Anti-Infective Lock Therapy – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline

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Introduction

ALT is used for the prevention or treatment of device-related bacteremia or fungemia resulting from the colonization of bacteria or fungi within the lumen of an intravascular device.[1] ALT as developed to allow a concentrated anti-infective solution to dwell within the catheter lumen for an extended time to eradicate infectious pathogens. Guidelines have been developed by international clinical groups for ALT management.[2]

The most commonly reported CLABSI pathogens are coagulase-negative staphylococci, *Staphylococcus aureus*, enterococci, *Candida* species, and Gram-negative bacilli.[3] Important pathogenic determinants of CRBSI include: (1) device material; (2) formation of fibrin sheaths around the catheter; (3) intrinsic virulence factors of the infecting organism (extracellular polymeric substance production, biofilm formation).[3] The formation of a biofilm within a catheter lumen limits the penetration of solution. Bacteria within a biofilm require a 100 to 1000 times greater anti-infective concentration to achieve killing versus planktonic bacteria. [4] Standard intravenous therapy does not reach a sufficient concentration in the catheter lumen to reduce microorganism burden within the biofilm of the catheter. One report concluded that, in hemodialysis patients with dialysis catheter-related infection, systemic vancomycin administration produces a therapeutic plasma concentration; however, during the intradialytic period, the diffusion of the vancomycin from the plasma into the catheter lumen was negligible.[5]

Additionally, the success of ALT is dependent on the stability and compatibility of the ALT solution.[6] The stability and compatibility of ALT solutions is dependent on a number of factors including: temperature, dwell time, syringe materials, pH, device materials, and anti-infective concentrations.[6]

Scope

Intended Users: Physicians, Advanced Practice Providers, Nurses, and Pharmacists

Objectives: To provide an evidence-based resource that will maximize the safe, efficacious and efficient use of anti-infective lock therapy

Target Population: Patients at risk for developing and/or diagnosed with a catheter-related bloodstream infection (CRBSI)

Clinical Questions Considered:

1. What is the sterility and stability of anti-infective lock therapy preparations?
2. What are the catheter salvage rates?

Definitions

1. **Anti-infective lock technique (ALT)**[7]: the installation of a highly concentrated anti-infective solution into a catheter lumen and allowing the solution to dwell for a specified period for the purpose of sterilizing the lumen.
2. **Catheter-related blood stream infection (CRBSI)**[8]: Defines the catheter as the cause of a blood stream infection. CRBSI is a clinical definition used when diagnosing or treating patients. Criteria for CRBSI include the following: Presence of bacteremia or fungemia in a patient who has an intravascular catheter; AND at least 1 positive blood culture obtained peripherally; AND clinical signs of infection (fever, chills, or hypotension); AND absence of infection at another site; AND one of the following: (a) Positive semiquantitative [>15 colony forming units (CFU) per catheter segment] or quantitative [$>10^2$ CFU per catheter segment] catheter tip culture, (b) Quantitative blood culture with a ratio >3:1 CFU/mL (catheter vs peripheral), (c) Differential time to positivity (blood culture from catheter is detected at least 2 hours before detection of peripheral blood culture).
3. **Central-line associated blood stream infection (CLABSI)**[8]**:** Describes a blood stream infection in a patient who had a recent central catheter. Used by the National Healthcare Safety Network (NHSN) for surveillance. Criteria for CLABSI include: Presence of bacteremia or fungemia (a single positive blood culture is required for most organisms, whereas 2 positive blood

cultures are required for skin flora organisms), AND presence of central line within 48 hours, AND absence of an infection at a different site.

4. **Catheter volume**: the intraluminal volume of the catheter
   4.1. French (Fr) scale[9] - describes the external diameter of the catheter (1Fr = 1/3mm) using an ascending scale (i.e., higher Fr size indicates larger catheter diameter)
   4.2. Gauge - describes both inner and outer diameter using a descending scale (i.e. higher gauge indicates smaller catheter diameter)
5. **Catheter overfill**: a specified volume *in addition to the catheter volume* that ensures that the ALT solution totally fills the catheter, including the portion closest to the blood interface
   5.1. For patient weighing fewer than 15 kg, the overfill volume is 0.1 mL.[10]
   5.2. For patient weighing 15 kg or greater, the overfill volume is 0.2 mL.[10]

Recommendations

1. ALT for the prevention of CRBSI

1.1. Routine use of ALT in general patient populations is not recommended.[2] *(UW Health Strong Recommendation, Low Quality of Evidence)*

1.2. Use of ALT is beneficial when vascular access device use is required for a long-term/indefinite duration and cannot easily be replaced in patients with a history of CRBSI despite maximal adherence to aseptic technique.[2] *(UW Health Strong Recommendation, Low Quality of Evidence)*

1.3. Selection of the ALT solution should consider the following: *(UW Health Strong Recommendation, Low Quality of Evidence)*

- 1.3.1. Catheter indication (e.g., hemodialysis, non-hemodialysis)
- 1.3.2. Catheter composition and compatibility with ALT solution(s) (e.g., prolonged exposure to ethanol can affect the integrity of certain catheter materials)[11]
- 1.3.3. History of CRBSIs and previous culture/sensitivity results
- 1.3.4. History of previous ALT use/failure
- 1.3.5. Need for anticoagulant as part of ALT therapy
- 1.3.6. Medication allergies or adverse drug reactions
- 1.3.7. Risk of systemic exposure and adverse effects associated with ALT (e.g. ethanol intoxication in pediatric population)[10]
- 1.3.8. Targeted microorganism(s)
- 1.3.9. Patient age (neonate, pediatric, adult)
- 1.3.10. Risks of adverse effects from ALT systemic exposure
- 1.3.11. Regimens available at UW Health (see Appendix 1 and Appendix 2)

2. ALT catheter salvage

2.1. ALT can be beneficial for patients with CRBSI involving long-term catheters with no signs of exit site or tunnel infection for whom catheter salvage is the goal.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.2. For CRBSI, antibiotic lock should not be used alone; instead, it is reasonable to be used in conjunction with systemic antimicrobial therapy.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.3. Dwell times for ALT solutions generally should not exceed 48 hours before reinstallation of lock solution. Reinstallation is probably indicated every 24 hours for ambulatory patients with femoral catheters.[12] (*UW Health Strong Recommendation, Low Quality of Evidence*)

- 2.3.1. For patients who are undergoing hemodialysis, the lock solution can be renewed after every dialysis session.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.4. Catheter removal is probably recommended for CRBSI due to *S. aureus* and *Candida* species, instead of treatment with ALT and catheter retention, unless there are unusual extenuating circumstances (e.g., no alternative catheter insertion site).[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.5. For patients with multiple positive catheter-drawn blood cultures that grow coagulase-negative staphylococci or Gram-negative bacilli and concurrent negative peripheral blood cultures,

antibiotic lock therapy may be considered without systemic therapy for ten to fourteen days.[4] (*UW Health Weak/Conditional Recommendation, Low Quality of Evidence*)

2.6. Long-term catheter removal is probably indicated in patients with CRBSI associated with any of the following conditions: severe sepsis; suppurative thrombophlebitis; endocarditis; bloodstream infection that continues despite 72 hours of antimicrobial therapy to which the infecting microbes are susceptible; or infections due to *S. aureus, P. aeruginosa*, fungi, or mycobacteria.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.7. Short-term catheter removal is probably indicated in patients with CRBSI due to Gram-negative bacilli, *S. aureus*, enterococci, fungi, or mycobacteria.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

2.8. In patients with CRBSI for whom catheter salvage is attempted, additional blood cultures are reasonable. Catheter removal is probably indicated if peripheral blood culture results (e.g., two sets of blood cultures obtained on a given day;) remain positive when blood samples are obtained 72 hours after the initiation of appropriate therapy.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

3. ALT pathogen-specific salvage recommendations.

3.1. An Infectious Diseases consult should be considered for the determination of CRBSI catheter-salvage recommendations. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

4. ALT dwell times

4.1. Dwell times should be specified as part of the ALT orders.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.2. Dwell times for ALT solutions generally should not exceed 48 hours before reinstallation of lock solution. Reinstallation is probably indicated every 24 hours for ambulatory patients with femoral catheters.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.2.1. For patients who are undergoing hemodialysis, the lock solution can be renewed after every dialysis session.[4] (*UW Health Strong Recommendation, Low Quality of Evidence*)

4.3. Minimum effective dwell time is not well defined and is dependent on the rate and extent of antimicrobial penetration into a biofilm penetration.[13-16]

4.4. Flushing of the instilled ALT solution through the catheter into the systemic circulation is not recommended as to reduce the risk adverse effects and the emergence of microorganism resistance. (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

5. Determining catheter volume

5.1. The volumes of common catheters currently used at UW Health are specified in the Flushing/Locking of Venous Access Devices – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline and Treatment of Central Venous Access Device Occlusion – Neonatal/Pediatric/Adult – Inpatient – Clinical Practice Guideline.

6. ALT solution-specific precautions and considerations

6.1. Stability and compatibility

6.1.1. The stability and compatibility of the ALT solution should be considered when ordering ALT for prophylaxis or treatment. ALT solutions without documented stability or compatibility should not be used.[6,7] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

6.1.2. Temperature, dwell time, and solution concentration can influence stability and compatibility. Also**,** stability may be altered by manufacturer changes that are not reflected in the published stability studies. ALT solutions should be examined for evidence of physical incompatibility (discoloration or precipitation) prior to instillation into the catheter**.** (*UW Health Strong Recommendation, Very Low Quality of Evidence*)

6.1.3. ALT solutions may be stable for short durations and require admixture in the clinical care area instead of the pharmacy. In these scenarios, it is reasonable for the

pharmacy servicing the ambulatory site to supply the necessary supplies and instructions for admixture of the ALT solution. (*UW Health Conditional Recommendation, Very Low Quality of Evidence*)

6.2. Ciprofloxacin

6.2.1. In clinical trials, admixed solution was allowed to dwell for at least 12 hours and was changed daily.[13] Some references cite ciprofloxacin is compatible with heparin, however, experience at UW Health has shown ciprofloxacin and heparin have variable compatibility. Therefore, ciprofloxacin lock solutions should not include heparin. (*UW Health Conditional Recommendation, Low Quality of Evidence*)

6.3. Daptomycin

6.3.1. Daptomycin has a unique mechanism of action involving a calcium-dependent dissipation of membrane potential, leading to the release of intracellular ions from the cell and the killing of bacteria. Daptomycin ALT solution requires the addition of calcium for antimicrobial activity. The addition of Lactated Ringer's to the daptomycin ALT provides 3.6 mEq/L of calcium ions.[17]

6.4. Ethanol and other alcohol-containing solutions[18]

6.4.1. Ethanol compatibility with heparin and trisodium citrate is variable.[6] Ethanol should not be considered compatible with heparin or trisodium citrate and neither heparin nor trisodium citrate should be used with ethanol in ALT. (*UW Health Strong Recommendation, Low Quality of Evidence*)

6.4.2. When ethanol lock solutions are considered, the effect of ethanol on the mechanical and structural integrity of the catheter should be considered.[11] (*UW Health Strong Recommendation, Low Quality of Evidence*)

6.4.3. It is reasonable to use of ethanol ALT with silicone and carbathane catheters only until sufficient data are available to ensure that ethanol has no effect on catheter integrity of non-silicone catheters (e.g. polyurethane catheters).[11,19] (*UW Health Strong Recommendation, Low Quality of Evidence*)

6.4.4. It is reasonable to aspirate and discard ethanol ALT from the catheter lumen and at the end of the dwell, and catheter should be flushed with 0.9% sodium chloride.[11,19] (*UW Health Strong Recommendation, Low Quality of Evidence*)

6.5. Gentamicin

6.5.1. Gentamicin precipitates at a concentration of 10 mg/mL or higher when mixed with heparin.[20]

6.6. Vancomycin

6.6.1. In vancomycin ALT solution, it is reasonable that the vancomycin concentration be at least 1000 times greater than the MIC of the microorganism involved.[4] (*UW Health Conditional Recommendation, Low Quality of Evidence*)

7. ALT Preparation

7.1. To maximize the sterility and stability of the ALT, it is reasonable to prepare all ALT aseptically in a pharmacy when feasible.[4] (*UW Health Strong Recommendation, Moderate Quality of Evidence*)

Table 1. Venous access devices (from Flushing/Locking of Venous Access Devices – Adult/Pediatric – Inpatient/Ambulatory Clinical Practice Guideline) [21-23]

Type of Device	Common Catheter Length	Insertion Location	Duration of Use
Umbilical Venous and Arterial Catheter (UVC/UAC)	< 5 cm	Inserted through the umbilical vein and joins the left portal vein or umbilical artery and joins arteries either at the thoracic or lumbar vertebral bodies	Short-term access up to 7 days after birth
Peripheral (PIV)	< 3 in	Terminates in a vein of the forearm or hand, location may vary in pediatric patients	Short-term access < 1 week
Midline	3 – 8 in	Peripheral device terminating in the basilic, cephalic or brachial vein distal to the shoulder	Access needed for ≤ 29 days, not appropriate for vesicant administration
Non-Tunneled Central	≥ 8 cm	Percutaneous device terminating in the superior or inferior vena cava	Short term access when peripheral not suitable, ex. resuscitation and central venous pressure monitoring
Peripherally Inserted Central (PICC)	≥ 20 cm	Peripheral device terminating in the superior or inferior vena cava	Medium-term (up to 6 months) access
Tunneled Central	≥ 8 cm	Implanted into the subclavian, internal jugular, or femoral veins	Frequent medium-term (up to 6 months) access and a PICC line is contraindicated
Implanted Central (Port)	≥ 8 cm	Tunneled under skin with port accessed by needle; implanted in subclavian or internal jugular vein terminating in the superior vena cava	Infrequent long-term (> 6 months) access
Dialysis and Apheresis	≥ 15 cm	Non-cuffed catheter placed in the neck or chest terminating in the superior or inferior vena cava	Long or short term access for the maintenance of dialysis therapy

Table 2. Central venous catheter type and capacity (from Central Venous Access Device Occlusion – Neonatal/Pediatric/Adult – Inpatient/Ambulatory/ED – Clinical Practice Guideline)

Catheter Type	Adult Capacity	Pediatric Capacity	Neonatal Capacity
Dialysis-Pheresis Catheters	Volume on catheter lumen (common 2 mL)	1 mL or less	
Implanted Venous Port	2 mL	1 mL or less	
Non-tunneled Triple Lumen (ex. Arrow)	1 mL	1 mL or less	
PICC	1 mL	1 mL or less	0.1 mL (1.9 Fr)
Powerline	1 mL	1 mL or less	
Tunneled Cuff Catheter (ex. Groshong)	1 mL	1 mL or less	
Tunneled or Non-Tunneled Central (ex. Hickman, Broviac)	2 mL	1 mL or less	
Umbilical Catheters (Double and Single Lumen 3.5 and 5 Fr)			0.5 mL or less

Disclaimer

Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

Methodology

Development Process

Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:

The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:

- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)

Time Period: 2000 to 2018

Search Terms:

- Antibiotic lock
- Antibiotic lock solution
- Antibiotic lock therapy
- Antimicrobial lock
- Antimicrobial lock therapy
- Antimicrobial lock solution
- Catheter-related infections
- Catheter-related blood stream infections
- Central venous catheter

Methods to Select the Evidence:

- Inclusion Criteria: time range (2000-18, studies conducted in which the primary language was English, randomized controlled trials
- Exclusion Criteria: Studies conducted prior to 2000, studies in which the primary language was not English, in-vitro data, animal models, case reports, studies without outcomes

Describe the inclusion/exclusion criteria used for selecting the literature; consider describing chosen variables such as language, study design, outcomes, and comparisons as appropriate.

Methods Used to Formulate the Recommendations:

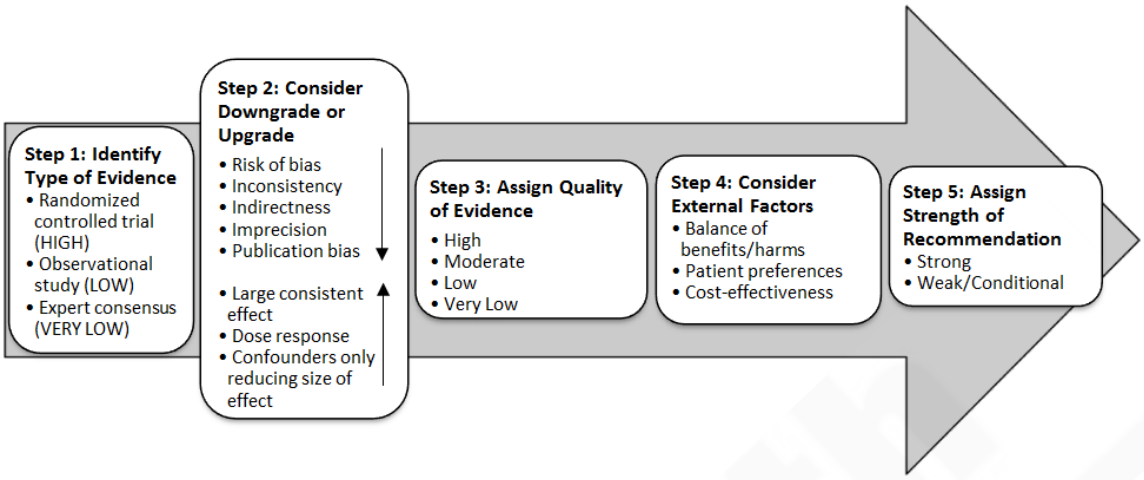
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:

Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

Strong (S)	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
Conditional (C)	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)

Recognition of Potential Health Care Disparities: None identified

Appendix 1. Non-hemodialysis ALT preparations available at UW Health

Lock	Base Solution	Record Number in HealthLink	Notes
Ciprofloxacin 2 mg/mL[13, A]	D5W	760332	
Ceftazidime 2 mg/mL and heparin 100 units/mL[6,24]	Normal saline	701155	
Daptomycin 1 mg/mL and heparin 100 units/mL[25, A]	Lactated Ringers	701156	
Daptomycin 5 mg/mL[17,26]	Lactated Ringers	Not available at UW Health	Available for ambulatory use only through Chartwell Midwest Wisconsin
Ethanol 50% (v/v)[10,19,27-33]	Normal Saline	701153	• **Do not use with polyurethane catheters** • Incompatible with heparin and sodium citrate
Ethanol 70% CVAD Occlusion (v/v)[10,19,27-33]	Sterile water	760352	
Vancomycin 2 mg/mL and heparin 100 units/mL[13]	Normal saline	701161	
Vancomycin 2 mg/mL and heparin 20 units/mL[13]	Normal saline	701160	

[A] Note: not available through Chartwell Midwest Wisconsin home infusion services

Appendix 2. Hemodialysis (HD) ALT preparations available at UW Health[A,B]

Lock	Base Solution	Record Number in HealthLink
Ceftazidime 10 mg/mL and heparin 5000 units/mL (HD)[6,34]	Normal saline	701154
Daptomycin 1 mg/mL and heparin 1000 units/mL (HD)[25]	Lactated Ringers	701157
Gentamicin 1 mg/mL and heparin 2500 units/mL (HD)[20]	Normal Saline	701158
Gentamicin 2.5 mg/mL and 4% sodium citrate base (40 mg/mL) (HD)[35]	No base	701159
Vancomycin 2.5 mg/mL and heparin 2500 units/mL (HD)[20]	Normal Saline	701162
Vancomycin 3 mg/mL and 4% sodium citrate base (40 mg/mL) (HD)[36]	No base	701163

[A] Note: Chartwell Midwest Wisconsin does not provide any HD ALT preparations
[B] ALT for HD include anticoagulant of high-dose heparin (1000 units/mL or greater) or sodium citrate (40 mg/mL)

Appendix 3. ALT preparations available from Chartwell Midwest Wisconsin home infusion services for central lines (May 2019)

Lock	Base Solution
Cefazolin 0.5 mg/mL and heparin 100 units/mL	Normal saline
Cefazolin 10 mg/mL and heparin 10 units/mL	Normal saline
Ceftazidime 0.5 mg/mL and heparin 100 units/mL	Normal saline
Ceftazidime 2 mg/mL and heparin 100 units/mL	Normal saline
Ciprofloxacin 0.125 mg/mL and heparin 100 units/mL	Normal saline
Daptomycin 5 mg/mL	Lactated Ringers
Daptomycin 5 mg/mL and heparin 100 units/mL or heparin 10 units/mL	Lactated Ringers
Ethanol 50%	Sterile water
Ethanol 70%	Sterile water
Vancomycin 25 mcg/mL, ciprofloxacin 0.002 mg/mL and heparin 10 units/mL	Normal saline
Vancomycin 50 mcg/mL, ciprofloxacin 0.002 mg/mL and heparin 10 units/mL	Normal saline
Vancomycin 0.5 mg/mL and heparin 100 units/mL	0.45% saline
Vancomycin 25 mcg/mL and heparin 10 units/mL	Normal saline
Vancomycin 2 mg/mL and heparin 10 units/mL	Normal saline
Vancomycin 2 mg/mL and heparin 100 units/mL	Normal saline
Vancomycin 2 mg/mL and heparin 20 units/mL	Normal saline

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