

Impact of a National Shortage of Sterile Ethanol on a Home Parenteral Nutrition Practice: A Case Series

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Abstract

Catheter-related bloodstream infection (CRBSI) is a common and life-threatening infectious complication of home parenteral nutrition (PN). CRBSI is associated with hospital admissions, morbidity, mortality, loss of venous access, and healthcare costs. Ethanol has bactericidal and fungicidal properties, making it an ideal locking solution for preventing CRBSI. The authors report 6 patients with a recurrence of CRBSI when ethanol lock (ETL) was withheld due to a national shortage. This is the first known report of the ramifications of a national ethanol shortage on redevelopment of CRBSI in home PN patients with a history of CRBSIs. This series further supports the existing literature showing that ETL is a viable therapy for the prevention of CRBSIs, warranting prospective research. The impact of an ethanol shortage due to a sole-source manufacturer supports the need for the Food and Drug Administration to regulate pharmaceutical products to avoid shortages. (*JPEN J Parenter Enteral Nutr.* 2011;36:476-480)

Keywords

ethanol lock; home parenteral nutrition; catheter-related sepsis

Clinical Relevancy Statement

Parenteral nutrition (PN) is not without risks or potential for life-threatening complications such as catheter-related bloodstream infection (CRBSI), but PN in the home setting has successfully maintained the nutrition status of patients with intestinal failure for decades. Traditional approaches to prevent CRBSIs have included selection of the catheter with the fewest number of lumens necessary, prompt removal of the catheter if no longer needed, maximal barrier precautions and aseptic technique at insertion, and caregiver education on hand hygiene during catheter maintenance.

Ethanol lock (ETL) is an emerging therapy in home PN patients with surmounting evidence proving the safety and effectiveness of this solution in preventing CRBSIs. The absence of ETL therapy due to a national shortage of sterile ethanol has led to a recurrence of CRBSIs in patients previously infection free during treatment with ETL. The effect of a national shortage of ethanol has detrimentally affected the ability of home PN programs to provide this therapy to prevent future cases of CRBSI, which affects healthcare costs and potentially influences quality of life for patients. Although this report has a small number of patients, it is an important addition to the surmounting evidence for the efficacy of ETL and the need for national regulation of PN-related drug components by the Food and Drug Administration.

Introduction

Catheter-related bloodstream infection (CRBSI) is a common and life-threatening infectious complication of home parenteral nutrition (PN). CRBSI is associated with hospital admissions, morbidity, and mortality, as well as affects healthcare costs. Efforts to decrease CRBSI include staff and patient training on catheter care, adherence to institution hand hygiene policies, maximal barrier precaution during catheter insertion, aseptic technique during catheter insertion, and removing catheters that are no longer necessary.¹ Other techniques to decrease CRBSI have been studied, and ethanol lock (ETL) is showing promising results for preventing CRBSIs in the home PN population.

Historically, ethanol was used to treat catheter occlusions caused by lipid emulsions.² More recently, ETL has been used as

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a means to avoid the main drawback of antibiotic lock, the potential for developing antibiotic resistance. Ethanol is cheap, bactericidal, and fungicidal, and it avoids concerns of resistance because alcohol denatures proteins.^{3,4} Optimal timing of ETL is thought to be immediately after a new catheter has been placed because biofilm begins to form on the internal surface of the catheter soon after placement. Although ETL is less likely to be as effective in older catheters where significant biofilm has had an opportunity to form, it may still play a role in preventing CRBSIs.

Opilla and colleagues³ studied 9 home PN patients with a crossover design using ETL. The patients had 81 CRBSIs before ETL and 9 CRBSIs after (8.3 per 1000 catheter-days vs 2.7 per 1000 catheter-days). A larger group of 31 patients on home PN at the Cleveland Clinic were studied before and after ETL. There was a statistically significant decrease in CRBSI admissions (10 per 1000 catheter-days vs 6.5 per 1000 catheter-days), showing the efficacy as well as safety of 70% ETL therapy.⁵

A retrospective review of pediatric patients requiring PN due to intestinal failure showed a decreased rate of CRBSIs from 9.9 per 1000 catheter-days to 2.1 per 1000 catheter-days after use of 70% ETL as preventative therapy.⁶ Similarly, Mouw and colleagues⁷ showed a reduction in CRBSIs (11.15 per 1000 catheter-days to 2.06 per 1000 catheter-days) in 10 pediatric patients with short bowel syndrome (SBS) using 70% ETL for prevention.

The goal of our program is to instill methods to prevent complications in patients requiring long-term PN or intravenous fluids (IVFs), especially CRBSIs, as the ramifications of infection can be not only costly but also fatal. To our knowledge, this is the first case series to report the unfortunate impact of recurrent CRBSIs in home PN patients with a past history of CRBSIs during a national ethanol shortage. Herein we report on 6 patients, 5 of whom quickly developed a CRBSI upon sudden discontinuation of ETL.

Methods

The Cleveland Clinic Home PN institutional review board–approved database was retrospectively reviewed for hospital admissions due to CRBSIs. Thirty readmissions for CRBSIs were identified. Each patient with an admission for CRBSI was reviewed for the presence or absence of ETL therapy or for recent discontinuation of ETL due to the national shortage of ethanol. Twenty-four patients with readmissions for CRBSIs were excluded because they never were prescribed ETL prior to the admission for CRBSIs. Patients with tunneled silicone catheters or implanted ports were included; patients with polyurethane catheters were excluded because ETL is not used in polyurethane catheters at our institution.

Blood cultures were drawn from both the catheter and the peripheral blood, and the organism was identified from the cultures collected. CRBSI was defined as a positive blood culture

from the catheter with the absence of infection from another source.

Of the 6 patients meeting the above criteria, the following information was also obtained from the database: age, gender, primary diagnosis, other diagnoses and past medical history, reason requiring PN or IVF, type of vascular access device, number of lumens of the vascular access device, date home PN initiated, start date of ETL, strength of ETL, date ETL held due to national shortage, date ETL resumed, dates of hospital admission for CRBSI, causative organism, past episodes of CRBSI and causative organism, and PN or IVF infusion schedule.

All 6 patients received 3 mL of 70% ETL therapy in a pre-filled syringe compounded by the homecare pharmacy. Prior to the national ETL shortage, patients were educated to instill ETL daily into the catheter after all PN or IVF infusions were completed to allow the ETL to dwell within the lumen of the catheter or the longest number of hours the PN is not infused (ie, 10–12 hours). Before starting the next cyclic PN or IVF infusion, the patient flushes the ETL through the catheter with 10 mL of 0.9% NaCl.

Case Reports

Patient 1

A 63-year-old woman with Crohn's disease had been on home PN for 22 months (starting August 10, 2010) due to malabsorption from a high-output enterostomy and an enterocutaneous fistula originating in the ileum. Her past medical history was also positive for rheumatoid arthritis, hypothyroidism, and venous thrombosis. She was started on 70% ETL after having an episode of *Enterococcus* sp CRBSI during a prior episode of home PN in 2009, and 70% ETL was also given to the patient at the reinitiation of home PN as of August 10, 2010, because of a past history of CRBSIs. The patient did not have any episodes of CRBSI until 70% ETL was held on May 2, 2011, due to a national shortage of sterile ethanol. Twelve days after the 70% ETL was discontinued, the patient was readmitted to the hospital with an *Escherichia coli* CRBSI and remained hospitalized for 6 days. The 70% ETL was resumed upon discharge home (May 20, 2011), and she has had no further episodes of CRBSIs. The patient had a single-lumen Hickman catheter during each occurrence of CRBSI.

Patient 2

A 63-year-old man with Crohn's disease had been on home PN for 24 months (starting July 15, 2009) due to SBS and malabsorption from a high-output jejunostomy after multiple surgeries for enterocutaneous fistulae. His past medical history was also positive for type 2 diabetes mellitus and venous thrombosis. After 2 episodes of CRBSI, *Malassezia furfur* fungemia in

January 2009 with a single-lumen peripherally inserted central catheter (PICC) and *Enterobacter aerogenes* in August 2009 via a double-lumen Hickman, the patient was started on 70% ETL therapy as of August 10, 2009. The patient remained free from repeated episodes of CRBSIs until 70% ETL was held on May 2, 2011, due to a national shortage of sterile ethanol. Twenty days after the 70% ETL was discontinued, the patient was readmitted to the hospital with an *Enterobacter aerogenes* CRBSI from his single-lumen Hickman and remained hospitalized for 7 days. The 70% ETL was resumed upon discharge home, and the patient has not had further episodes of CRBSIs since.

Patient 3

A 54-year-old woman with Crohn's disease had been on home PN or IVF for nearly 8 years (starting September 2003) due to SBS with a high-output ileostomy after multiple surgeries for enterocutaneous fistulae. Her past medical history was also significant for cirrhosis, gastroesophageal reflux disease, osteoporosis, asthma, iron deficiency anemia, and venous thrombosis. This patient had 14 episodes of CRBSIs (from organisms including methicillin-resistant *Staphylococcus aureus* [MRSA], *Klebsiella pneumoniae*, *Candida albicans*, *E coli*, *Enterococcus* sp, coagulase-negative staphylococcus), with the last episode of CRBSI occurring in August 2009. After 70% ETL was started in August 2009, the patient experienced a decrease in episodes of CRBSIs and had 4 occurrences (from organisms including *K pneumoniae*, *E coli*, *Candida glabrata*, and *Pseudomonas aeruginosa*). The 70% ETL was held on May 2, 2011, due to a national shortage, and 23 days later, the patient was admitted to the hospital with a CRBSI caused by MRSA and remained hospitalized for 6 days. The 70% ETL was resumed at the time of discharge, and the patient has not had another episode of CRBSI since. The patient has had multiple tunneled catheters over the years; the majority of her Hickman catheters have had 2 lumens.

Patient 4

A 30-year-old woman with Crohn's disease had been on home PN since April 2010 for SBS with malabsorption from a high-output end ileostomy. The patient's history was positive for surgical repair of enterocutaneous fistulae, reversal of diverting jejunostomy, depression, and iron deficiency anemia. After an episode of a polymicrobial CRBSI from coagulase-negative staphylococcus and *Staphylococcus epidermidis* in August 2010 with a single-lumen Hickman, the patient was initiated on 70% ETL. While hospitalized for surgical closure of a jejunostomy and off of 70% ETL while hospitalized (routine hospital protocol), in November 2010 she developed a CRBSI in her single-lumen Hickman from *Staphylococcus aureus*. The 70% ETL was resumed upon hospital discharge, and she had no other recurrence of CRBSIs. Her 70% ETL was held on May 2, 2011, due to a national shortage of

sterile ethanol, and 26 days later the patient was readmitted to the hospital with an *Staphylococcus epidermidis* CRBSI from the double-lumen Hickman, and she remained hospitalized for 7 days. The 70% ETL was resumed upon discharge home, and the patient has not had further episodes of CRBSI since.

Patient 5

A 37-year-old man with SBS due to surgery for a ruptured appendix had been on home PN since March 2011 due to malabsorption from a high-output ileostomy. The patient's history was positive for depression, seizures, and venous thrombosis. The patient was started on 70% ETL therapy after a CRBSI from *Clostridium perfringens* in March 2011; he had a single-lumen Hickman catheter. The 70% ETL was held on May 5, 2011, due to a national shortage of sterile ethanol, and the patient was readmitted to the hospital 24 days later for a CRBSI due to *E coli* and remained hospitalized for 10 days. The patient was resumed on 70% ETL as of July 12, 2011, and the patient has not had any further episodes of CRBSI.

Patient 6

A 56-year-old man with Crohn's disease had been on home PN since 2005 due to SBS and malabsorption with a high-output colostomy (25 cm of small bowel attached to 30 cm of colon). He was followed by another home PN program until his home PN management was transitioned to Cleveland Clinic on October 1, 2008. The patient's history was positive for repair of enterocutaneous fistula, osteoporosis, and PN-induced liver disease. The patient was started on 70% ETL therapy through a single-lumen Hickman upon transferring care on October 1, 2008, after having 2 CRBSIs from *Acinetobacter lwoffii* in July 2008 and an unknown species of gram-negative bacilli in August 2008. He had not had any recurrence of CRBSIs since initiation of ETL in 2008. His 70% ETL was held on April 29, 2011, due to a national shortage of sterile ethanol, and the patient was readmitted to the hospital 89 days later for a CRBSI due to *Corynebacterium* sp and remained hospitalized for 7 days. The patient was resumed on 70% ETL as of August 3, 2011, and the patient has not had any further episodes of CRBSI.

Results

Each of the 6 patients from this case series received ETL through a silicone-tunneled Hickman catheter (via either the subclavian or internal jugular vein) due to a prior history of CRBSIs. Four of the 6 patients had a single-lumen catheter at the time the CRBSI recurred, and 2 had double-lumen catheters. Each patient had a decreased incidence or no further episodes of CRBSI after initially starting on ETL.

All 6 patients had SBS and an enterostomy and were prescribed the standard dose and strength of ETL (3 mL of 70%

Table 1. Comparison of Causative CRBSI Bacteria Associated With ETL Shortage and Causative Bacteria Associated With Prior Episodes of CRBSIs

Patient	Causative Bacteria Associated With ETL Shortage CRBSIs	Prior Causative Bacteria in Episode(s) of CRBSIs
1	<i>Escherichia coli</i>	<i>Enterococcus</i> sp
2	<i>Enterobacter aerogenes</i>	<i>Enterobacter aerogenes</i> <i>Malassezia furfur</i>
3	Methicillin-resistant <i>Staphylococcus aureus</i>	Methicillin-resistant <i>Staphylococcus aureus</i> <i>Klebsiella pneumoniae</i> <i>Candida albicans</i> <i>Escherichia coli</i> <i>Enterococcus</i> sp Coagulase-negative staphylococcus <i>Candida glabrata</i> <i>Pseudomonas aeruginosa</i>
4	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus epidermidis</i> Coagulase-negative staphylococcus
5	<i>Escherichia coli</i>	<i>Clostridium perfringens</i>
6	<i>Corynebacterium</i> sp	<i>Acinetobacter lwoffii</i> Gram-negative bacilli (unknown species)

Bold font indicates the causative organism from the current episode of CRBSI and a past episode of CRBSI are the same. CRBSI, catheter-related bloodstream infection; ETL, ethanol lock.

ETL). All 6 patients required daily infusion of home PN or IVF, therefore requiring daily access of the central venous catheter. Most patients (83%) had a diagnosis of Crohn's disease, 66% had a past history of deep vein thrombosis, and 83% received PN or IVF cycled over 12 hours (1 case infused over 10 hours). Five patients (83%) were receiving PN, whereas only 1 patient was receiving IVF.

After complete withholding of ETL, 5 of the 6 patients presented with CRBSIs within 1 month (overall average of 32 days; range, 12–89 days). All of the patients were hospitalized for treatment of CRBSI, with an average hospital length of stay of 7.1 days. Table 1 lists the causative organisms for each of the new cases of CRBSI as well as the causative organisms from prior episodes of CRBSI for each of the 6 patients.

Discussion

Five of the 6 patients reported in this series had had no CRBSIs from the time of ETL initiation until discontinuation of ETL due to the national ethanol shortage. It is unclear if compliance with ETL was an issue in patient 3, as she had recurrent CRBSIs despite ETL therapy, although ETL did decrease the frequency of CRBSI episodes. There was no observed difference based on gender (3 cases male, 3 cases female), the number of lumens of the catheter, or age.

Hamilton and colleagues⁸ reported on a comparison between patients newly discharged with home PN with a fistula or stoma and those patients without a fistula or stoma and the associated complications (infectious, metabolic, or mechanical) within 90 days. The presence of an ostomy or fistula was significantly associated with having at least 1 type of

home PN-related complication. Interestingly, each of the 6 patients had SBS and an enterostomy. We suggest that patients with high-output gastrointestinal losses (enterostomy, venting percutaneous gastrostomy tubes, fistulae) and a central line for PN or IVF may be at an increased risk for CRBSIs. Future research projects may look to examine this concept further with a larger sample size, especially with the long-term home PN population. It is critical in these patients with a fistula or stoma specifically to avoid femoral-placed catheters as recommended by the Centers for Disease Control and Prevention.¹

Most patients in this report also had Crohn's disease, and we question whether patients with Crohn's disease have increased susceptibility for infection possibly from immunosuppression drug therapy treatments. Unfortunately, because of the retrospective design, we are unable to report on the past or present medical therapies for Crohn's disease in these patients with regard to timing of the CRBSIs occurred. Many of our patients seek tertiary care for colorectal surgery at our institution; however, they are treated medically for Crohn's disease by other providers, leading to incomplete records for retrospective electronic review.

Three cases of CRBSI were caused by *Enterobacter* sp, MRSA, and *Staphylococcus epidermidis*. These 3 patients "relapsed" with a new CRBSI from the same causative bacteria they had in a past episode of CRBSI when ETL was not given. Interestingly, 2 patients had an *E coli* CRBSI with the ETL shortage and previously never had a CRBSI from *E coli*. Because of the small number of cases, it is presently unclear if this is significant but nonetheless an interesting observation.

The days spent hospitalized for CRBSI have a large impact on hospital and healthcare system costs, morbidity, mortality, and arguably a potential impact on quality of life. Previous

work has estimated the cost of CRBSIs to range from \$33,000 to \$55,000 per occurrence.^{9,10} The costs associated with CRBSI admissions can possibly be decreased with the ability to provide ETL as a preventative therapy in the home setting. Prospective studies with ETL should examine not only efficacy of ETL in preventing CRBSI but also a cost-savings analysis. We suggest that prospective studies institute ETL in all home PN patients with silicone catheters prophylactically as a standard of care and compare catheter infection rates before and after ETL.

Our program attempts to reduce the use of multilumen catheters whenever possible. In long-term tunneled catheters, intraluminal hub contamination is the usual cause for CRBSIs. An inexpensive method to prevent CRBSIs is needed (with low risk for side effects, free of potential for the development of resistance, and easy for patients to use). ETL has been shown to be a promising therapy for prevention of CRBSI. Benefits of using ethanol include no concern for resistance (as in antibiotic lock therapy), low cost, and the innate bactericidal and fungicidal properties of ethanol.^{3,4} Potential side effects reported in the literature by patients are minimal and include a warm flush after instilling the ethanol lock into the catheter, a metallic taste, a feeling of dizziness, and/or nausea.

For home PN or IVF patients with a silicone catheter, the standard practice at our institution is to initiate ETL either as prophylaxis or after the initial episode of CRBSI. A dose of 3 mL of 70% ethanol is administered after cycled PN or IVF infusions are complete, allowing the solution to dwell in the lumen of the catheter for the longest number of hours that the patient is disconnected from PN or IVF (usually 12 hours) until they resume their PN or IVF infusion. The 70% ETL solution is flushed through the catheter with normal saline before resuming PN or IVF.

Conclusion

Existing literature has shown that ETL therapy can be successful in dramatically reducing CRBSIs in the home PN population.^{3,5,7,11} This novel case series is the first to report the ramifications of a national ethanol shortage on the redevelopment of CRBSIs in home PN patients with a history of prior episodes of CRBSIs. Despite the inherent limitations of case

reports, this series further supports the existing literature showing that ETL is a viable therapy for preventing CRBSIs. Although this report has a small number of patients, it is an important addition to the surmounting evidence for the efficacy of ETL. Furthermore, the impact of the shortage of ethanol due to only 1 manufacturing company within the United States producing this product supports the need for the Food and Drug Administration to regulate pharmaceutical products related to PN, especially ethanol, electrolyte additive, and trace elements, to avoid sole-supplier production and shortages.

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