TITLE: ANTIBIOTIC (ALT) AND ETHANOL (ELT) LOCK THERAPY FOR THE MANAGEMENT OF CENTRAL VENOUS CATHETER-RELATED INFECTIONS

GUIDELINES:

Antibiotic lock therapy (ALT) and ethanol lock therapy (ELT) are options in the management of central venous catheter-related infections. These therapies should never be used as monotherapy treatment of active infections, and specific criteria regarding patient eligibility, pharmacy preparation, and nursing management are presented. It is the responsibility of the ordering practitioner to verify that the patient meets all criteria for use.

PURPOSE:

To develop guidelines for the use of antibiotic lock therapy and ethanol lock therapy in the treatment and prevention of catheter-related infections in adult and pediatric patients.

APPLICABILITY:

Prescribers, nurses, and pharmacists

PROCEDURE:

Background
The use of central venous catheters (CVC) has increased dramatically in recent years. As use has increased, so has the rate of catheter-related infections. Infection remains one of the most devastating complications associated with vascular access devices, especially with long-term total parenteral nutrition (TPN) use.\(^1\) CVCs are expensive and difficult to implant and remove, and vascular access sites may be limited, especially in the pediatric population.\(^2\) ALT and ELT have been proposed as means of managing catheter-related infection.

ALT involves instilling an antibiotic solution into a catheter hub and allowing the solution to dwell for a set period of time. The goal of the therapy is to eradicate organisms from an infected line and to prevent colonization of a sterile line. Several antibiotics, with or without heparin, have been suggested for use in ALT therapy. Due to the role of host proteins such as fibrin, fibrinogen, and fibronectin as adhesins in the catheter lumen, heparin may be a beneficial additive in such therapies.\(^4\) The main concern of using heparin in ALT is drug stability. Large concentrations of heparin used in ALT can lead to inadvertent systemic heparinization, especially in the pediatric population. In addition, heparin must not be used in patients with a history of heparin-induced thrombocytopenia (HIT), or who have an active hypocoagulable state. As such, formulations are provided which
do (and do not) contain heparin (Table 1) (note: ethanol is INCOMPATIBLE with heparin).

Similar to ALT, ELT consists of filling and closing a catheter lumen with an ethanol solution to prevent or treat catheter-related infections. The advantages of ethanol lock therapy include the prevention/eradication of colonization of the offending organism irrespective of the sensitivity of the organisms to an antibiotic. A 70% ethanol-lock is adequate for prevention of infection because an ethanol concentration above 40% is able to inhibit bacterial growth in established biofilms. However, a 70% ethanol-lock must dwell in the catheter for a minimum of 2 hours in order to be effective. A recent retrospective study involving pediatric hematology-oncology patients showed a benefit from ethanol-lock therapy in treating and preventing CVC infections. Most patients in the study received one five-day course of lock therapy. However, one patient received seven courses safely, and a case in the literature cites the successful and safe use of lock therapy for three years in a TPN-dependent patient.

For inadvertent push administrations or extravasations of these lock solutions, please review Nursing Management section of this policy or the NYP Treatment of Intravenous Infiltrations and Extravasations Policy.

1. For inpatients at NewYork-Presbyterian, use of ALT/ELT requires approval from the Infectious Diseases (ID) service.

2. ALT/ELT is NOT recommended as monotherapy for active systemic infection. ALT/ELT is not intended for concurrent or sequential therapy. As such, three scenarios for their use is intended:
   a. For active infection, concurrent with systemic antibiotics. The data for this scenario is mostly derived from small, uncontrolled, observational trials utilizing a variety of different antibiotic solutions in patients receiving TPN. As such, no definitive conclusions regarding efficacy can be made at this time.
   b. As “mop-up” therapy in patients with CVC-associated infection, but in whom replacement of line is not feasible. Lock therapy in these patients is intended to increase the likelihood that the line will be eradicated of organism colonization.
   c. Preventative therapy in patients with recurrent CVC-associated infection. Such therapy may in some cases be long-term (even life-long). Although TPN-dependent patients are the most common candidates for preventative therapy, most of the data is derived from studies in hematology/oncology patients. In addition, most of these studies did not use lock solutions per se, but rather antibiotic flushes.

3. The lock may be performed by a RN or at home by the patient or caregiver that has demonstrated competency in line care. It must be ordered by a physician or other authorized prescriber.
4. Patient candidate criteria:
   a. General lock therapy eligibility
      1. Patients who have experienced multiple bacterial infections of their central line within a short period of time OR
      2. Patients in whom replacement of infected CVC is not feasible.

   1. ELT
      a. Patients age $\geq 6$ months OR if $< 6$ months, must be $\geq 6$ kg, have normal hepatic function tests, and be inpatient during the course of ethanol treatment.
      b. Negative history of allergy to ethanol.
      c. Patient has not received oral or IV: metronidazole (Flagyl®, 48 hours), disulfiram (Antabuse®, 7 days), isoniazid (Nydrazid®, 24 hours) previously within the designated hours. These agents interact with alcohol and cause severe nausea and vomiting and are therefore contraindicated when alcohol is being administered.
      d. Patients whose catheter hardware is NOT composed of polyurethane (see #6 below)

   2. ALT
      a. Patients without documented allergies to requested antibiotics.
      b. If heparin is to be used, patient must not have history of heparin-induced thrombocytopenia (HIT) or have an active hypocoagulable state.

5. Lock therapy should be initiated and instilled without dwell disruption for the duration of the therapy. It should not be used as a flush/lock solution concurrently when the central line is being accessed for multiple daily doses of intravenous medications because the patient could receive multiple doses of ethanol/antibiotic.
   b. If patient has a single lumen catheter or port, another line (peripheral or PICC) may need to be placed for IV antibiotic courses.
   c. If patient has a double lumen catheter, the lock solution can be placed in one lumen for 24 hours while the other lumen is used for infusions. During the next 24-hour period, the other lumen can be locked with an lock solution “dwell” while first lumen is used for infusions.

6. Type of catheter
   a. ELT: The PICCs currently utilized at NYP are manufactured by Bard Access Systems. These catheters are made of polyurethane, and there have been reports of catheter breaking and cracking when exposed to ethanol. **As such, ELT will be utilized ONLY when the catheter/port hardware that will be exposed to ethanol is not**
composed of polyurethane (unless proven compatible). The most common alternate material is silicone. **It is the responsibility of the ordering practitioner to verify that the catheter hardware is not composed of polyurethane.**

b. ALT: Hickman, Groshong, Mahukar, Hohn, Broviac, Percath, Mediport, Port-a-Cath, and PICCs
   1. Data suggests that ALT is less effective in treating infections in implantable ports than in infections in other types of CVCs.4
   2. Only intraluminal infections are candidates for lock therapy, since lock therapy would be ineffective in extraluminal infection.

7. Recommended ALT formulations (Table 1):

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Anticoagulant</th>
<th>Dwell Time</th>
<th>Chemical Stability</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (1 mg/mL)</td>
<td>Heparin (100 units/mL)</td>
<td>≥ 24 hours</td>
<td></td>
<td>Robinson JL, et al. JAC 2005.</td>
</tr>
<tr>
<td>Vancomycin (1 mg/mL)</td>
<td>None</td>
<td>≥ 24 hours</td>
<td></td>
<td>Domingo P, et al. CID 1999.</td>
</tr>
<tr>
<td>Cefazolin (5 mg/mL)</td>
<td>Heparin (2500 units/mL)</td>
<td>≥ 72 hours</td>
<td></td>
<td>Krishnasami Z, et al. Kidney Int 2002.</td>
</tr>
<tr>
<td>Gentamicin (1 mg/mL)</td>
<td>Heparin (2500 units/mL)</td>
<td>≥ 72 hours</td>
<td></td>
<td>Krishnasami Z, et al. Kidney Int 2002.</td>
</tr>
<tr>
<td>Gentamicin (5 mg/mL)</td>
<td>None</td>
<td>≥ 12 hours</td>
<td>↓ 39%/8-12h</td>
<td>Benoit JL, et al. CID 1995.</td>
</tr>
<tr>
<td>Amikacin (1mg/mL)</td>
<td>None</td>
<td>≥ 24 hours</td>
<td></td>
<td>Domingo P, et al. CID 1999.</td>
</tr>
<tr>
<td>Vanc (2.5 mg/mL) + Gent (1 mg/mL)</td>
<td>Heparin (2500 units/mL)</td>
<td>≥ 72 hours</td>
<td></td>
<td>Krishnasami Z, et al. Kidney Int 2002.</td>
</tr>
<tr>
<td>Cefaz (5 mg/mL) + Gent (1 mg/mL)</td>
<td>Heparin (2500 units/mL)</td>
<td>≥ 72 hours</td>
<td></td>
<td>Krishnasami Z, et al. Kidney Int 2002.</td>
</tr>
</tbody>
</table>
8. Catheter volumes and dosages

a. Doses are determined by the catheter volume with a maximum volume of 5 mL. In general, the literature is consistent in recommending 2 to 5 mL lock volumes in adult patients on ALT. In these patients, if the catheter volume cannot be determined, it appears appropriate to approximate.

<table>
<thead>
<tr>
<th>ALT catheter volumes</th>
<th>Patient &lt; 10 kg</th>
<th>Weight 10 – 30 kg</th>
<th>Patient &gt; 30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-tunneled Central Venous Catheter (i.e. PICC, Subclavian, Triple lumen)</td>
<td>2 mL</td>
<td>3 mL</td>
<td>3 mL</td>
</tr>
<tr>
<td>Tunneled Central Venous Catheter (i.e. Broviac, Hickman)</td>
<td>3 mL</td>
<td>3 mL</td>
<td>5 mL</td>
</tr>
</tbody>
</table>

b. ELT volumes should be more precisely determined, if possible, with a maximum volume of 2 mL. Please recall that ELT should not be used in patient’s age < 6 months, unless the patient weighs ≥ 6 kg.

<table>
<thead>
<tr>
<th>ELT catheter volumes</th>
<th>Dose Volume (mL)</th>
<th>Maximum volume to be dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-lumen Tunneled Catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broviac 4.2 Fr (ID 0.7 mm)</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>Broviac 6.6 Fr (ID 1 mm)</td>
<td>0.8</td>
<td>2</td>
</tr>
<tr>
<td>Medcomp Catheter</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>Double-lumen Tunneled Catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hickman Double Lumen 7 Fr Distal (red) (ID 1 mm)</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>Hickman Double Lumen 9 Fr Proximal (white) (ID 0.7 mm)</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td>Medcomp 8 F or 10 F</td>
<td>1.2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Port-A-Cath</strong></td>
<td><strong>2</strong></td>
<td></td>
</tr>
<tr>
<td>Any port</td>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>
Physician Ordering:
1. ELT
   a. The practitioner will write an order for ELT denoting the exact volume and duration of each dwell of 74% ethanol solution to be instilled into the catheter.
      i. Example Order: “ETHANOL-LOCK THERAPY - Please instill ___ mL of 74% ethanol solution into the patient’s catheter lumen after TPN is cycled off. Withdraw the ethanol solution prior to administration of other medications or reinitiation of TPN. Flush before and after with 5 mL of normal saline.”
      ii. When writing TPN for patients on the ethanol-lock, the practitioner will delete the heparin from the TPN to avoid possible incompatibility issues.
      iii. The practitioner will also verify that the catheter material is compatible with ethanol.
2. ALT
   a. The practitioner will write an order for ALT denoting the specific solution requested the exact volume of solution to be instilled into the catheter, duration of each dwell, and the number of dwells per day.
      i. Example Order: “ANTIBIOTIC-LOCK THERAPY- Please instill ___ mL of ____solution into the patient’s catheter lumen in between antibiotic infusions. Withdraw the antibiotic solution prior to administration of other medications. Flush before and after with 5mL of normal saline.”

Pharmacy Preparation and Dispensing:
1. ELT
   a. Ethanol lock solutions will be compounded and dispensed daily.
   b. A standing order will be used to enter the ethanol-lock solution on to the patient’s profile.
   c. Pharmacy will prepare a single use syringe of 74% ethanol with 24 hour expiration for each patient. (74% ethanol solution – 74 percent ethanol solution (ethyl alcohol) per instructions below:

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>COMPOUNDING INSTRUCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>98% dehydrated Alcohol</td>
<td>1. Obtain a 12 mL empty sterile syringe</td>
</tr>
<tr>
<td>0.9% Sodium Chloride for Inj</td>
<td>2. Draw up 3 mL (from 1- 5 mL amp) dehydrated ethyl alcohol with a filter needle</td>
</tr>
<tr>
<td>(preservative free)</td>
<td>3. Using a 3 mL syringe, draw up 1mL of preservative-free 0.9% Sodium Chloride for Inj. Add this to the 3 mL ethyl alcohol (in the 12 mL syringe).</td>
</tr>
<tr>
<td>To make: 4 mL 74% ethyl alcohol</td>
<td></td>
</tr>
</tbody>
</table>
d. Deliver the ethanol-lock for the exact volume prescribed, up to 2 mL.
e. Label: “For central venous catheter lock use only. Do not infuse into patient. Do not use with heparin flush.”
f. Expiration: 24 hours.

2. ALT
   a. Antibiotic lock solutions will be compounded and dispensed daily
   b. A standing order will be used to enter the antibiotic-lock solution on to the patient’s profile.
   c. Pharmacy will prepare 5 mL of the solution in 12 mL syringes and send the syringe(s) to the floor each day. One 12 mL syringe with 5mL of antibiotic lock solution will be sent for each dwell time. Syringes will be labeled with 24 hour expiration.
   d. Label: “For catheter lock use only. Do not infuse into patient. Do not use if precipitate seen. Call pharmacy”
   e. Expiration: 24 hours.
   f. Specific pharmacy compounding instructions as follows:

<table>
<thead>
<tr>
<th>Antibiotic Final Concentration (total quantity 5mL)</th>
<th>Pharmacy Preparation</th>
</tr>
</thead>
</table>
| Vancomycin (1 mg/mL) + Heparin (100 units/mL)     | 1. Dilute 500 mg vancomycin product with 10mL NS (50 mg/mL).  
  2. Using 3 mL syringe, transfer 1 mL of 50 mg/mL vancomycin into 50 mL NS bag. Draw back syringe and flush into bag to ensure maximum transfer of drug.  
  3. Using another 3 mL syringe, take 1 mL of 5000 units/mL heparin product and transfer into the NS bag.  
  4. Using 12 mL syringe, draw out 5 mL of finished solution. |
| Vancomycin (1 mg/mL)                               | 1. Dilute 500 mg vancomycin product with 10 mL NS (50 mg/mL).  
  2. Using 3 mL syringe, transfer 1 mL of 50 mg/mL vancomycin into 50 mL NS bag.  
  3. Draw back syringe and flush into bag to ensure maximum transfer of drug.  
  4. Using 12 mL syringe, draw out 5 mL of finished solution. |
| Cefazolin (5 mg/mL) + Heparin (2500 units/mL)      | 1. Dilute 500 mg cefazolin product with 10 mL NS (50 mg/mL).  
  2. Using 1 mL syringe, withdraw 0.5 mL solution, and transfer into 12 mL syringe.  
  3. Add 2.5 mL of 5000 units/mL heparin product.  
  4. QS to 5 mL with NS. |
Cefazolin (10 mg/mL)  
1. Dilute 500 mg cefazolin product with 10 mL NS (50 mg/mL).
2. Using 12 mL syringe, withdraw 1 mL of 50 mg/mL cefazolin solution.
3. QS to 5 mL with NS.

Gentamicin (1 mg/mL) + Heparin (2500 units/mL)  
1. Using 10 mg/mL (2 mL) pediatric product, withdraw 0.5 mL (5 mg) in a 1 mL syringe, and transfer this to 12 mL syringe.
2. Add 2.5 mL of 5000 units/mL heparin product.
3. QS to 5 mL with NS.

Gentamicin (5 mg/mL)  
1. Using 10 mg/mL (2 mL) pediatric product, withdraw 2.5 mL in a 12 mL syringe.
2. Add 2.5 mL of NS to obtain 5 mL of a concentration of 5 mg/mL.

Amikacin (1 mg/mL)  
1. Using 250 mg/mL 2 mL product, withdraw 100 mg (0.4 mL) using a 1 mL syringe.
2. Transfer to 100 mL NS bag to obtain a final concentration of 1 mg/mL.
3. Draw out 5 mL and place in 12 mL syringe.

Vancomycin (2.5 mg/mL) + Gentamicin (1 mg/mL) + Heparin (2500 units/mL)  
1. Dilute 500 mg vancomycin product with 10 mL NS (50 mg/mL).
2. Using 12 mL syringe, transfer 5 mL (250 mg) to a 50 mL NS bag.
3. Using a 3 mL syringe, withdraw 2.5 mL of this solution, and transfer to a 12 mL syringe.
4. Using a 1 mL syringe, withdraw 0.5 mL (5 mg) of gentamicin 10 mg/mL product, and place into 12 mL syringe.
5. Add 2.5 mL of 5000 units/mL heparin product.

Cefazolin (5 mg/mL) + Gentamicin (1 mg/mL) + Heparin (2500 units/mL)  
1. Dilute 500 mg cefazolin product with 10 mL NS (50 mg/mL).
2. Using a 1 mL syringe, withdraw 0.5 mL (25 mg) and transfer to a 12 mL syringe.
3. Using a 1 mL syringe, withdraw 0.5 mL (5 mg) of gentamicin 10 mg/mL product, and place into 12 mL syringe.
4. Add 2.5 mL of 5000 units/mL heparin product.
5. QS to 5 mL with NS.
Nursing Management:

1. General Considerations
   a. Ethanol and antibiotic lock solutions are not intended for injection directly into the systemic circulation. They are instilled for purposes of “locking” the catheter for the specified period of time and are to be withdrawn prior to administering a dose of a medication or TPN or other infusion.
   b. The nurse will instill the solution into the catheter lumen(s) using the appropriate volume ordered and allow the solution to dwell for the appropriate time based on the frequency of medications/nutrition (minimum dwell time for ELT = 2 hours). Prior to initiating this procedure, the nurse should carefully check the order for the amount to be instilled (ELT syringes dispensed by the pharmacy should contain the exact amount to be instilled, but ALT syringes will all contain a volume of 5mL, which may be different from the volume ordered).
      i. Instillation of lock solution:
         1. Cleanse hands with alcohol-based hand hygiene product or scrub hands 30 seconds with antimicrobial soap before procedure.
         2. Put on sterile gloves; use aseptic technique throughout procedure.
         3. Clean injection cap with alcohol for 30 seconds and let dry.
         4. Attach a 12 mL syringe filled with 5 mL of normal saline.
         5. Unclamp catheter and gently irrigate catheter using push-pause method with normal saline to assure patency of the catheter.
         6. Clamp catheter and remove saline syringe.
         7. Insert lock syringe into catheter injection cap. Inject appropriate volume of lock solution (per physician’s order) using a slow, push/pause method. Clamp catheter and remove syringe.
         8. Label catheter to indicate that the lumen contains either an ethanol or antibiotic lock solution.
   c. When the lumen is needed for medications/nutrition, the nurse will use the same technique and aseptic procedure as described above to:
      i. Withdraw the lock solution (the exact same amount of volume as initially instilled in the catheter)
      ii. Flush with 5 mL of normal saline
      iii. Administer the ordered medication/nutrition
      iv. Flush with 5 mL of normal saline
      v. Instill the new lock solution.
      vi. Label catheter to indicate that the lumen contains either an ethanol or antibiotic lock solution.
d. As part of the flushing technique, the push-pause method should be used. It creates turbulence to clear out the interior lumen(s) free of possible blood clots that may be attached without an increase in pressure (push in saline, pause of two seconds, continue with this method until flush complete).

2. ELT
   a. Ethanol is INCOMPATIBLE with heparin, so DO NOT use heparinized saline flushes with any patient currently on the ethanol-lock therapy. To avoid this potential problem further, chronic TPN patients receiving the ethanol-lock therapy will have the heparin removed from their TPN.

3. ALT
   a. In regards to stability, the antibiotic-lock solutions are stable for at least 24 hours at room temperature. However, the nurse should always verify that no precipitate has formed in the solution (to ensure physical compatibility).

4. Inadvertent Injection of the Lock Solution into the Systemic Circulation
   a. ELT- In case of an accident, the ethanol may be flushed into the systemic circulation. If the ethanol-lock solution can not be withdrawn from the catheter, unfortunately it will have to be administered to the patient. Ethanol infusions are fairly safe, and have been used in pediatric patients for other reasons, such as methanol or ethylene glycol ingestion (for example – antifreeze ingestion). The patient should be monitored for the following signs and symptoms: tiredness, headaches, dizziness, nausea, and light-headedness. Notify the MD/PA/NP of the inadvertent administration.
   b. ALT- In case of an accident, the antibiotic lock solution may be flushed into the systemic circulation. If the lock solution can not be withdrawn from the catheter, unfortunately it will have to be administered to the patient. In most cases, accidental flushing will not result in significant systemic exposure to the antibiotic, and as such should be safe. The primary concern with routine flushing of ALT is exposing the system to low concentrations of antibiotics, and thus facilitating the development of antibiotic resistance. Notify the MD/PA/NP of the inadvertent administration.

RESPONSIBILITY:

Joint Subcommittee on Anti-Infective Use

REFERENCES:

8 Crnich CJ, Halfmann JA, Crone WC, Maki DG. The effects of prolonged ethanol exposure on the mechanical properties of polyurethane and silicone catheters used for intravascular access. Infect Control Hosp Epidemiol 2005 26(8)708-14

POLICY/GUIDELINE DATES:
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