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Ethanol-Lock Therapy for the Prevention of Central Venous Access Device Infections in Pediatric Patients With Intestinal Failure

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Background: Central venous access device (CVAD) infections are a major complication in pediatric patients receiving long-term parenteral nutrition (PN) and are particularly prevalent in patients with intestinal failure. This study evaluated the outcomes of outpatient ethanol-lock therapy (ELT) for the prevention of CVAD infections in children with intestinal failure. *Methods:* In this retrospective analysis, the primary outcome measure was the rate of bloodstream infection (BSI) due to CVAD infections per 1,000 catheter days, and secondary measures included type of organisms cultured and complications of ELT. *Results:* Over the course of 2 years, 15 patients received outpatient ELT. Sixty-seven percent were male; patients had a mean ± standard deviation age at enrollment of 5.6 ± 6.9 years and body weight of 19.9 ± 15.4 kg. Mean duration of ELT was 263 ± 190 days. Mean BSI rate per 1,000 catheter days significantly decreased from 8.0 before ELT to 1.3 after ELT ($P < .01$). Seventy-three percent of patients remained infection free throughout the entire study period. Adverse events potentially related to ELT included thrombosis (n = 1), difficulty withdrawing blood from the CVAD, requiring thrombolytic administration (n = 3), and repair of the CVAD for leakage/tear (n = 20). The rate of CVAD repair for leakage/tear with ELT was compared to prior rates per 1,000 catheter days and was found to be elevated after initiation of ELT (6.4 ± 10.0 vs 3.1 ± 5.2; $P = .20$). No signs and symptoms of ethanol intoxication were observed. *Conclusions:* ELT for the prevention of CVAD infections in pediatric intestinal failure patients significantly decreased BSI rates and may be used for extended periods of time in an outpatient setting. (*JPEN J Parenter Enteral Nutr.* 2011;35:67-73)

Keywords: bloodstream infections; intestinal failure; ethanol-lock therapy; parenteral nutrition; vascular access device

Infection remains the most devastating complication associated with central venous access devices (CVADs), especially with use of long-term parenteral nutrition (PN).[1] It is estimated that 250,000 to 500,000 CVAD-associated bloodstream infections (BSIs) occur annually with an estimated attributable mortality of 12% to 35% for each infection. The marginal cost to the healthcare system is $56,000 per episode, with an estimated total cost to the healthcare community of $2.3 billion annually.[2-4] In addition, length of stay is increased by up to 6 days in the intensive care unit (ICU) and by approximately 21 days in the hospital.[4]

Even for patents receiving home PN, repeated central CVAD infections dramatically affect quality of life given the need for multiple antibiotic regimens administered at home. These regimens interfere with the tasks of daily living, PN administration, work schedules, and school attendance. Pediatric patients in particular are at increased risk for CVAD infections. In many series, the risks of such infections range from 1 to 4 per 1,000 catheter days.[5-10] Such infections may significantly affect a child's morbidity and mortality. BSIs have been associated with an increased risk of hepatic injury in pediatric patients, and prevention of BSIs could potentially decrease the incidence of PN-associated liver disease, another devastating complication in this population.[11] Venous access sites are quite limited in the pediatric population, so attention should be given to the

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frequency with which CVADs are replaced because of infection.[2] In an effort to save limited access sites, CVAD salvage has been attempted in patients in stable condition with uncomplicated infections unless the causative agent mandates CVAD removal (eg, *Candida* species [spp]).[12] The most common pathogens cultured from CVAD infections are coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus* spp, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Candida* spp.[2,13]

One novel approach to the prevention of CVAD infection is ethanol-lock therapy (ELT). Similar to antibiotic-lock therapy, ELT consists of filling and closing a CVAD lumen with a solution (in this case ethanol) to prevent or treat CVAD-related infections. Recent studies have shown a benefit from ELT in treating and preventing CVAD infections.[14-18] However, less is known about the efficacy in children, particularly those with intestinal failure, the population at highest risk of VAD infections.[19-22] One study suggested efficacy in this group,[16] and our aim was to retrospectively review the charts of 15 patients in the University of Michigan Children's Intestinal Rehabilitation Program with either short bowel syndrome (SBS) or medical intestinal failure (IF) who had received outpatient ELT for the prevention of CVAD infections from July 2006 to April 2008. Our aim was both to assess ELT efficacy and determine how well this treatment could be used in an outpatient setting and what potential adverse events may occur with its use.

Methods

Inclusion and Exclusion Criteria

This was a retrospective chart review of 15 patients cared for in the University of Michigan Children's Intestinal Rehabilitation Program from July 2006 to April 2008. Institutional review board approval was obtained before initiation of the study. We included: (1) patients younger than 25 years receiving outpatient ELT; (2) patients weighing ≥5 kg; (3) patients with silicone-based CVAD with determined CVAD volume; and (4) high-risk patients, defined as having any 1 of the following 3 criteria: (a) of 2 previous CVADs replaced because of infection in the previous 18 months; (b) 2 previous infections in current CVAD that failed to clear with a full antibiotic course or were associated with the development of antibiotic resistance (eg, vancomycin-resistant enterococcus); or (c) limited remaining CVAD access. We excluded patients 25 years or older and those weighing <5 kg.

Ethanol Formulation

Similar to the concentration used for the removal of lipid precipitate in previous studies, a 70% ethanol-lock solution was administered daily while the patient's CVAD was not in use, primarily while cycled off PN, with a minimum dwell time of 2 hours. The solution[23,24] was made from 98% dehydrated ethanol and sterile water for injection. This solution was given a 9-day stability according to United States Pharmacopeia Chapter 797 guidelines.[25,26] Given the incompatibility of 70% ELT with either citrate or heparin, the CVAD was flushed before and after administration of PN or other medications with 5 to 10 mL normal saline.[25] The ethanol-lock solution was withdrawn after the initial dose to avoid introducing bacteria into the patient's body after disruption of the biofilm. Ethanol was also routinely withdrawn from the CVAD daily thereafter to prevent potential intoxication in pediatric patients.

Technique

All CVADs treated with ethanol lock were constructed of silicone because of the potential weakening of polyurethane VADs by a 70% ethanol-lock solution.[27] In addition, the luminal volume of each CVAD was measured to minimize systemic exposure of ethanol in the patient. This measurement was determined by using a 3-mL syringe filled with 1 mL normal saline and drawing back the syringe plunger until the first drop of blood was present in the syringe. The patient's CVAD volume was the final volume present in the syringe minus 1 mL (initial starting volume). To ensure complete coverage of the CVAD with 70% ethanol-lock solution, a 0.1-mL overage was added to all CVAD volumes for patients weighing <15 kg, and a 0.2-mL overage was added to all CVAD volumes for patients weighing ≥15 kg. The determined CVAD volume plus the overage was considered the patient's ethanol-lock solution volume. To ensure safety in the exposure of children to ethanol toxicity, a grid was developed (Table 1) to determine the maximum theoretical blood level of ethanol that would occur if the child received the full volume of ethanol lock. This allowed us to target a safety margin whereby the ethanol-lock volume would never exceed that of a blood serum level of 0.04% or one-half of an anticipated intoxication dosage (0.08%).

Definition of CVAD Infection

Using the Centers for Disease Control and Prevention 2002 guidelines,[28] a CVAD infection was defined as a patient demonstrating systemic symptoms, including fever, tachycardia, hypotension, and/or rigors. In addition to demonstrating these symptoms, patients had to have a

Table 1. Estimated Blood Ethanol Level If Ethanol-Lock Infused Into Patient

Volume of Ethanol Lock, mL	Patient Weight, kg									
	2.5	5	10	15	20	30	40	50	60	70
0.1	0.035	0.0175	0.00875	0.005833	0.004375	0.002917	0.002188	0.00175	0.001458	0.00125
0.2	*0.07*	0.035	0.0175	0.011667	0.00875	0.005833	0.004375	0.0035	0.002917	0.0025
0.3	**0.1050**	*0.0525*	0.0263	0.0175	0.0131	0.0088	0.0066	0.0053	0.0044	0.0038
0.4	**0.1400**	*0.0700*	0.0350	0.0233	0.0175	0.0117	0.0088	0.0070	0.0058	0.0050
0.5	**0.1750**	**0.0875**	*0.0438*	0.0292	0.0219	0.0146	0.0109	0.0088	0.0073	0.0063
0.6	**0.2100**	**0.1050**	*0.0525*	0.0350	0.0263	0.0175	0.0131	0.0105	0.0088	0.0075
0.7	**0.2450**	**0.1225**	*0.0613*	*0.0408*	0.0306	0.0204	0.0153	0.0123	0.0102	0.0088
0.8	**0.2800**	**0.1400**	*0.0700*	*0.0467*	0.0350	0.0233	0.0175	0.0140	0.0117	0.0100
0.9	**0.3150**	**0.1575**	*0.0788*	*0.0525*	0.0394	0.0263	0.0197	0.0158	0.0131	0.0113
1.0	**0.3500**	**0.1750**	**0.0875**	*0.0583*	*0.0438*	0.0292	0.0219	0.0175	0.0146	0.0125
1.1	**0.3850**	**0.1925**	**0.0963**	*0.0642*	*0.0481*	0.0321	0.0241	0.0193	0.0160	0.0138
1.2	**0.4200**	**0.2100**	**0.1050**	*0.0700*	*0.0525*	0.0350	0.0263	0.0210	0.0175	0.0150
1.3	**0.4550**	**0.2275**	**0.1138**	*0.0758*	*0.0569*	0.0379	0.0284	0.0228	0.0190	0.0163
1.4	**0.4900**	**0.2450**	**0.1225**	**0.0817**	*0.0613*	*0.0408*	0.0306	0.0245	0.0204	0.0175
1.5	**0.5250**	**0.2625**	**0.1313**	**0.0875**	*0.0656*	*0.0438*	0.0328	0.0263	0.0219	0.0188
1.6	**0.5600**	**0.2800**	**0.1400**	**0.0933**	*0.0700*	*0.0467*	0.0350	0.0280	0.0233	0.0200
1.7	**0.5950**	**0.2975**	**0.1488**	**0.0992**	*0.0744*	*0.0496*	0.0372	0.0298	0.0248	0.0213
1.8	**0.6300**	**0.3150**	**0.1575**	**0.1050**	*0.0788*	*0.0525*	0.0394	0.0315	0.0263	0.0225
1.9	**0.6650**	**0.3325**	**0.1663**	**0.1108**	**0.0831**	*0.0554*	*0.0416*	0.0333	0.0277	0.0238
2.0	**0.7000**	**0.3500**	**0.1750**	**0.1167**	**0.0875**	*0.0583*	*0.0438*	0.0350	0.0292	0.0250
2.1	**0.7350**	**0.3675**	**0.1838**	**0.1225**	**0.0919**	*0.0613*	*0.0459*	0.0368	0.0306	0.0263
2.2	**0.7700**	**0.3850**	**0.1925**	**0.1283**	**0.0963**	*0.0642*	*0.0481*	0.0385	0.0321	0.0275
2.3	**0.8050**	**0.4025**	**0.2013**	**0.1342**	**0.1006**	*0.0671*	*0.0503*	*0.0403*	0.0335	0.0288
2.4	**0.8400**	**0.4200**	**0.2100**	**0.1400**	**0.1050**	*0.0700*	*0.0525*	*0.0420*	0.0350	0.0300
2.5	**0.8750**	**0.4375**	**0.2188**	**0.1458**	**0.1094**	*0.0729*	*0.0547*	*0.0438*	0.0365	0.0313
2.6	**0.9100**	**0.4550**	**0.2275**	**0.1517**	**0.1138**	*0.0758*	*0.0569*	*0.0455*	0.0379	0.0325
2.7	**0.9450**	**0.4725**	**0.2363**	**0.1575**	**0.1181**	*0.0788*	*0.0591*	*0.0473*	0.0394	0.0338
2.8	**0.9800**	**0.4900**	**0.2450**	**0.1633**	**0.1225**	**0.0817**	*0.0613*	*0.0490*	*0.0408*	0.0350
2.9	**1.0150**	**0.5075**	**0.2538**	**0.1692**	**0.1269**	**0.0846**	*0.0634*	*0.0508*	*0.0423*	0.0363
3.0	**1.0500**	**0.5250**	**0.2625**	**0.1750**	**0.1313**	**0.0875**	*0.0656*	*0.0525*	*0.0438*	0.0375

Table shows estimated blood ethanol level based on using 70% ethanol, the weight of the patient, and estimated blood volume of 80 mL/kg. Boldface type indicates intoxicated ≥ 0.08. Italic type indicates at least half of the intoxicated level.

positive blood culture obtained from a peripheral vein and/or the CVAD (after removal of the ethanol-lock solution). Other sources of septicemia (eg, urologic, pulmonary) were excluded as possible sources of the positive BSI.

Statistics

Results are reported as mean ± standard deviation (SD). Data were analyzed for statistical differences using either an unpaired *t* test or χ^2 analysis. Statistical significance was determined by a P value < .05.

Results

Fifteen patients with a mean age of 5.6 years and mean weight of 19.9 kg at initiation of ELT received outpatient ELT from July 2006 to April 2008. Duration of ELT ranged from 23 to 652 days, with a mean duration of 263 days. Patient demographics are listed in Table 2.

Seventy-three percent of patients remained infection free throughout the entire study period. A statistically significant decrease in the mean number of BSIs per 1,000 catheter days was observed in our patient population, 8.0 before ELT vs 1.3 post-ELT (P < .001) (Tables 3 and 4).

Table 2. Patient Demographics

Characteristic	
Male, % (n)	67 (10)
Age, y, mean ± SD (range)	5.6 ± 6.9 (0.5–21.4)
Weight at initiation of ELT, kg, mean ± SD (range)	19.9 ± 15.4 (5.9–52.6)
Medical diagnosis, % (n)	
Short bowel syndrome	87 (13)
Medical intestinal failure	13 (2)
Type of CVAD, n	
Single-lumen tunneled VAD	13
Double-lumen tunneled VAD	1
Subcutaneous port	1
Volume of ELT, mL, mean ± SD (range)	0.49 ± 0.26 (0.2–1)
Duration of ELT, d, mean ± SD (range)	263 ± 190 (23–652)

CVAD, central venous access device; ELT, ethanol-lock therapy; SD, standard deviation; VAD, venous access device.

Table 3. Outcome of Ethanol-Lock Therapy (ELT)

	Pre-ELT	Post-ELT	*P* Value
No. of infections in 6 mo, mean ± SD (range)	1.9 ± 1.5 (0–6)	0	<.001
No. of infections in 12 mo, mean ± SD (range)[a]	2.9 ± 2 (0–7)	0.2 ± 0.5 (0–2)	<.001
Bloodstream infection rate, mean/1,000 catheter days ± SD (range)	8.0 ± 5.4 (0–19.2)	1.3 ± 3.0 (0–10.6)	<.001
Life-threatening CVAD infection, % (n)	47 (7)	0 (0)	.015
Antibiotic-lock therapy, % (n)	33 (5)	0 (0)	.037
Fungal infection, % (n)	33 (5)	0 (0)	.037
Vancomycin-resistant enterococcus infection, % (n)	27 (4)	0 (0)	.059
CVAD replacements, % (n)	87 (13)	0 (0)	.002
Repair of CVAD for leakage/disruption, mean/1,000 catheter days ± SD (range)	3.1 ± 5.2 (0–16.4)	6.4 ± 10 (0–31.9)	.200

CVAD, central venous access device; SD, standard deviation.
[a]Organisms listed in Table 4.

Four patients developed at least 1 BSIs after ELT therapy (3 patients with 1 infection, 1 patient with 2 infections). All 5 infections were either *Staphylococcus aureus* (n = 3) or *S epidermidis* (n = 2). Two additional patients experienced tunneled-site infections that required antibiotic therapy. None of these 4 patients required an ICU admission, nor did any require removal of their CVAD. In addition, although one third of our patients suffered from fungal CVAD infections before ELT, no infections were noted after ELT was started. No catheters were replaced because of a BSI. Seven catheters were removed during the course of the study; this included 3 because of CVAD malfunction, 2 because they were no longer needed, and 4 for other reasons.

Adverse events observed in the study included the development of a deep vein thrombosis in 1 patient, which required treatment with a 3-month course of enoxaparin. The thrombosis occurred in the same leg as the CVAD, which was removed and replaced. Ethanol lock was not discontinued in this patient. Three families complained of difficulty withdrawing the ethanol-lock solution; however, complaints were intermittent in nature. Families occasionally required that the ethanol be injected systemically to clear the line, and all of these families noted resolution of line blockage with the use of intraluminal instillation of a thrombolytic agent. Interestingly, 20 occurrences of CVAD leakages or disruption were identified in 7 patients. Disruption occurred in either one or both of the layers of the silastic tubing. Each required a repair of the CVAD. Although high, the incidence of CVAD repair for leakage or disruption per 1,000 catheter days was not significantly different than that noted before initiation of ELT therapy (Table 3). Although ethanol levels were not obtained in our group, no signs or symptoms of intoxication were observed in any the patient.

Discussion

CVAD infections are a devastating complication of long-term central venous access, especially with PN use. These infections are particularly problematic for pediatric patients, who have limited sites available for central venous access.[28] Prevention of CVAD infections is important in

Table 4. Organisms Associated With Bloodstream Infection (BSI)

	Pre-ELT[a]	Post-ELT
Gram-positive organism (n)	*Staphylococcus epidermidis* (14; 9 methicillin-resistant) *Enterococcus faecalis* (9) Vancomycin-resistant enterococci (2) α-hemolytic streptococci (1) *Bacillus cereus* (1) *Enterococcus faecium* (1) *Kocuria kristinae* (1) *Staphylococcus aureus* (1) *Staphylococcus* spp (1)	*Staphylococcus aureus* (3; 1 methicillin-resistant) *Staphylococcus epidermidis* (2; 2 methicillin-resistant)
Gram-negative organism (n)	*Klebsiella pneumoniae* (7) *Citrobacter* spp (2) *Escherichia coli* (2) *Acinetobacter baumannii* (1) *Enterobacter cloacae* (1) *Klebsiella oxytoca* (1) *Morganella morganii* (1) *Stenotrophomonas maltophilia* (1)	None observed
Other organism (n)	*Candida albicans* (4) *Candida parapsilosis* (2) Species not documented (1)[b]	None observed

spp, species.
[a]Organisms associated with BSI in 12 months before initiation of ethanol-lock therapy.
[b]Infection occurred outside hospital.

conserving central venous access sites, decreasing life-threatening infections, and optimizing quality of life in pediatric patients. ELT has been beneficial in various pediatric patient populations[14-16] and in adult PN[18] and immunocompromised patients.[17] Unlike antimicrobial locks (eg, vancomycin, gentamicin), ELT is not dependent on antimicrobial sensitivity of the organism. Thus, a potential advantage is to decrease the use of repeated courses of antimicrobial therapy and prevent resistant organisms from infecting or colonizing the patient. The prevention of these resistant organisms may also reduce the use of broad-spectrum antibiotics.[29] This may be of particular value for infections with multiresistant organisms. A 70% ethanol-lock solution is adequate for treatment or prevention of infection because an ethanol concentration >40% inhibits bacterial growth in established biofilms. A 70% ethanol-lock solution must dwell in the CVAD for a minimum of 2 hours to be effective.[30] However, the 2009 update of the Infectious Diseases Society of America's guidelines for the management of intravascular catheter-related infection[31] continues to recommend antibiotic-lock therapy as a viable option to manage patients with catheter-related infection. In regard to use of ethanol lock, these guidelines state, "At this time, there are insufficient data to recommend an ethanol lock for the treatment of catheter-related bloodstream infection."[31] Unfortunately, these guidelines only reference 1 current retrospective study[15] that examined ethanol lock in pediatric patients, despite the publication of several other studies and case reports on this topic.

In addition, in patients requiring CVADs because of intestinal disorders such as SBS and IF, BSIs and secondary colonization of the CVAD are often considered to be the result of bacterial translocation of gram-negative, anaerobic organisms from the small and large intestines.[32,33] In fact, this was observed in our patients before ELT, whereas only gram-positive, aerobic organisms associated with skin flora were observed after ELT (Table 4). ELT seems to be effective in preventing these commonly observed infections and colonization.

In our 15 patients, we found a daily 70% ELT regimen to be effective in the prevention of CVAD infections. Seventy-three percent of patients remained infection free throughout the study period, with a statistically significant reduction in BSIs per 1,000 catheter days. Four patients experienced 5 CVAD infections consisting of either *S aureus* or *S epidermidis*, both of which are known to be difficult to eradicate from CVADs because of the creation of an extensive biofilm layer.[34] Interestingly, no CVAD had to be replaced during the study period because of an infection. Other groups have found success with the intermittent use of ELT (eg, every other day).[18] Whether a reduced frequency of ELT would be as efficacious remains to be determined in this group of pediatric patients.

Given the unclear nature of the long-term effects of daily ethanol exposure to pediatric patients, the decision

was made to withdraw the ethanol-lock solution from the CVAD each day to limit ethanol exposure.[35] For this reason, each patient's CVAD volume was measured before initiation of therapy, with a small overage volume added to ensure complete coverage of the CVAD. This procedure is extremely important in pediatric patients, who are undergoing active neurological development.

Our findings should also educate providers of ELT about the potential risk of weakening the CVAD. We observed an increase in the need to repair CVADs for leakages and disruptions to the external catheter while patients were receiving daily ELT, although this increase was not statistically significant. Ethanol is known to weaken silicone CVADs and is not recommended in polyurethane CVADs, given the risk of complete disruption of the CVAD.[27] This increase was observed most often in the younger patients (<3 years), and this may be attributable to stresses placed on the external portion of the catheter, which can be subjected to extensive wear and tear (eg, patient pulling on the catheter, catheter becoming caught on other items). Further, the thinner and smaller luminal size of these CVADs in young infants may lead to increased risk of weakening the catheter than occurs older children.

Use of a daily 70% ELT for the prevention of CVAD infections was effective and safe in 15 outpatients in the University of Michigan Children's Intestinal Rehabilitation Program. ELT has been shown to be a promising alternative to antimicrobial-lock therapy for the prevention of CVAD infections. One of the potential shortcomings of this report is its retrospective nature. A prospective, randomized controlled trial is needed to further assess the effectiveness and safety of daily ELT in pediatric patients for the prevention of CVAD infections.

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