Inclusion Criteria
- Infants/Children with long term central catheters who have a history of multiple catheter-related bloodstream infections

Exclusion Criteria
- None

Critically Analyze the Evidence
The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

<table>
<thead>
<tr>
<th>Quality</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
</tr>
<tr>
<td>Low</td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
</tr>
<tr>
<td>Very Low</td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
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PICO Question 1: In children, are 70% ethanol locks compared to antibiotic locks safer and more effective for the prevention of CLABSIs?

Recommendation(s): Unable to make a recommendation due to limited evidence. (1-17)

A review of the literature found no studies that compared the use of ethanol and antibiotics locks to determine which intervention is superior. The body of evidence on antibiotic locks is limited due to few studies comparing different antibiotics to determine the most effective lock solution for the prevention of central line bloodstream infections. The use of antibiotic locks have been shown to decrease the risk of central line blood stream infections (1-9); however, there is concern for development of antibiotic resistance. (1-4,6-9) Although there is a large amount of heterogeneity, multiple meta-analyses comparing a wide variety of different antibiotic lock solutions utilizing different dwell periods have reported statistically significant reductions in the incidence of catheter related blood steam infections. (2,3,6,8,9) A meta-analysis completed in 2009, evaluated sixteen studies on the use of antibiotic locks in a mixed population including hemodialysis, oncology, and neonatal patients. For the trials on the oncology population (which were largely pediatric), the pooled results showed a borderline statistical significant benefit of antibiotic-based lock solutions (IDD, -0.52 per 1000 catheter-days; 95% CI: -1.07 - 0.02). (8) The review could not refute the possibility of the development of antibiotic resistant organisms and supported the CDC in recommending to not routinely use antibiotic lock therapy. (8) Safdar (2006) was a meta-analysis of seven trials to determine the efficacy of vancomycin (25 μg/mL) - heparin lock or flush solutions in the reduction of central line associated infections. The study reported an overall risk ratio of 0.49 (95% CI: 0.26 - 0.95; p = 0.03), indicating a significant reduction in the risk of blood stream infections for patients randomized to receive a vancomycin lock or flush solution. (6)

Studies on ethanol lock therapy are limited by their small populations and the risk of catheter thrombosis. (6,10) In a meta-analysis of four studies on the use of ethanol locks in pediatric patients, the intervention was shown to significantly reduce the risk of CRBSI by 81% (RR 0.19, 95% CI: 0.12 - 0.32; p <0.00001). (13) However, one of the studies listed in the meta-analysis described that rate of central venous access device repair for leakage/tear was found to be elevated after initiation of ethanol lock therapy (6.4 ± 10.0 vs. 3.1 ± 5.2; p = 0.2). (11) Slobbe et al. (2010) was a randomized control trial of 376 adults to evaluate the efficacy of daily ethanol locks with a fifteen minute dwell time. The study reported a non-significant reduction of catheter related blood stream infections of 41%. (17) In a retrospective cohort study of 10 pediatric patients, a 70% ethanol solution was instilled daily for a minimum dwell time of four hours. The rate of catheter related blood stream infections decreased from a mean of 10.2 ± 6.2 per 1000 catheter days to 0.9 ± 1.8 per 1000 catheter days (p = 0.005). Ethanol was discontinued in two patients due to catheter thrombosis. (16) In a randomized control trial of 64 adults, patients received either an intraluminal 70% ethanol solution or heparinized saline locks daily for a dwell time of 2 hours.

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Researchers reported that catheter associated blood stream infections were less prevalent in the treatment group (0.60/100 catheter-days) compared to the placebo group (3.11/100 catheter-days; OR = 0.18, 95% CI: 0.05 - 0.65, p = 0.008). (19)

PICO Question 2: In children, what is the effect of IV Lock Therapy on catheter integrity?

Recommendation(s):
Strong recommendation with low quality evidence that ethanol lock therapy has a negative effect on the integrity of polyurethane catheters. (11,18-20)

Strong recommendation with low quality evidence that ethanol and antibiotic lock therapy does not have a clinically significant effect on silicone catheters. (11,18-20)

Silicone catheters have primarily been used in research evaluating the effects of ethanol lock therapy due to the concern that ethanol impairs the integrity of polyurethane catheters. A retrospective study that evaluated the effect of daily 70% ethanol locks on central venous access device infections for silicone catheters, reported that the rate of central venous access device repair for leakage or tear was elevated although nonsignificant after initiation of ethanol lock therapy (6.4 ± 10.0 vs. 3.1 ± 5.2; p = 0.2). (11) Cnich et al. (2005) tested the effects of prolonged exposure to 70% ethanol on the mechanical integrity of polyetherurethane and silicone intravascular catheters. There was no significant difference found for force required to break segments, elongation, or strain for the silicone and polyetherurethane catheters at all time points. The modulus of toughness of the polyetherurethane or silicone catheters were not significantly different from controls, except for on day 21 where there was a reduction found in the silicone catheters. The study reported minimal differences in the modulus of elasticity and wall thickness for the polyetherurethane catheters. However, the researchers concluded that the effect on clinical performance of these catheters is likely to be negligible. (18) An in vitro study to assess the ultrastructural integrity and the chemical release of silicone catheters after 15 days of immersion in normal saline, 60% ethanol, or 95% ethanol at 37°C reported no difference in the observations of the internal surface of the catheters. No difference was observed in the release of silicone species from catheters between 0.5% sodium chloride solution and the 60% ethanol solution; however, there was a significant difference when catheters were immersed in 95% ethanol (p <0.01). (19) Msakni et al. (2007) evaluated the stability of Carbothane catheters after immersion in 40% ethanol, 60% ethanol, 95% ethanol, and normal saline at 37°C. The study concluded that only a 40% ethanol solution for a dwell time of 30 minutes can be considered safe for prevention of central line associated infections in carbothane dialysis catheters. (20)

PICO Question 3: In children, what are the contraindications (i.e. age, weight, diagnosis) and safety concerns for the use of ethanol and antibiotic IV lock therapy for the prevention of CLABSI?

Recommendation(s):
Consensus recommendation that antibiotic and ethanol lock therapy is contraindicated in patients receiving continuous infusions that cannot be interrupted, weigh ≤5 kg, have an allergy to ethanol or the chosen antibiotic, and/or age ≤6 months.

Consensus recommendation that ethanol lock therapy is contraindicated in patients with catheter size <2 French per lumen.

A review of the literature revealed no studies specifically investigating contraindications and safety concerns for the use of ethanol and antibiotic lock therapy. The exclusion criteria for studies evaluating the effectiveness of ethanol and antibiotic lock therapy, feedback from experts, and consensus from the multidisciplinary content expert team were utilized in making this recommendation.

PICO Question 4: In children, does ethanol or antibiotic IV lock therapy affect lab results?

Recommendation(s): Strong recommendation with low quality evidence that ethanol or antibiotic IV lock therapy does not affect lab results when proper procedure for drawing labs are followed. (6,21-24)

A meta-analysis of seven trials to evaluate the use of vancomycin (25 μg/mL) - heparin lock or flush solutions for the prevention of central line associated infections, reported no detectable antibiotic levels from two of the studies evaluated. (6) A case series of nine adults with a history of recurrent central line infections that were prophylactically given 70% ethanol lock therapy 2-7 times per week with a dwell time of 2 to 4 hours, reported that laboratory results did not change on any of the patients after beginning the intervention. (21) A randomized control trial that compared the use of gentamicin 5 mg/mL and heparin 5000 units/mL to a heparin lock placebo in adult dialysis patients found all gentamicin levels to be less than 0.2 mg/L. (22) IV antibiotic locks containing gentamicin at high concentrations (40 mg/mL) was found to result in a median predialysis gentamicin level of 2.8 mg/L while trials using IV antibiotic locks with a lower concentration of gentamicin resulted in levels less than 0.2 mg/L in a systematic review of seven studies evaluating a wide variety of antibiotic locks in adult dialysis patients. (2) In a randomized control trial of eighty-five neonates administered a vancomycin-heparin lock solution for a dwell period of 20-60 minutes per day, one patient had a detectable vancomycin level. (23) In a retrospective review of 10 children with short bowel syndrome, patients received a 70% ethanol lock during at least a portion of their “cycled off” period for home TPN. Researchers reported that one patient had two episodes of blood-culture negative DIC while on ethanol lock therapy. (24)

PICO Question 5: In children with ethanol or antibiotic IV lock therapy, what is the effect of withdrawing the agent after dwell time compared with flushing the agent on patient adverse events?
Recommendation(s): Strong recommendation with low quality evidence that IV ethanol or antibiotic locks should be aspirated and discarded after the dwell period. (11,12,14-16,21,24,25)

There were no studies found that directly compared aspirating versus flushing the IV locks after dwell periods. Multiple studies reported in their methods section the procedure used to remove the IV locks after the dwell time. (11,12,14-16,21,24,25) A retrospective review of 23 children evaluating the effect of 70% ethanol lock instilled thrice weekly on the rate of CLABSI outlined that the ethanol solution was withdrawn from the catheter and discarded after the four hour dwell period. There were no adverse event reported in this study. (13) A second retrospective cohort study of 10 children to evaluate the effect of a 70% ethanol lock administered daily for a four hour dwell period delineated that the ethanol lock solution was flushed after the dwell time. This study reported that the ethanol lock solution was discontinued in 2 of the 10 patients due to catheter thrombosis with no other adverse effects reported. (16) Saxena et al. 2006 compared the efficacy of cefotaxime-heparin locks with standard heparin locks for the prevention of catheter thrombosis and catheter associated blood stream infections. The antibiotic locks were dwelled for the interdialytic period, aspirated and discarded. There were no adverse events reported in this study. (25)

PICO Question 6: In children with ethanol or antibiotic IV lock therapy, what are the minimum, maximum, and optimal dwell times of the agent to prevent CLABSI?

Recommendation(s): Weak recommendation with low quality evidence that the suggested minimum frequency to administer IV lock therapy to prevent CLABSI is at least three times a week for a dwell time of at least two hours. (11,12,14-17,23,24)

No studies were found that directly compared the effectiveness of different dwell times for IV lock therapy in the prevention of CLABSI. Four studies administered IV ethanol locks daily for a dwell time of 2-14 hours with each study reporting a reduction in central line blood stream infections. (11,15,16,24) Of these four studies, three had a statistically significant reduction in infections with the dwell time ranging from a minimum of 2-4 hours. (11,15,16) Cober et al. (2010) administered 70% ethanol locks daily for a minimal dwell time of 2 hours in pediatric intestinal failure patients. The study found that 73% of patients remained infection free with a significant reduction in mean blood stream infection rate per 1,000 catheter days from 8.0 before ethanol lock therapy to 1.3 afterwards (p <0.01). (11) A retrospective study of ten parenteral nutrition dependent intestinal failure patients evaluated the use of 70% ethanol locks for a minimum dwell period of 4 hours. Patients began ethanol lock therapy after a total of 91 CRBSIs with a mean of 10.2 ± 6.2 per 1000 catheter days. Patients received ethanol locks for an average of 227 ± 64 days with only 3 CRBSI occurring (0.9 ± 1.8 per 1000 catheter days [p = 0.005]). (16) A randomized control trial of 376 adult patients compared the efficacy of a 70% ethanol lock to a heparin placebo in the prevention of CLABSI. Each lumen of the participants randomized to the treatment group’s CVC was locked with 70% ethanol daily for a dwell period of 15 minutes. For ethanol locks, the incidence of endoluminal CRBSIs per 1000 CVC-days was 0.7 (95% CI: 0.4 - 1.3), compared to 1.19 (95% CI: 0.7 - 1.9) for the placebo group (incidence rate-ratio, 0.59; 95% CI: 0.27 - 1.3; p = 0.19). This implied a non-significant reduction of 41% for patients treated with ethanol locks. (17) A retrospective review of 23 intestinal failure children to assess the efficacy of a thrice weekly 70% ethanol lock for a minimum dwell time of four hours reported a decrease in infection rate from 9.9 per 1000 catheter days to 2.1 per 1000 catheter days (p = 0.03). (12) The study by Pieroni et al. (2013) was a retrospective review of fourteen adult home parental nutrition patients that administered 70% ethanol locks once a week for a dwell time of two hours. The researchers found a significant decrease in infection rates from 9.8 to 2.7 CABSIs per 1000 catheter days (p <0.001) with initiation of ethanol lock therapy. (14)

In the review of the literature for IV lock therapy, most studies that evaluated the effectiveness of antibiotic locks were completed in the adult hemodialysis population with a dwell time during the interdialytic period. A randomized control trial of 85 neonates that evaluated the safety and efficacy of a vancomycin heparin lock in the prevention of CRBSIs allotted dwell times of 20 or 60 minutes for two or three times daily. The study found definite CRBSI occurred in 8 (18.8%) of the 43 neonates in the control group and none of the 42 in the vancomycin-heparin-lock group (p = 0.006). (23)

PICO Question 7: In children with ethanol or antibiotic IV lock therapy, what medications are contraindicated?

Recommendation(s): Strong recommendation with low quality evidence that ethanol lock therapy should not be used in patients receiving metronidazole. (26-29)

Strong recommendation with low quality evidence that heparin and citrate form a visible precipitate when combined with ethanol. (26-29)

Four in vitro studies explored the stability of antibiotic and ethanol lock solutions. Bastani et al. (2005) determined the stability of vancomycin 100 µg/mL and gentamicin 100 µg/mL in a 5000 units/mL heparin solution stored at 4°C for prolonged periods. The researchers found no statistical difference in the mean concentrations, bactericidal activity, and mean value of anti-Xa activity for heparin over a four week period. (24) A study by Anthony et al. (1999) tested the stability of vancomycin 500 µg/mL, cefazolin 500 µg/mL, ticarcillin-clavulanic acid 500 µg/mL, cefazidime 500 µg/mL, or ciprofloxacin 125 µg/mL combined with 100 units/mL of heparin in saline at 25 or 37°C for intervals of up to 10 days. The study found that vancomycin, cefazolin, ticarcillin-clavulanic acid, and ciprofloxacin had less than a 10% decrease in their activities after 10 days. Cefazidime was recommended to have a dwell time no longer than seven days due to a decrease in activity of 28 to 36% at seven days. (27) After testing the stability of vancomycin 10 mg/mL, cefazolin 10 mg/mL, cefazidime 10 mg/mL, and gentamicin 5 mg/mL in combination with 5000 units/mL of heparin inside polyurethane central line catheters for 72 hours, Vercaigne et al. (2000) reported a decrease in absorbance values for all antibiotic-heparin combinations (cefazolin 27.4%, vancomycin 29.7%, cefazidime 40.2%, and gentamicin 8%; p <0.001), suggesting an interaction with the catheter surface. Researchers noted that the remaining concentration of antibiotic should be sufficient to decrease the frequency of
infections associated with central venous catheters even though there was a decrease in absorbance values. The study also tested the stability of ciprofloxacin 10 mg/mL and 5000 units/mL of heparin under the same conditions and noted a visible precipitate. Another in vitro study tested the stability of 70% ethanol at 23-25°C over 14 days in bacteriostatic water and sterile water. When tested alone, at least 96% of the initial concentration of ethanol was present at 14 days. When 70% ethanol in sterile water or bacteriostatic water was combined with heparin 1000 units/mL, a visible precipitate was noted within 5 seconds. Combining 70% ethanol with 10 units/mL heparin or anticoagulant citrate solution resulted in a visible precipitate within 90 minutes.

Another in vitro study tested the stability of 70% ethanol at 23-25°C over 14 days in bacteriostatic water and sterile water. When tested alone, at least 96% of the initial concentration of ethanol was present at 14 days. When 70% ethanol in sterile water or bacteriostatic water was combined with heparin 1000 units/mL, a visible precipitate was noted within 5 seconds. Combining 70% ethanol with 10 units/mL heparin or anticoagulant citrate solution resulted in a visible precipitate within 90 minutes.

**Critical Points of Evidence**

**Evidence Supports**
- Ethanol lock therapy has a negative effect on the integrity of polyurethane catheters. *(11,18-20)* – Strong recommendation, low quality evidence
- IV ethanol or antibiotic locks should be aspirated and discarded after the dwell period. *(1,11,12,14-16,21,24,25)* – Strong recommendation, low quality evidence
- The suggested minimum frequency to administer IV lock therapy to prevent CLABSI is at least three times a week for a dwell time of at least two hours. *(11,12,14-17,23,24)* – Weak recommendation, low quality evidence
- Heparin and citrate form a visible precipitate when combined with ethanol. *(26-29)* – Strong recommendation, low quality evidence

**Evidence Against**
- Ethanol and antibiotic lock therapy does not have a clinically significant effect on silicone catheters. *(11,18-20)* – Strong recommendation, low quality evidence
- Ethanol or antibiotic IV lock therapy does not affect lab results when proper procedure for drawing labs are followed. *(2,6,21-24)* – Strong recommendation, low quality evidence
- Ethanol lock therapy should not be used in patients receiving metronidazole. *(26-29)* – Strong recommendation, low quality evidence

**Evidence Lacking/Inconclusive**
- The effectiveness for prevention of CLABSIs and safety of 70% ethanol locks compared to antibiotic locks. *(1-17)* – Unable to make a recommendation
- Antibiotic and ethanol lock therapy is contraindicated in patients receiving continuous infusions that cannot be interrupted, weigh ≤5 kg, have an allergy to ethanol or the chosen antibiotic, and/or age ≤6 months. – Consensus recommendation
- Ethanol lock therapy is contraindicated in patients with catheter size less than 2 French per lumen. – Consensus recommendation

*NOTE: The references cited represent the entire body of evidence reviewed to make each recommendation.*
Begin

Patient:
- Dependent on central venous access

Age > 6 months†
- Infusions can be stopped
- Weight > 5 kg†

No → Off Algorithm

Yes → Initiate preventative IV Lock Therapy

Off Algorithm

Call VAT Team^:
- To determine type of catheter and lumen size
- To measure lumen fill space

Polyurethane catheter**: Patient on Metronidazole (Flagyl) therapy*
- Lumen size < 2 French*

Yes → Ethanol Lock Therapy

No → Patient and physician preference

Antibiotic Lock Therapy
References


Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing External Guidelines
   - Guidelines for the Prevention of Intravascular Catheter-Related Infections, Centers for Disease Control and Prevention; Infusion Nursing Standards of Practice, Infusion Nursing Society; Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection, Infection Diseases of America; Strategies to Prevent Central Line-Associated Blood Stream Infections in Acute Care Hospitals, Agency for Healthcare Research and Quality

3. Literature Review of Relevant Evidence

4. Critically Analyze the Evidence
   - 4 meta-analyses, 7 randomized controlled trials, and 16 nonrandomized studies

5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in an IV Lock Therapy evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the diagnosis/management of IV Lock Therapy in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

Version History

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<tr>
<th>Date</th>
<th>Action</th>
<th>Comments</th>
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