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Reduction of Central Line–Associated Bloodstream Infections and Line Occlusions in Pediatric Intestinal Failure Patients Receiving Long-Term Parenteral Nutrition Using an Alternative Locking Solution, 4% Tetrasodium Ethylenediaminetetraacetic Acid

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Abstract

Background: Patients with intestinal failure (IF) are dependent on parenteral nutrition (PN), however, they are at risk of central line–associated bloodstream infections (CLABSIs) and line complications. Four-percent tetrasodium ethylenediaminetetraacetic acid (EDTA) solution is an effective nonantibiotic, antimicrobial, antibiofilm, and anticoagulant agent. Our objective was to determine 4% tetrasodium EDTA efficacy in preventing CLABSIs and reducing line occlusions in pediatric IF patients. *Methods:* We conducted a retrospective cohort study of patients managed at 2 tertiary Canadian pediatric centers between April 2016 and December 2018 who received 4% tetrasodium EDTA solution under the brand name Kitelock. Data were collected for 12 months pre and post-Kitelock. CLABSIs and alteplase administration were compared using a Wilcoxon matched-pairs signed-rank test. Data were reported as medians and frequencies. *Results:* Twenty patients were included (10 boys; median age, 83 months [range, 8–232 months]). The rate of CLABSIs before 4% tetrasodium EDTA was 2.7+4 per 1000 catheter days. Patients received 4% tetrasodium EDTA for a median of 365 (278–365) days, with no infections in the 12 months post-therapy ($P = .002$). Median rates of occlusive episodes for the entire cohort before 4% tetrasodium EDTA were 0 (0–5.0) and 0 (0–2.0) after starting therapy ($P = .018$). In patients with previous occlusions (n = 9), the median episodes of alteplase use previously was 5.5 (2.7–19.2) compared with 2.7 (0–2.7) ($P = .018$). *Conclusions:* Our preliminary findings suggest 4% tetrasodium EDTA solution is effective in reducing CLABSIs and catheter occlusions in pediatric patients with long-term central-access. (*JPEN J Parenter Enteral Nutr.* 2020;00:1–7)

Keywords

central venous catheter; central line–associated bloodstream infection; intestinal failure; parenteral nutrition; pediatrics; sepsis

Clinical Relevancy Statement

Pediatric intestinal failure (IF) is a devastating and chronic medical condition, resulting in patients requiring prolonged parenteral nutrition (PN). Patients with IF are susceptible to numerous long-term complications related to their disease management. One of the most significant challenges is related to the management of the central venous catheter, which is required to administer PN. Complications related to line blockages and central line–associated bloodstream infections are numerous and result in a cascade of other complications. Various locking solutions have been trialed in the prevention of central-line complications; however,

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there are a variety of challenges related to these solutions. A 4% tetrasodium ethylenediaminetetraacetic acid lock solution, Kitelock, has recently been approved for use in Canada in the pediatric population and is reported as an effective nonantibiotic antimicrobial, antibiofilm, and anticoagulant agent. Our early experience with Kitelock highlights its effectiveness at preventing infections and occlusions that can have a significant impact on the outcomes of patients with IF.

Introduction

Intestinal failure (IF) results when the absorption of nutrients and fluids from the intestinal tract is inadequate to support hydration, growth, and survival.[1] IF is caused by short-bowel syndrome, dysmotility disorders, or mucosal enteropathies,[2] with short-bowel syndrome being the most common cause of IF in children.[3] Although enteral autonomy is the treatment goal, if possible, patients with IF are dependent on parenteral nutrition (PN) delivered through a central venous catheter (CVC) for many months or years.

CVCs provide a route for delivery of PN and medication administration and access for repeated blood sampling. CV access is an absolute requirement for these patients; however, the presence of CVCs may result in infectious, thrombotic, and mechanical complications. Central line–associated bloodstream infections (CLABSIs) are a significant cause of morbidity and mortality in pediatric patients with IF who are PN dependent.[4,5] CLABSI is 3 times more common in pediatric patients and higher in IF patients than in those with other underlying disease processes.[6,7] CLABSIs also contribute to other complications in IF, including IF-associated liver disease (IFALD), venous thrombosis, and delayed intestinal adaptation.[4,8,9] In addition, the loss of venous access sites is an indication for intestinal-transplantation listing.[1]

Several CVC locking solutions have been used. Heparin has been the standard of care worldwide for pediatric IF patients to prevent thrombosis, but there is no data to suggest that it prevents infection.[10] In Europe, Taurolidine is commonly used and with good results.[11–13] In North America, ethanol locks have been used broadly. Ethanol locks have been successful in reducing the rate of CLABSIs in the pediatric PN-dependent and oncology population.[5,14–16] A meta-analysis published in 2012 revealed an 81% and 72% reduction in CLABSIs and catheter replacements, respectively, with daily use of 70% ethanol lock in pediatric IF patients.[7] As a result, ethanol locks have been adopted by many intestinal rehabilitation programs. There has, however, been growing concern regarding catheter patency rates with daily ethanol use because of precipitate formation at an estimated rate of 15%.[7] In addition, shortages of pharmaceutical ethanol in North America have made its availability inconsistent. In Canada, ethanol shortages were prolonged, so our intestinal rehabilitation programs began looking for an alternative option.

Recently, Health Canada approved a 4% tetrasodium ethylenediaminetetraacetic acid (EDTA) lock solution, Kitelock, to maintain patency and decrease the risk of bacterial colonization and biofilm formation within CVCs in adults. Tetrasodium salt of EDTA has been shown to disrupt in vivo and ex vivo–generated biofilms by destabilizing the structural integrity of microogranisms at the cellular level.[17,18] A randomized controlled clinical trial in adults showed significant improvement when compared with heparin, with respect to microbial colonization of CVC devices.[19] Four-percent tetrasodium EDTA solution is a clear, colorless, and sterile solution that contains no preservatives, latex, antibiotics, or ethanol and is nonpyrogenic. We began using 4% tetrasodium EDTA at our centers in 2016 and 2017, respectively. Our objective in this study was to determine 4% tetrasodium EDTA solution efficacy in the prevention of CLABSIs and line occlusions in pediatric IF patients receiving long-term PN.

Methods

We performed a retrospective crossover study of pediatric IF patients receiving home PN who were managed by a multidisciplinary intestinal rehabilitation program at either The Hospital for Sick Children in Toronto, Canada, or at McMaster Children's Hospital in Hamilton, Canada. A protocol was initiated on April 1, 2016, at both institutions. Patients receiving 4% tetrasodium EDTA solution were treated for 12 months, with the study period ending December 31, 2018. For each individual, data were collected for 12 months prior to the initiation of 4% tetrasodium EDTA solution.

Inclusion criteria included the following: (1) patients managed by the intestinal rehabilitation program at 1 of the 2 institutions listed above, (2) dependence on home PN, (3) history of >1 prior CLABSI or repeated use of alteplase for blocked or sluggish line, (4) aged <18 years, (5) presence of a tunneled CVC or peripherally inserted central catheter (PICC), (6) weight of ≥5 kg for a single-lumen catheter or ≥9 kg for a subcutaneous port, and (7) a minimum dwell time of 4 consecutive hours daily. Patients were excluded if there was a known hypersensitivity, allergy, or reaction to EDTA; a temporary CVC (jugular or femoral); severe coagulopathy; or failure to obtain consent from the patient or care provider.

Patients had 4% tetrasodium EDTA solution instilled into the CVC (1 mL for a CV line and 3 mL for a subcutaneous port-a-catheter) for 4–24 hours daily while the patient was cycled off their PN. At the completion of the dwell period, the solution was either aspirated back by the care provider and discarded or flushed through the line, and medication/PN administration was restarted. At the

initiation of the protocol, the lock solution was withdrawn from the catheter. This was changed to flushing the solution on the basis of caregiver preference and comfort. All patients continued to have their lock solution flushed throughout the observation period. The 4% tetrasodium EDTA solution therapy was performed daily, replacing the standard heparin lock or ethanol lock care.

Data collection included patient demographics, diagnosis, intestinal anatomy, frequency of CLABSIs, frequency of CVC exchanges, and pharmaceutical record of administration of alteplase. A CLABSI was defined as a positive blood culture from the CVC not related to another source of bacteremia. Data were compared by using a related-sample Wilcoxon signed-rank test. Data were reported as medians with interquartile ranges and frequencies with proportions. Infection rates and catheter replacements were adjusted per 1000 CVC days and compared preinitiation and postinitiation of 4% tetrasodium EDTA solution. Analysis was performed on the whole cohort and separately for patients who had previously received ethanol lock. An $\alpha < .05$ was considered significant.

This was an investigator-initiated study. Kitelock was provided in-kind by the manufacturer, SterileCare (Montreal, Canada), but the industry partner was not involved in study design, data analysis, or interpretation of results. The study was approved by the research ethics boards of each institution.

Table 1. Patient Characteristics (N = 20).

Age, mo	83 (11–232)
Boys, %	10 (50)
Gestational age, wk	36 (34–39)
Birth weight, kg	2.36 (2.11–3.20)
Etiology, %	
Necrotizing enterocolitisAtresia	1 (5)
Abdominal wall defect	2 (10)
Volvulus	5 (25)
Hirschsprung disease	4 (20)
Other	1 (5)
	7 (35)
PN duration, d	2251 (941–2831)
Previous use of ethanol locks, %	10 (50)
Intestinal anatomy% residual small bowel	18.5
remaining% residual large bowel	(8.5–90.5)62.5
remainingStoma present, %Gastrostomy	(9.3–100)
tube present, %Ileocecal valve resected,	6 (30)
%DysmotilitySmall-bowel bacterial	18 (90)
overgrowth	4 (22.2)
	7 (35)7 (35)
Alive, %	20 (100)
Transplant	0

Values represent status at initiation of Kitelock therapy. Values are medians with interquartile range or frequencies with percentages (%). Other etiologies: radiation enteritis and chronic intestinal pseudoobstruction.
PN, parenteral nutrition.

Results

Since the institution of a 4% tetrasodium EDTA protocol on April 1, 2016, a total of 20 patients were initiated on 4% tetrasodium EDTA lock therapy at both institutions and made up the study cohort (15 participants from The Hospital for Sick Children and 5 from McMaster Children's Hospital). There were 10 boys, with a median age of 83 months at the start of 4% tetrasodium EDTA therapy. The median gestational age was 36 weeks (34–39 weeks), with a median birth weight of 2.63 kg (2.11–3.2 kg) (Table 1).

Patient characteristics are shown in Table 1. The most common diagnosis of IF was gastroschisis (25%) and midgut volvulus (20%). The median residual percentage of small-bowel length expected for age was 18.5% (8.5%–90.5%).[20] The median number of days of PN exposure was 2251 days (941–2831 days), and 10 patients (50%) had received prior ethanol lock.

In the entire cohort of 20 patients, the rate of CLABSIs decreased from 2.7 (0–4) per 1000 CVC days to 0 (0–2.7) per 1000 CVC days ($P = .002$) after 1 year of treatment (Figure 1A). In the 12 months prior to using 4% tetrasodium EDTA lock solution, 12 patients had CLABSIs. Although most patients developed CLABSIs once within the 12 months, 1 patient had 6 CLABSIs and another had 4. Only 4 patients developed CLABSIs in the 12 months of receiving 4% tetrasodium EDTA lock solution, 3 patients developed 2 within the year, and the other patient had only the single episode. All those that developed CLABSIs while on 4% tetrasodium EDTA lock solution had a history of CLABSIs within the 12 months prior. Ten patients were receiving 70% ethanol lock solution prior to transitioning to 4% tetrasodium EDTA. For these patients, the incidence of CLABSIs decreased from 1.4 (0–4.8) per 1000 CVC days to 0 (0–1.4) per 1000 CVC days ($P = .039$) (Figure 2A). Gram-positive bacteria were more common than Gram-negative organisms, and there was 1 fungal infection in this cohort (Table 2).

Four-percent tetrasodium EDTA lock solution was associated with a median reduction in CVC occlusions in the whole cohort from 0 (0–5.0) per 1000 CVC days to 0 (0–2.0) per 1000 CVC days ($P = .018$) (Figure 1B). Five patients developed an episode of CVC occlusion while receiving 4% tetrasodium EDTA lock therapy. All were resolved with a single treatment of alteplase; none required line removal. For the subpopulation of patients (n = 10) who received previous ethanol lock therapy, the rate of occlusions decreased from 1.37 (−2.7) per 1000 CVC days to 0 (0–0.7) per 1000 CVC days but was not statistically significant ($P = .104$) (Figure 2B). The rate of occlusions in patients that had a history of occlusions requiring the use

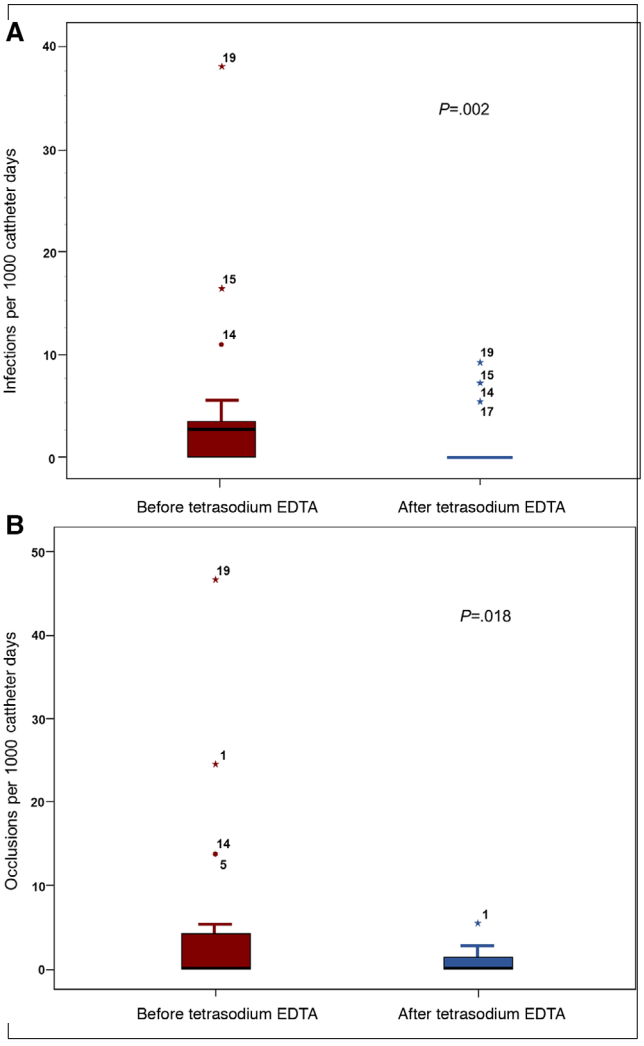

Figure 1. CLABSI and occlusion rates before and after tetrasodium EDTA therapy. (A) CLABSIs per 1000 CVC days for 12 months before and after tetrasodium EDTA therapy. (B) Occlusions per 1000 CVC days for 12 months before and after tetrasodium EDTA therapy. Wilcoxon sign-rank test for paired samples (n = 20). CVC, central venous catheter; CLABSI, central line–associated bloodstream infection; EDTA, ethylenediaminetetraacetic acid.

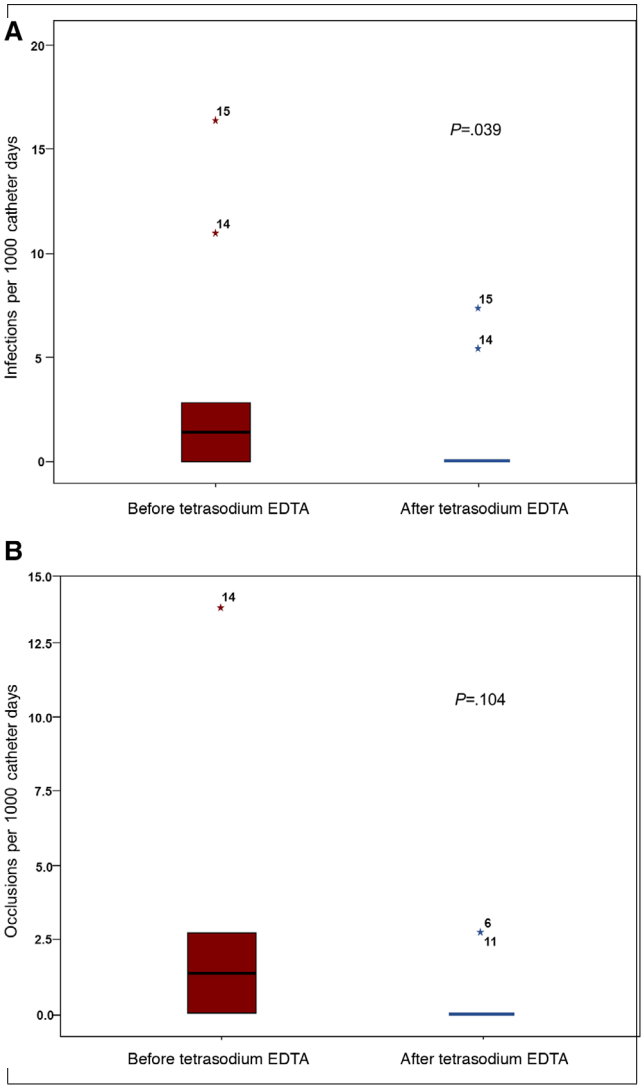

Figure 2. CLABSI and occlusion rates before and after 4% tetrasodium EDTA therapy in patients previously receiving ethanol lock. (A) CLABSIs per 1000 CVC days for 12 months before and after tetrasodium EDTA therapy. (B) Occlusions per 1000 CVC days for 12 months before and after tetrasodium EDTA therapy. Wilcoxon sign-rank test for paired samples. All patients had been receiving 70% ethanol lock therapy prior to initiation of tetrasodium EDTA (n = 20). CVC, central venous catheter; CLABSI, central line–associated bloodstream infection; EDTA, ethylenediaminetetraacetic acid.

of alteplase decreased from 5.5 (2.7–19.2) per 1000 catheter days to 2.7 (0–2.7) per 1000 catheter days ($P = .018$). The total use of alteplase before and after initiation of 4% tetrasodium EDTA lock-solution therapy was 47 compared with 7, respectively.

Overall, 4% tetrasodium EDTA lock-solution therapy was well tolerated. One patient (5%) had an adverse event that may have been attributed to the therapy. This patient developed unexplained discomfort with withdrawal of the solution from the CVC. Physical examination, biochemistry, and vascular imaging revealed no abnormality, and the therapy was discontinued. A second patient developed complications from their underlying condition, resulting in a need for uncycling of their PN with no locking period, so therapy was stopped. No other complications were reported.

Discussion

Sepsis in the pediatric population has significant implications in terms of development, morbidity, and mortality.[4,5,8]

Pediatric IF patients are at particular risk for CLABSIs, as they often have low birth weight and are relatively immunocompromised due to chronic illness and malnutrition and because of contamination of the CVC by bacteria originating from skin or the intestine via translocation through an unhealthy mucosa.[21] CLABSIs and line occlusions result in CVC removal and replacement in children with IF who have limited venous access sites.[22] Over 5 million CVCs are inserted annually in the United States, with ~400,000 CLABSIs reported annually.[23,24] This results in an attributable cost of $34,508–$56,000 USD per episode[25] and a mortality of 12%–35%.[26,27]

Sepsis is a major risk factor for IFALD in two-thirds of patients.[28] IFALD is multifactorial and results from prematurity, lack of enteral nutrition, infectious episodes, and PN composition.[14,15,28]. Diamond et al demonstrated that for every septic episode per 1000 CVC days, the odds ratio for developing advanced cholestatic liver disease (defined as a serum conjugated bilirubin > 100 umol/L) increased by 3%.[29] IFALD remains a potential cause of end-stage liver disease, and when progressive and intractable, combined liver and intestinal transplantation becomes necessary for survival. Prevention of CLABSIs in chronic PN patients is crucial, as each episode further diminishes the hepatic reserve.[30] Sepsis also has a negative association with enteral autonomy. Belza et al demonstrated in a time series analysis that for every septic event per 1000 catheter days, the hazard ratio for achieving enteral autonomy decreased by 5% in a cohort of short-bowel syndrome infants.[31]

Additionally, cytokine release associated with a systemic inflammatory response has been linked to changes in brain structure[32,33] that may result in neurodevelopmental impairment.[34] A recent study by So et al, looking at neurodevelopmental outcomes in children with IF, demonstrated a significant correlation between the number of septic episodes in the first 2 years of life and lower reported scores on the Vineland-II daily living and socialization subscales and overall adaptive learning.[8] In addition, length of hospitalization during the first 2 years of life also has been shown to correlate with lower scores in gross motor skills, daily living, and overall adaptive living.[8]

Prevention of CLABSIs is imperative, considering its impact on adaptation, liver function, quality of life, and neurocognitive outcome.[5] We adopted a 70% ethanol lock protocol in our intestinal rehabilitation program in 2009 to its desired effects as an antimicrobial and antifibrinolytic. Seventy-percent ethanol locks have been used for both the treatment and prevention of CLABSIs, with success.[7,35–38] Ethanol locks have been successful in reducing the rate of CLABSIs in the pediatric PN-dependent and oncology population.[5,14–16] In a prospective, double-blind, randomized trial, 70% ethanol-lock use compared with heparinized saline demonstrated a significant reduction in the incidence of CLABSIs,[39] and this has become the standard of care for children with recurrent CLABSIs at many institutions. However, there is a growing concern regarding catheter patency rates with daily ethanol use. Ethanol-locks (ELs) have been associated with an increase in rates of CVC occlusion, resulting in removal for noninfectious indications.[36] Occlusions have been attributed to ethanol interaction with plasma protein[40] and induction of heparin precipitation,[41] resulting in loss of critical central access, multiple invasive procedures, and missed PN administration. As mentioned above, there have also been issues with the availability of ethanol locks. In Canada, since 2016, ethanol was no longer being produced and was only available through special access. Additionally, there have been previous reports of ethanol shortages in the United States. with increased rates of infection during these periods.[42,43]

Our search for an alternative locking solution led us to 4% tetrasodium EDTA lock solution, Kitelock. This product was recently approved by Health Canada to maintain patency and decrease the risk of bacterial colonization and biofilm formation within CVCs in adults. Tetrasodium EDTA's mechanism of action is multifactorial. It chelates metal ions that are involved in the structural integrity of organisms. It is also involved in the release of cellular lipopolysaccharides and disrupts the cellular membrane of bacteria.[44] In assessment of the potential risk of systemic chelation due to administration of EDTA, the concentration of EDTA found in a single-use 3-mL vial of Kitelock catheter solution is low (1.2–3.6 mg/kg) compared with the therapeutic doses used for chelation therapy. The LD_{50} dose is 500–700 mg/kg[1], 140× greater than the Kitelock dose required for a triple-lumen venous catheter. In toxicology and safety studies in animals and humans, Kitelock demonstrated a high margin of safety. There was neither evidence of hemolytic or mutagenic effects or evidence of sensitization or skin irritation when 4% tetrasodium EDTA solution was tested.[45] In a multicenter, randomized clinical trial associated with the use of Cathasept (former name of Kitelock), there were no safety concerns and no episodes of hypocalcemia for ≤8 months in adult hemodialysis patients.[4]

Four-percent tetrasodium EDTA lock solution was well tolerated among our patient population. Initially, our protocol stipulated aspiration of the 4% tetrasodium EDTA solution 4–24 hours following its administration; however, this was a barrier to some parents, as they were not comfortable aspirating from their child's CVC unsupervised. Given the safety profile of 4% tetrasodium EDTA solution, and the fraction of dose administered to these CVCs compared with doses shown to result in chelating effects, the protocol was adapted to have parents either aspirate or flush the solution after the dwell time. This would administer a maximal dose of 3 mL of 4% tetrasodium EDTA for patients with a subcutaneous port-a-catheter and 1 mL for those with a tunneled CVC or PICC line. Patients had their

Table 2. CVC Outcomes (N = 20).

	Pre–4% tetrasodium EDTA	Post–4% tetrasodium EDTA	*P*-value
No. of CVC per 1000 CVC days	2.7 (2.7–5.2)	0 (0–2.7)	.071
CLABSI organisms			
Gram-positive[a]	19	7	
Gram-negative[b]	6	0	
Fungal	1	0	
Total	26	7	
#CLABSIs per 1000 CVC days	2.7 (0–4.0)	0 (0–0)	.002
#CLABSIs per 1000 CVC days in patients previously on ethanol locks (n = 10)	1.4 (0–4.8)	0 (0–1.4)	.039
#CVC occlusions per 1000 CVC days	0 (0–5.0)	0 (0–2.0)	.018
#CVC occlusions per 1000 CVC days in patients previously on ethanol locks (n = 10)	1.4 (0-4.8)	0 (0–0.7)	.104
#CVC occlusions per 1000 CVC days in patients with previous occlusions requiring alteplase (n = 9)	5.48 (2.7–19.2)	2.7 (0–2.7)	.018

Values are medians with interquartile ranges or frequencies with percentages (%).
CLABSI, central line–associated bloodstream infection; CVC, central venous catheter; No., number.
[a] Gram (+): Staphylococcus, Pseudomonas.
[b] Gram (−): *E. coli*, *Citrobacter freundii* complex.

serum calcium levels routinely monitored, and no concerns were identified, and no patient required an adjustment of their PN calcium requirements because of the change to flushing the 4% tetrasodium EDTA solution. No patients were removed from our study cohort because of difficulties with the use of the lock solution or concerns for the safety of its use.

Over the study period, we observed a significant reduction in the incidence of CLABSIs among pediatric IF patients previously treated with heparin, but there was also a significant reduction in those who had been receiving ethanol lock therapy immediately prior to starting 4% tetrasodium EDTA lock solution. In addition, we demonstrated a significant reduction in the occurrence of central-line occlusions among patients with 4% tetrasodium EDTA and decreased use of Alteplase.

The limitations of this study are common across many similar studies. Despite being a multicenter cohort, our study size was limited to only 20 patients. Furthermore, the population of IF pediatric patients is heterogeneous, with a relatively large range of diagnoses, patient ages, and therefore, CVC sizes. In spite of these factors, our findings showed clinical and statistical significance.

In summary, our results demonstrate a significant decrease in the number of CLABSIs after initiation of 4% tetrasodium EDTA lock solution compared with both heparin and ethanol lock therapy. This supports a superior antimicrobial effect. Furthermore, we found a significant reduction in the number of CVC occlusions when patients were on 4% tetrasodium EDTA lock therapy. Overall, these preliminary findings are promising and support 4% tetrasodium EDTA lock solution as an effective prophylactic, nonantibiotic antimicrobial lock solution for pediatric IF patients receiving long-term PN. Larger interventional studies are required.

Statement of Authorship

J, Quirt, C. Belza, Y. Avitzur, N. Pai, R.-F. Clause, and P. Wales contributed to conception and design of the research; J. Quirt, C. Belza, S. Wong-Sterling, R.-F. Clause, and F. Markovic contributed to acquisition, analysis, or interpretation of the data; J. Quirt, C. Belza, and P. Wales drafted the manuscript. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

References

1. Beath S, Pironi L, Gabe S, et al. Collaborative strategies to reduce mortality and morbidity in patients with chronic intestinal failure including those who are referred for small bowel transplantation. *Transplantation*. 2008;85(10):1378-1384.
2. Wales PW, de Silva N, Kim JH, et al. Neonatal short bowel syndrome: a cohort study. *J Pediatr Surg*. 2005;40(5):755-762.
3. Kaufman SS, Atkinson JB, Bianchi A, et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. *Pediatr Transplant*. 2001;5(2):80-87
4. Diamond IR, de Silva N, Pencharz PB, et al. Neonatal short bowel syndrome outcomes after the establishment of the first Canadian multidisciplinary intestinal rehabilitation program: preliminary experience. *J Pediatr Surg*. 2007;42(5):806-811.
5. Mouw E, Chessman K, Lesher A, et al. Use of an ethanol lock to prevent catheter-related infections in children with short bowel syndrome. *J Pediatr Surg*. 2008;43(6):1025-1029.
6. Howard L, Ashley C. Management of complications in patients receiving home parenteral nutrition. *Gastroenterology*. 2003;124(6):1651-1661.

7. Oliveira C, Nasr A, Brindle M, et al. Ethanol locks to prevent catheter-related bloodstream infections in parenteral nutrition: a meta-analysis. *Pediatrics*. 2012;129(2):318-329
8. So S, Patterson C, Gold A, et al. Neurodevelopmental outcomes of infants with intestinal failure at 12 and 26 months corrected age. *Early Hum Dev*. 2019;130:38-43.
9. Raad II, Luna M, Khalil SA, et al. The relationship between the thrombotic and infectious complications of central venous catheters. *JAMA*. 1994;271(13):1014-1016.
10. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Clin Infect Dis*. 2011;52(9):e162-e193.
11. Bisseling TM, Willems MC, Versleijen MW, et al. Taurolidine lock is highly effective in preventing catheter-related bloodstream infections in patients on home parenteral nutrition: a heparin-controlled prospective trial. *Clin Nutr*. 2010;29(4):464-846.
12. Chu HP, Brind J, Tomar R, et al. Significant reduction in central venous catheter-related bloodstream infections in children on HPN after starting treatment with taurolidine line lock. *J Pediatr Gastroenterol Nutr*. 2012;55(4):403-407.
13. Al-Amin AH, Sarveswaran J, Wood JM, et al. Efficacy of taurolidine on the prevention of catheter-related bloodstream infections in patients on home parenteral nutrition. *J Vasc Access*. 2013;14(4): 379-382.
14. Metcalf SC, Chambers ST, Pithie AD. Use of ethanol locks to prevent recurrent central line sepsis. *J Infect*. 2004;49(1):20-22.
15. Dannenberg C BU, Rothe A, Beet J, Korholz D. Ethanol-lock technique in the treatment of bloodstrem infections in pediatric oncology patients with broviac catheter. *J Pediatr Hematol Oncol*. 2003;25(8):616-621.
16. Onland W, Shin CE, Fustar S, et al. Ethanol-lock technique for persistent bacteremia of long-term intravascular devices in pediatric patients. *Arch Pediatr Adolesc Med*. 2006;160(10):1049-1053.
17. Kite P, Eastwood K, Sugden S, et al. Use of in vivo-generated biofilms from hemodialysis catheters to test the efficacy of a novel antimicrobial catheter lock for biofilm eradication in vitro. *J Clin Microbiol*. 2004;42(7):3073-3076.
18. Percival SL, Kite P, Eastwood K, et al. Tetrasodium EDTA as a novel central venous catheter lock solution against biofilm. *Infect Control Hosp Epidemiol*. 2005;26(6):515-519.
19. Kanaa M, Wright MJ, Akbani H, et al. Cathasept line lock and microbial colonization of tunneled hemodialysis catheters: a multicenter randomized controlled trial. *Am J Kidney Dis*. 2015;66(6): 1015-1023.
20. Struijs MC, Diamond IR, de Silva N, et al. Establishing norms for intestinal length in children. *J Pediatr Surg*. 2009;44(5):933-938.
21. System NNIS. National nosocomial infections surveillance system report, data summary from January 1992 through June 2004. *Am J Infect Control*. 2004;32(8):470-485.
22. Casey L, Lee K-H, Rosychuk R, et al. 10-year review of pediatric intestinal failure: clinical factors associated with outcome. *Nutr Clin Pract*. 2008;23(4):436-442.
23. Raad II, Hanna HA. Intravascular catheter-related infections: new horizons and recent advances. *Arch Intern Med*. 2002;162(8):871-878.
24. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. *Lancet Infect Dis*. 2007;7(10):645-657.
25. Zimlichman E, Henderson D, Tamir O, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med*. 2013;173(22):2039-2046.
26. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. *JAMA*. 1994;271(20):1598-1601.
27. Rello J, Ochagavia A, Sabanes E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. *Am J Respir Crit Care Med*. 2000;162(3 Pt 1):1027-1030.
28. Sondheimer JM AE, Cadnapaphornchai M. Infection and cholestasis in neonates with intestinal resection and long-term parenteral nutrition. *J Pediatr Gastroenterol Nutr*. 1998;27(2):131-137.
29. Diamond IR, de Silva NT, Tomlinson GA, et al. The role of parenteral lipids in the development of advanced intestinal failure-associated liver disease in infants: a multiple-variable analysis. *JPEN J Parenter Enteral Nutr*. 2011;35(5):596-602.
30. Hess RA, Welch KB, Brown PI, et al. Survival outcomes of pediatric intestinal failure patients: analysis of factors contributing to improved survival over the past two decades. *J Surg Res*. 2011;170(1):27-31.
31. Belza C, Fitzgerald K, de Silva N, et al. Predicting Intestinal adaptation in pediatric intestinal failure: a retrospective cohort study. *Ann Surg*. 2017.
32. Shah DK, Doyle LW, Anderson PJ, et al. Adverse neurodevelopment in preterm infants with postnatal sepsis or necrotizing enterocolitis is mediated by white matter abnormalities on magnetic resonance imaging at term. *J Pediatr*. 2008;153(2):170-5, 75.e1.
33. Lee I, Neil JJ, Huettner PC, et al. The impact of prenatal and neonatal infection on neurodevelopmental outcomes in very preterm infants. *J Perinatol*. 2014;34(10):741-747.
34. Schlapbach LJ, Aebischer M, Adams M, et al. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics*. 2011;128(2):e348.
35. Wales PW, Kosar C, Carricato M, et al. Ethanol lock therapy to reduce the incidence of catheter-related bloodstream infections in home parenteral nutrition patients with intestinal failure: preliminary experience. *J Pediatr Surg*. 2011;46(5):951-956.
36. Wolf J, Connell TG, Allison KJ, et al. Treatment and secondary prophylaxis with ethanol lock therapy for central line-associated bloodstream infection in paediatric cancer: a randomised, double-blind, controlled trial. *Lancet Infect Dis*. 2018;18(8):854-863.
37. Wolf J, Shenep JL, Clifford V, et al. Ethanol lock therapy in pediatric hematology and oncology. *Pediatr Blood Cancer*. 2013;60(1):18-25.
38. Schoot RA, van Ommen CH, Stijnen T, et al. Prevention of central venous catheter-associated bloodstream infections in paediatric oncology patients using 70% ethanol locks: A randomised controlled multicentre trial. *Eur J Cancer*. 2015;51(14):2031-2038.
39. Sanders J, Pithie A, Ganly P, et al. A prospective double-blind randomized trial comparing intraluminal ethanol with heparinized saline for the prevention of catheter-associated bloodstream infection in immunosuppressed haematology patients. *J Antimicrob Chemother*. 2008;62(4):809-915.
40. Schilcher G, Schlagenhauf A, Schneditz D, et al. Ethanol causes protein precipitation—new safety issues for catheter locking techniques. *PLoS One*. 2013;8(12):e84869.
41. Restrepo D, Laconi NS, Alcantar NA, et al. Inhibition of heparin precipitation, bacterial growth, and fungal growth with a combined isopropanol–ethanol locking solution for vascular access devices. *J Pediatr Surg*. 2015;50(3):472-477.
42. Corrigan M, Kirby DF. Impact of a national shortage of sterile ethanol on a home parenteral nutrition practice: a case series. *JPEN J Parenter Enteral Nutr*. 2012;36(4):476-480.
43. Ralls MW, Blackwood RA, Arnold MA, et al. Drug shortage-associated increase in catheter-related blood stream infection in children. *Pediatrics*. 2012;130(5):e1369-e1373.
44. Percival SL, Kite P, Eastwood K, et al. Tetrasodium EDTA as a novel central venous catheter lock solution against biofilm. *Infect Control Hosp Epidemiol*. 2005;26(6):515-519.
45. Shatnawei A, Parekh NR, Rhoda KM, et al. Intestinal failure management at the Cleveland Clinic. *Arch Surg*. 2010;145(6):521-527.