Ethanol-Lock Technique for Persistent Bacteremia of Long-term Intravascular Devices in Pediatric Patients

Wes Onland, MD; Cathy E. Shin, MD; Stana Fustar, RN, CRNI; Teresa Rushing, PharmD, BCPS; Wing-Yen Wong, MD

Objectives: To use the ethanol-lock technique (in conjunction with systemic antibiotics) to salvage central lines from removal and to prevent persistence of catheter-related infections among pediatric patients with long-term intravascular devices.

Design: Medical records of patients treated with ethanol locks were retrospectively reviewed from June 1, 2004, through June 22, 2005.

Setting: Childrens Hospital Los Angeles, Los Angeles, Calif, a tertiary care pediatric hospital.

Patients: Forty children with diverse underlying disorders were treated for 51 catheter-related infections using the Childrens Hospital Los Angeles ethanol-lock technique.

Interventions: Eligible infected central lines were instilled with a dose volume of 0.8 to 1.4 mL of 70% ethanol into the catheter lumen during 12 to 24 hours and then withdrawn. The volume of ethanol used was based on the type of intravascular device.

Main Outcome Measures: Clearance of infection and incidence of recurrence.

Results: Of the 51 ethanol-lock treatments in 40 children, no catheters were removed because of persistent infection. Eighty-eight percent (45/51) of the treated episodes cleared without recurrence (defined as a relapse within 30 days with the same pathogen). Twelve (75%) of 16 polymicrobial isolates and 33 (94%) of 35 monomicrobial isolates were successfully treated. There were no adverse reactions or adverse effects reported.

Conclusion: This retrospective study supports the use of the ethanol-lock technique in conjunction with systemic antibiotics as an effective and safe method to retain the use of a previously infected central venous catheter, decrease the need for line removal, and eradicate persistent pathogens in catheter-related infections.

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Long-term intravascular devices (IVDs) are crucial for the care of children requiring chemotherapy, apheresis, parenteral nutrition, frequent transfusion of blood products, or prolonged intravenous medications. However, catheter-related infections (CRIs) are a major complication of IVDs, necessitating removal and replacement when venous access sites are severely limited. Most nosocomial bloodstream infections in pediatric patients are related to the use of an IVD. Bacterial colonization of the catheter hub and lumen is a significant problem in patients with long-term IVDs, leading to increased patient morbidity, costs and length of hospitalization, and mortality in critically ill patients. The incidence of IVD-related infection ranges from 3% to 60%, with a rate of 0.2 to 2.4 infections per 1000 catheter-days. Repeated replacement of IVDs should be prevented because of the added cost of care, the delay in therapy, and the problem of limited access sites, especially in young children. To salvage infected IVDs, several methods of prophylaxis or treatment have been developed, such as antibiotic locks with or without anticoagulation agents or antiseptic chamber–containing hubs, with variable success. Dannenberg et al used ethanol locks in oncology patients with CRIs, in conjunction with systemic antibiotics. To our knowledge, there have been no other reports on the use of ethanol-lock techniques for the treatment of CRIs. The ethanol-lock technique was introduced at Childrens Hospital Los Angeles, Los Angeles, Calif, in early 2004. In this study, we report our experience with the ethanol-lock technique, as an adjunctive therapy to systemic antibiotics, to intraluminally...
disinfect and salvage long-term IVDs among children with CRIs.

**METHODS**

A retrospective review of patients’ medical records and pharmacy dispensing records of ethanol locks from June 1, 2004, through June 22, 2005, was undertaken after appropriate approval from the Childrens Hospital Los Angeles Institutional Review Board. Catheter-related infections were as defined by the Centers for Disease Control and Prevention.12 No concomitant peripheral blood cultures were obtained.

Eligibility criteria for ethanol-lock treatment included age older than 6 months, a patent lumen before initiation of ethanol locks, a negative history of allergy to ethanol, and persistence of positive blood cultures (persistent positive blood cultures after 48 hours’ administration of appropriate intravenous antimicrobial therapy) or incidence of multiple CRIs. Only silicone catheters qualified for ethanol-lock procedures.

The instilled ethanol lock had to dwell for 12 to 24 hours in a single-lumen IVD. After this period, the ethanol lock was withdrawn and discarded, followed by an isotonic sodium chloride solution flush. This procedure was repeated for 5 consecutive days. A separate peripheral line was placed for infusion. During the next 24 hours, the other lumen was locked with ethanol, while the first lumen was used for infusions. Both lumens were alternately treated for 10 days. Any adverse effects of the treatment were documented. Details of the ethanol-lock procedure are summarized in Table 1.

**RESULTS**

Data from 51 ethanol-lock treatments on 40 patients and 42 catheters were analyzed. Two patients received a second IVD of the same type that they previously had, and in both cases the catheter was removed after a CRI that was not treated with ethanol locks. The patients’ characteristics are summarized in Table 2. There were more boys than girls. The median age was 3.9 years (age range, 1.9-13.5 years). Solid tumors accounted for 38% (15/40) of the underlying diagnoses. Other diagnoses included severe immunocompromise after bone marrow or
small-bowel transplantation (23% [9/40]) and gastrointestinal disorders requiring long-term dependence on parenteral nutrition associated with short-bowel syndrome, pseudo-obstruction syndrome, or microvillous inclusion syndrome (23% [9/40]). Most of the 42 catheters were Hickman catheters (40% [17/42]), followed by Broviac catheters (26% [11/42]) and Port-A-Cath catheters (21% [9/42]).

Among the 40 patients, 34 were treated once with ethanol locks, 5 were treated twice, and 1 received the therapy 7 times during the study period. We registered 3863 catheter-days in 40 patients from the day of insertion (or the previous CRI not treated with ethanol locks) until the date of the first positive CRI, an infection rate of 10 per 1000 catheter-days. The total number of catheter-days among 42 catheters was 8054 days, with an infection rate of 6.3 per 1000 catheter-days (Table 2). The distribution of catheter-days from insertion to the first CRI (median, 34.5 catheter-days [interquartile range, 16-85 catheter-days] and the total catheter-days (median, 126.5 catheter-days [interquartile range, 70-258 catheter-days]) were not normally divided.

**Table 3** lists the organisms isolated. Monomicrobial culture was isolated in 69% of the CRIs. Gram-positive organisms accounted for 57% of 51 infections; 35% of them were coagulase-negative staphylococci. Polymicrobial isolates grew in 16 CRIs (31%); 1 CRI (2%) was a mixed culture of yeast and bacteria. In 38% of the polymicrobial isolates, there were more than 2 different bacteria. More gram-negative isolates grew out of the polymicrobial cultures (49%) than out of the monomicrobial cultures.

All of the IVDs treated with ethanol locks were successfully retained and used. Five of the catheters were later removed when patients ended their chemotherapy or before allogeneic bone marrow transplantation, as standard practice. All of these removals occurred after 30 days (Table 4). One of the patients died of disease progression unrelated to a CRI.

In 6 cases, bacteremia recurred within 30 days with the same pathogen (Table 5). These recurrences occurred in 3 patients and comprised 4 different polymicrobial isolates in the first CRIs that recurred in the subsequent CRIs. In patient 8 in Table 5, the pathogen (Klebsiella pneumoniae) recurred twice with different pathogens in a polymicrobial isolate.

Ethanol-lock treatments were well tolerated in all children. No adverse effects were reported.

**COMMENT**

Infection of long-term IVDs results from invasion of organisms present at insertion sites, contaminated infusates, hematogenous seeding of the catheter tips, and contamination of the hubs, the hubs being the most common site of CRIs. Microorganisms causing CRIs are en-
countered in 2 forms, the planktonic free-floating form and the sessile form, with bacteria embedded in a biofilm. In most cases, the planktonic free-floating form can effectively be eradicated by appropriate systemic antibiotics. The sessile form poses a significant and often persistent problem. Bacteria adherent to implanted medical devices or damaged tissue can cause persistent infections by forming a biofilm. These bacteria encase themselves in a hydrated matrix of polysaccharide and protein, causing their inherent resistance to antibiotic therapy, neutrophil function, phagocytes, and antibodies. Another part of this biofilm that is composed of host-derived glycoproteins, such as fibrinogen, fibronectin, collagen, and laminin, enhances bacterial adherence to foreign material. Susceptibility tests using in vitro biofilm models have shown survival of bacterial biofilms after treatment with antibiotics at concentrations hundreds of times (or even 1000 times) the minimum inhibitory concentration of the bacteria measured in a suspension culture.

We performed a retrospective review of the efficacy and safety of ethanol locks as an adjunctive therapy to systemic antibiotics in persistent CRIs among children with long-term IVDs. Ethanol is an effective disinfectant against a broad range of microorganisms, including bacteria and fungi. Two hours of exposure to 70% ethanol is required to kill established biofilms of gram-positive bacteria, gram-negative bacilli, and Candida species in vitro. The number of infections in our study period per 1000 catheter-days (6.3 infections) is higher than that reported in the study by Dannenberg et al. This is probably because 5 of the 42 catheters were inserted before the beginning of the study period, and these catheter-days without CRIs were excluded in the analyses. Other reasons may include our inclusion of younger and sicker children, different groups of underlying illnesses, and various types of catheters at high risk for CRIs. To minimize venipunctures in these children with significant venous access difficulties, no peripheral blood cultures were obtained. Cultures of blood samples, drawn from an indwelling IVD, were assessed in a study by Martinez et al. The positive predictive value of IVD and peripheral blood cultures was low (63% and 73%, respectively) and required clinical interpretation and conformation; however, the negative predictive values were 99% and 98%, respectively, obviating the need for a concomitant separate peripheral blood culture.

None of the catheters treated with ethanol were removed, and 45 (88%) of the 51 CRIs showed no recurrence within 30 days with the same pathogen. Of the recurrences in 3 patients (Table 5), patient 6 had methicillin-resistant Staphylococcus aureus at the time of the catheter insertion. After the recurrence of methicillin-resistant S aureus in patient 6, ethanol locks were not instilled and the IVD was removed. Patient 7, with stage IV neuroblastoma requiring intensive chemotherapy, had a recurrence of coagulase-negative staphylococci 27 days after the first CRI, which was treated with ethanol locks, and a second recurrence 29 days after the first recurrence. Patient 8, with 3 recurrences in 7 CRIs, had short-bowel syndrome and was dependent on parenteral nutrition. Five of the 7 CRIs were treated with ethanol locks for a second or third time, with good effect. The IVDs in patients 2 and 3 were not removed. Because this was a retrospective review, we could not evaluate the DNA type of each pathogen and whether the CRI was localized intraluminally.

Coagulase-negative staphylococci, S aureus, aerobic gram-negative bacilli, and Candida albicans are most commonly associated with CRIs. We found equal numbers of the different bacteria but also found a considerable amount of polymicrobial isolates, constituting 49% of the gram-negative bacteria grown, and a mixed bacterial and fungal isolate. Of the polymicrobial isolates, 75% (12/16) did not show a recurrence, and of the 35 monomicrobial isolates, 94% (33/35) were successfully treated. The treatments of 2 yeast isolates were also successful.

Despite the limitations of this retrospective study, our results suggest that using the ethanol-lock technique for persistent CRIs in children with long-term IVDs is effective in salvaging the line, with a low rate of recurrences. It is a safe, well-tolerated, and low-cost method, without risks of inducing multiresistant bacteria. A prospective, randomized, double-blind trial comparing the ethanol-lock technique with placebo and the alternatives would be needed to determine the best method to treat persistent CRIs.

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Correspondence: Wing-Yen Wong, MD, Division of Hematology-Oncology, Childrens Hospital Los Angeles, 4650 Sunset Blvd, Mail Stop 54, Los Angeles, CA 90027 (wwong@chla.usc.edu).
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Table 5. Recurrence Within 30 Days With the Same Pathogen in 3 Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Interval Between CRIs, d</th>
<th>Pathogen of First CRI</th>
<th>Pathogen of Subsequent CRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>19</td>
<td>MRSA</td>
<td>MRSA†</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>CNS</td>
<td>CNS</td>
</tr>
<tr>
<td>8</td>
<td>30†</td>
<td>Serratia marcescens†</td>
<td>S marcescens</td>
</tr>
<tr>
<td>17</td>
<td>K pneumonia†</td>
<td>K pneumonia†</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CNS, coagulase-negative staphylococci; CRI, catheter-related infection; MRSA, methicillin-resistant Staphylococcus aureus.

*At the subsequent CRI, no ethanol locks were used, and the intravascular device was removed.
†In polymicrobial isolate.
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REFERENCES