < 0.001).

Occlusions and Thromboses. In examining pediatric patients receiving ELT in the ICU setting, Valentine[24] noted no incidence of thrombosis in either group. Similarly, Ardura and colleagues[34] showed no statistical difference in median incidence of thrombosis (0 vs 0, p = 0.250) when comparing patients prior to and after receiving ELT. Mezoff and colleagues[40] showed that patients receiving ELT had non–statistically significant decreased rates of occlusion (0.28 vs 0.56 per 1000 catheter days, p = 0.056) when compared with the same patients prior to ELT. While Chiba and colleagues[31] did not use a comparator group, they found a low rate of CVC occlusion (2%) in patients who used ELT.

Conversely, several studies showed an increased incidence of thromboses in patients using ELT. In the study of Meckmongkol and colleagues,[42] the median number of thromboses significantly increased with use of ELT (0 to 3, p = 0.003) compared to without ELT. Lopes et al[45] showed a nonsignificant increased risk of thrombosis in patients receiving ELT in comparison to those who received standard therapy (0 vs 1; RR, 2.14; 95% CI, 1.67–2.74; p = 0.946). Corroborating these data, the study of Mokha and colleagues[41] showed a nonsignificant increase in the mean number of occlusions and catheter replacements due to occlusions (0.82 to 2.94 per 1000 catheter days, p = 0.070 and 0.66 to 2.94 per 1000 catheter days, p = 0.070, respectively) with ELT compared with no ELT. Wolf and colleagues[28] similarly found that significantly more participants receiving ELT, compared with heparin, had at least 1 occlusion event (28 vs 15; RR, 1.8; 95% CI, 1.1–2.9; p = 0.012) and had a significantly shorter time to first CVC occlusion (median, 10.5 vs 62 days; p = 0.020). The ELT group had a nonsignificant increased number of CVC fractures or splits (6 vs 4; RR, 1.4; 95% CI, 0.7–6.5; p = 0.74).[28] Abu-El-Haija et al[43] also showed a nonsignificant increased risk of thrombosis (OR, 10.50; 95% CI, 0.99–1.00; p = 0.36) as well as more frequent line replacements with ELT compared with heparin, noting that 75% of the replacements were due to line breakage or thrombosis.

Length of Stay. Four studies assessed the effect of ELT on patient LOS.[26,30,33,42] Ardura and colleagues[34] reported a nonsignificant decrease in median LOS with ELT when compared to no ELT (66 days [range, 5–177] vs 12 days [range, 1–231], p = 0.130). In the prospective study of McGrath et al,[26] prophylactic ELT (administered within 36 hours of admission) resulted in a nonsignificantly shorter mean LOS when compared to ELT treatment (administered at time of positive blood culture) (124 ± 51 hours vs 208 ± 151 hours, p = 0.15). In a retrospective chart review of pediatric patients with malignancy, the LOS adjusted to that attributable to CVC infection was significantly shorter with ELT than no ELT (1.6 ± 1.5 days vs 2.9 ± 3.0 days, p = 0.018).[30] In contrast, Meckmongkol and colleagues[42] found that the median number of inpatient days for patients who received ELT was significantly longer than for those who did not (36 days [IQR, 6–60] vs 14 days [IQR, 0–26], p = 0.030).

Meta-Analysis.

Mean CVC Infections. A total of 123 subjects from 8 studies that assessed mean CVC infections prior to and after initiation of ELT met inclusion criteria for the meta-analysis. In studies where the median and range were presented, the mean and SDs were estimated by using conversion methods described by Hozo et al.[46] Using the random-effects model, Figure 2 shows a statistically significant difference (−5.79; 95% CI, −9.08 to −2.51; p <0.001), indicating that ELT is more effective in reducing CVC infections than standard of care, which was systemic antimicrobial therapy alone.

Number of CVC Infections. A total of 188 subjects on ELT and 193 subjects on comparators from 2 studies that assessed the number of CVC infections also met the inclusion criteria for the meta-analysis (Figure 1). The results of the fixed-effects model indicate a statistically significant measure of effect in favor of ELT (OR, 0.42; 95% CI, 0.23–0.75; p = 0.004), indicating a decreased likelihood of developing a CVC infection with use of ELT. Sensitivity analysis conducted by sequentially eliminating each study did not show statistical significance.

Discussion

This meta-analysis shows that use of ELT is associated with significantly fewer CVC-related infections in comparison to use of heparin locks or no prophylactic therapy. This corroborates results in prior meta-analyses in the pediatric patient population.[47–51] Uniquely, this meta-analysis includes all studies with sufficient data for analysis and does not limit by patient diagnosis, study design, or catheter type.

Several definitions for BSIs were used in the articles we included in our review and meta-analysis. Two studies using the endpoint of CVC infection found a decrease in CVC infection rate, though only one of these differences was significant.[36,41] When the definition was expanded to include BSIs, 2 additional studies showed a statistically significant decrease with use of ELT in comparison to no ELT.[37,40] One study used CRBSI as the endpoint and found a statistically significant decrease in infection rate after initiation of ELT[38]; another study using CABSI as the endpoint showed similar results.[39] The only study included in the meta-analysis that showed an increase in CVC-related infection failed to show a significant increase in CRBSI after ELT initiation.[42] This study was completed in pediatric patients with intestinal failure and did not use a consistent ELT protocol amongst patients in the study, likely because it was retrospective in nature. This study

Table 2. Characteristics of 15 Studies Included in Review but Not Included in the Meta-Analysis

Reference	Study Design	Patient Population/ Diagnosis	Age	Comparator	Sample Size	Clinical Outcome	With ELT Therapy	Without ELT Therapy	Reason for Exclusion
Blackwood[23]	Prospective study	Congenital heart defect, ESRD, SCID, intestinal failure, infection	Range: 4 mo–17 yr	None	15	Catheter salvage	N/A	N/A	No comparator group
Hess[22]	Retrospective review	Intestinal failure	N/A	None	171	Mortality	N/A	N/A	No comparator
Kawano[21]	Case series	Intestinal failure	Median (range): 67 mo (1–131)	None	4	CRBSI per 1000 catheter days	Mean ± SD: 3.13 ± 2.80	Mean ± SD: 6.77 ± 2.48	No comparator
McGrath[25]	Retrospective review	Patients with a central line and blood stream infection	Range (Mean ± SD; median): 2 mo–19 yr (6.5 ± 6.1 yr; 3.8 yr)	None	59	CLABSI eradication	N/A	N/A	No comparator group
McGrath[26]	Prospective study	Hematology/ oncology	Mean: 7.5 yr (0.8 mo–18 yr)	None	36	CRI	N/A	N/A	No comparator group
Onland[27]	Retrospective review	Various	Median (IQR): 3.9 (1.9–13.5) yrs	None	40	CRI	N/A	N/A	No comparator group
Valentine[24]	Retrospective review	Patients with a central line and blood stream infection	Mean (range): 6 mo (77 days–20 yr)	None	20	Catheter sterilization	N/A	N/A	No comparator group
Chaudhary[30]	Retrospective review	Hematologic disorders, solid tumors, leukemia, lymphoma	Mean ± SD Control: 8.2 ± 6.2 yr ELT: 9.4 ± 5.6 yr	Systemic antimicrobial therapy alone	ELT = 55 Non-ELT = 69	LOS	N/A	N/A	All CABSI patients and assessed treatment failure
Chiba[31]	Prospective multicenter study	Long-term indwelling silicone CVC and suspected CRBSI	Median (range): 9.4 yr (2–23)	None	42	CRBSI	N/A	N/A	All CABSI patients and assessed treatment failure

Table 2. Characteristics of 15 Studies Included in Review but Not Included in the Meta-Analysis *(cont.)*

Dannenberg[29]	Retrospective review	Malignant tumor	Median (range): 10.5 yr (2–18)	Systemic antimicrobial therapy alone	28	CRI	N/A	N/A	All CLABSI patients and assessed treatment failure
Wolf[28]	Parallel-design, randomized, double-blind, placebo-controlled, group-sequential, superiority trial	Cancer or hematologic disorders	Mean ± SD ELT: 8.8 ± 6.3 yr Control: 8.3 ± 6.7	Heparin lock	ELT = 48 Non-ELT = 46	CLABSI	N/A	N/A	All CLABSI patients and assessed treatment failure
Rajpurkar[32]	Case series	Hemophilia	Range, 3–13 yr	None	3	CVAD infection	N/A	N/A	Case series
Oliveira[33]	Retrospective review	Intestinal failure	N/A	Omega-3 lipid emulsion, intestinal rehabilitation program, serial transverse enteroplasty	196	Mortality due to liver failure and sepsis	N/A	N/A	Change data only
Ardura[34]	Prospective and retrospective QI analysis	Intestinal failure	Median (range): 3 yr (0.25–18)	Pre-post	24	CCABSI per 1000 catheter days	Mean, 0.64	Mean, 7.01	No measure of variation
Mouw[35]	Retrospective review	Cycled home parenteral nutrition who received ELT	Mean (range): 3.6 mo (3–27)	Pre-post	10	CRI per 1000 catheter days	Rate, 2.06	Rate, 11.15	No measure of variation

CABSI, catheter-associated bloodstream infection; CCABSI, central catheter–associated bloodstream infection; CLABSI, central line–associated bloodstream infection; CRBSI, catheter-related bloodstream infection; CRI, catheter-related infection; CVAD, central venous access device; CVC, central venous catheter; ELT, ethanol lock therapy; ESRD, end-stage renal disease; LOS, length of stay; N/A, not available; SCID, severe combined immunodeficiency; QI, quality improvement

Table 3. Ethanol Lock Protocols of Studies Included in Meta-Analysis

Reference	Catheter Type	Ethanol Concentration	Duration (dwell time)	Volume Determination	Frequency	Flush
Abu-El-Haija[43]	Single-lumen silicone CVC	70% ethanol	4 hr	1–3 mL determined by aspirating CVC until blood returned	Daily	Before and after PN with 5–10 mL NS
Cober[37]	Silicone-based CVC	70% ethanol from 98% dehydrated ethanol and sterile water	Minimum 2 hr	Between 0.1–3 mL determined by using aspiration technique until blood was noted	Daily	Before and after PN with 5–10 mL NS
Jones[36]	Silicone tunneled CVC	70% ethanol from 98% dehydrated ethanol and sterile water	Minimum 4 hr	Aspiration until blood returned; this was used as lock solution volume	3 times weekly	N/A
Lopes[45]	Single-lumen silicone CVC	70% ethanol	4 hr	1–3 mL determined by aspirating CVC until blood returned	Daily	Before and after PN with 5–10 mL NS
Meckmongkol[42]	Silicone tunneled CVC	70% ethanol	30 min–16 hr	Aspiration until blood returned; this was used as lock solution volume	Daily	N/A
Mezoff[40]	Non-polyurethane CVC	70% ethanol from 98% dehydrated alcohol	2–12 hr	N/A	N/A	Before and after ELT with at least 5 mL of NS
Mokha[41]	Single- or double-lumen silicone tunneled CVC	70% ethanol	2–4 hr	1–3 mL	Daily	Before and after PN with 5–10 mL NS
Pieroni[39]	Silicone tunneled CVC	70% ethanol	2 hr	Weight <30 kg: 1 mL Weight >30 kg: 2 mL	Weekly	Before and after ELT with 5 mL NS
Schoot[44]	Silicone tunneled CVC	70% ethanol	2 hr	1.5–3 mL	Weekly	Flushed with NS and closed with heparin
Wales[38]	Silicone tunneled CVC	70% ethanol	Minimum 4 hr	1–3 mL determined by aspirating CVC until blood returned	Daily	N/A

CVC, central venous catheter; ELT, ethanol lock therapy; N/A, non available; NS, normal saline; PN, parenteral nutrition

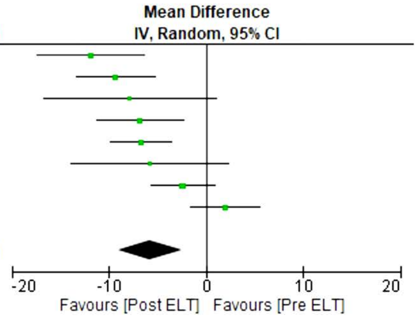
also had the longest recorded ethanol dwell times of any included study, up to 16 hours in some patients, potentially increasing the likelihood of catheter integrity compromise. ELT was also not continued if the patient had documented CRBSI.

Length of stay was assessed by 4 studies in this review, of which 3 reported a decrease in LOS after implementation of ELT compared with no or prophylactic ELT.[26,30,34] However, in 1 study the number of inpatient days was significantly longer in those who received ELT.[42] This study also showed an increase in CRBSI with ELT and subsequently concluded that the morbidity associated with ELT, combined with no improvement in CRBSIs, should encourage providers to be cautious when implementing ELT. Possible reasons for the differences in study outcome is that this study used various

Figure 2. Forest plots of mean CVC infections pre and post ELT.

	Post ELT			Pre ELT				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Abu-El-Haija 2014	1.9	3.95	7	13.8	6.26	7	11.8%	-11.90 [-17.38, -6.42]
Wales 2011	0.9	1.8	10	10.2	6.2	10	14.0%	-9.30 [-13.30, -5.30]
Pieroni 2013	3.76	6.84	14	11.62	15.49	14	7.7%	-7.86 [-16.73, 1.01]
Jones 2010	3.32	6.01	23	10.12	9.17	23	13.3%	-6.80 [-11.28, -2.32]
Cober 2011	1.3	3	15	8	5.4	15	15.2%	-6.70 [-9.83, -3.57]
Mokha 2017	4.59	8.42	13	10.39	12.29	13	8.5%	-5.80 [-13.90, 2.30]
Mezoff 2017	3.14	5.19	22	5.53	5.93	22	15.0%	-2.39 [-5.68, 0.90]
Meckmongkol 2018	7.9	7.29	19	5.92	3.12	19	14.6%	1.98 [-1.59, 5.55]
Total (95% CI)			**123**			**123**	**100.0%**	**-5.79 [-9.08, -2.51]**

Heterogeneity: Tau² = 15.95; Chi² = 29.84, df = 7 (P = 0.0001); I² = 77%
Test for overall effect: Z = 3.46 (P = 0.0005)



CVC, central venous catheter; df, degrees of freedom; ELT, ethanol lock therapy; IV, inverse variance.

ELT dwell times, ranging from 30 minutes to 16 hours, and the small sample size of 19 patients.[42]

This review also illuminates concerns about possible adverse events due to ELT. Patients receiving ELT had increased rates of CVC breakage and replacement and thrombosis compared with those not receiving ELT. In examining those studies that collected data on catheter salvage, the number of central catheter replacements and reinsertions was lower with use of ELT.[34,36,38,39] However, there were increased catheter breakages, repairs, and replacements due to said breakages in multiple studies with ELT,[37,41,45] which is corroborated by other data.[43] It is challenging to determine whether the increased rates of breakage and replacement were due to ELT because the studies did not adjust for other potential causes of CVC damage. Similarly, with the variety of protocols used in these studies, it is challenging to ascertain whether ELT was the cause, or if other facets of the protocol may have been responsible for catheter breakage or need for repair. Of note, there were no noticeable differences in time, duration, or volume of ELT amongst those that showed higher risk of catheter breakage.

Two studies showed no difference in incidence of thrombosis[24,34] and one showed decreased rates of occlusion with ELT.[40] In contrast, several studies showed an increased incidence of thrombosis in patients who used ELT.[28,40,41,45] However, in the study of Lopes et al,[45] the incidence of catheter obstruction was 1 in the ELT group compared with zero in the control, showing a low incidence of obstruction overall. This contrasts with the study conducted by Wolf et al, [28] which had a high incidence of CVC occlusion in both the ELT and placebo groups (28/48 vs 15/46, respectively). These studies defined occlusion as an event requiring thrombolytic therapy. While the clinical implications were not discussed in the analyses, it does raise concern that addition of ELT could lead to an increased risk of thrombosis that could negatively affect the patient. It is also challenging to determine if the thrombosis was exclusively due to the addition of ELT, because the incidence of thrombosis was not adjusted for any patient-specific factors in these studies. However, none of these studies documented harm to the patient because of occlusion.

Owing to the variability in definition of CVC infection, as well as the variety in ELT protocols used, it is challenging to determine the optimal protocol to decrease CVC infection and increase likelihood of bacterial eradication while reducing the risk of thrombosis and catheter breakage. Many studies also did not explicitly state the comparator group being analyzed, making it challenging to determine the potential effectiveness of ELT compared with another therapy. Additionally, many types of studies were included in this review and meta-analysis, from case series to randomized controlled trials, increasing the variability in the study procedures used. The analysis also shows significant heterogeneity, and many studies did not report adverse reactions or determine if adverse reactions seen were likely due to ELT, making it difficult to draw robust clinical conclusions regarding adverse reactions.

Conclusion

This review and meta-analysis supports the efficacy of ELT to prevent CVC-related infection in pediatric patients. Trends point toward use of a 70% ethanol solution of 1 to 3 mL for 2 to 4 hours anywhere from 3 times a week to daily. Further study is warranted to determine the optimal procedure for ethanol lock prevention and the incidence of adverse events related to use of ELT.

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