

University of Wisconsin Hospital and Clinics Guidelines for Anti-Infective Lock Solutions

Guidelines developed by UWHC Drug Policy Program

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1.0 Background

Anti-infective lock solutions are used to prevent or treat device-related bacteremias that result from colonization of bacteria within the lumen of an intravascular device. The most common pathogens associated with colonization are cutaneous organisms (*Staphylococcus aureus*, *coagulase-negative Staphylococcus* and *Candida* species), although gram-negative bacilli may also be present. The anti-infective lock technique (ALT) was developed to allow a concentrated antibiotic or antiseptic solution to dwell within the catheter lumen for an extended period of time.

Central venous catheters (CVC) or implanted vascular devices can become contaminated with microorganisms by various mechanisms either at the time of insertion or with later use. Microorganisms can migrate through the percutaneous (extraluminal) route either at the time of insertion or days later. Intraluminal contamination can occur through manipulation of the intravascular device (IVD) hub either at time of insertion or later with device use. Organisms can also travel from a remote source infection via the bloodstream and contaminate the intraluminal surface of the device.¹

Device-related bloodstream infection (BSI) usually requires systemic antimicrobial therapy and catheter removal.¹ For needed long-term devices, catheter salvage is often desirable. The instillation of an anti-infective lock solution into the IVD has been studied for both prevention and treatment of long-term catheter-related bacteremia. Studies on the use of ALT for the prevention of IVD-related BSI have shown that vancomycin-containing lock solutions can reduce the risk of device-related infection by approximately 50%.² The evidence supporting the use of ALT for the treatment of IVDs that are infected is less robust but suggests improvements in salvage rates of 20-30% depending on causative organism.^{3,4}

To be practical in the acute care setting, the anti-infective lock should display efficacy over a sufficiently short dwell time to be useful in hospitalized patients with competition for intravenous "line time". The time required for exposure to the concentrated anti-infective is approximately 60 minutes or longer (if there is not a critical need for access, then the dwell times should extend as long as possible).¹ Longer dwell times are possible in patients with hemodialysis catheters or implantable ports that are not routinely accessed on a daily basis.

The formation of a biofilm within the catheter lumen limits penetration of anti-infective solution. Bacteria within the biofilm require 100 to 1000 times greater anti-infective concentration to achieve killing versus planktonic bacteria.⁵ Standard intravenous therapy does not reach high enough concentration to reduce bacterial burden within the biofilm of the catheter lumen. Therefore, pharmacologic concentrations of anti-infectives are used in anti-infective lock therapy either alone for prophylaxis or in combination with systemic therapy for treatment of catheter-related bacteremia. Bastani et.al. demonstrated 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 anti-infective from the plasma into the catheter lumen is negligible.⁶ Use of an anti-infective lock between dialysis sessions is necessary to provide continuous exposure of the bacteria within the catheter to a high concentration of anti-infective.

Stability and compatibility of the anti-infective lock solution in combination with an anticoagulant must be considered when ordering an anti-infective lock solution. Temperature, dwell time, addition of anticoagulant or other anti-infectives all influence stability. Antimicrobial activity may be inhibited by

addition of an anticoagulant. When ethanol lock solutions are considered, the effect of ethanol on the mechanical and structural integrity of the catheter must be considered.⁷

2.0 Objectives

- 2.1 To provide information to clinicians on the appropriate indications, anti-infective concentrations and dwell times for anti-infective flush and lock solutions in pediatric and adult patients with a variety of catheters. Available regimens based on clinical studies or case reports, not in vitro data.
- 2.2 To provide information on stability and compatibility of solutions.
- 2.3 To include evidence for anti-infectives available at UWHC.

3.0 Definitions:

- 3.1 Anti-infective lock: solution that is instilled into the lumen of a catheter and removed after a specified period of time (or when access device next used). The process of instillation and removal is the anti-infective lock technique (ALT).

4.0 Indications and regimens approved for the use of anti-infective lock solutions in the prevention and treatment of catheter-related bloodstream infections. All orders for non-HD catheter ALT requires Infectious Disease approval. HD catheter ALT requires either Nephrology or Infectious Disease approval.

4.1 Prophylaxis⁸

- 4.1.1 **Do not routinely use anti-infective solutions to prevent catheter related infections**
- 4.1.2 **Use prophylaxis with anti-infective lock solutions only in special circumstances. Infectious Disease approval is required for non-HD catheter ALT. Nephrology or Infectious Disease approval required for HD catheter ALT.**
 - 4.1.2.1 Vascular access device is required for long term/indefinite use and cannot easily be replaced in a patient with a history of catheter-related blood stream infections despite stringent infection control.
- 4.1.3 **Table 3: Prophylaxis Regimens in long-term CVC: pediatric/adult (non-hemodialysis)**
Listed concentrations for anti-infective(s) and heparin are **final concentration per ml** of admixed solution. Dwell time minimum one hour.

Vancomycin	Cipro	Ceftaz	Heparin	Dwell time	Reference
25 microgram	2 microgram		10 unit	minimum one hour	9
2 milligram (see 4.1.4)			100 unit	2mL lock between use	10
		2 milligram	100 unit	2mL lock between use	10

Abbreviations; Cipro, ciprofloxacin; Ceftaz, ceftazidime

- 4.1.4 **For vancomycin 2 mg/100 unit heparin/mL lock listed above, draw vancomycin concentration (peripheral only) at a mid-point between lock instillations to check for detectable vancomycin concentration. The concentration should be non-detectable.**

4.1.5 Table 5: Adult Prophylaxis Regimen: Hemodialysis

Listed concentrations for anti-infectives and heparin are **final concentration per mL** of admixed solution

Anti-infective Lock Solution	HD Catheter	Vancomycin	Gentamicin	Heparin	Reference
Vanco + heparin	T CVC	2.5milligrams		2500 units	11
Gent + heparin	TCVC		1 milligram	2500 units	11

Abbreviations; Vanco,vancomycin; Gent, gentamicin

Although the standard concentration of heparin used for dialysis is 1000uit/mL, the clinical trials used a higher concentration of heparin. Lower concentrations of heparin need to be validated prior to use.

4.2 Treatment^{5,20}

4.2.1 Tunneled Central Venous Catheter (CVC) or Intravascular Device (IVD)

4.2.1.1 Catheter removal is the treatment of choice for persistent bacteremia related to CVC use.

4.2.1.2 Remove CVC or IVD if:

4.2.1.2.1 **Complicated infection** (endocarditis, septic thrombosis, osteomyelitis, etc.) or

4.2.1.2.2 **Uncomplicated infection** with *Candida* species, *Staphylococcus aureus* or *Pseudomonas aeruginosa*. **The CVC or IVD should *always be removed with device-related Staphylococcus aureus bacteremia since low success rate increases risk of recurrence or endocarditis.***

4.2.1.2.3 **Treat with systemic antimicrobial therapy per Infectious Disease recommendation after CVC or IVD removed.**

4.2.1.3 ***The salvage rate for catheters is very low regardless of causative organism and should be considered for removal.***

4.2.1.4 ***If retention of CVC or IVD is deemed absolutely necessary***, ALT therapy *may* increase the chance of salvage. The presence of a biofilm within the catheter requires careful selection of anti-infective, concentration and dwell time of optimize efficacy without selecting for resistance.

4.2.1.4.1 **Anti-infective lock solution with standard systemic IV anti-infective therapy per Infectious Disease recommendation.**

4.2.1.4.2 **Table 4: Salvage regimens with anti-infective lock (ALT) if decision to retain tunneled CVC/IVD. Infectious Disease approval required for non-HD catheter ALT. Nephrology or Infectious Disease approval required for HD catheter ALT.**

Organism	Decision to remove CV or IVD?	Decision to retain CVC/IVD?	Salvage regimen	Salvage regimen failure?
<i>S aureus</i>	Yes-remove CVC/IVD and treat with systemic anti-infective per Infectious Disease recommendation	No-low success rate		
<i>Coagulase-negative Staphylococcus</i>	May retain-see salvage therapy	Yes – use salvage therapy	Systemic treatment plus ALT(anti-infectives and duration per Infectious Disease)	Remove CVC/IVD if persistent or relapsing bacteremia or clinical deterioration
Gram- negative bacilli	If yes-remove CVC/IVD and treat with systemic anti-infectives per Infectious Disease recommendation	If yes – use salvage therapy	Systemic treatment plus ALT(anti-infectives and duration per Infectious Disease)	If no response, remove CVC/IVD and treat with systemic anti-infectives per Infectious Disease
<i>Candida spp</i>	Yes-remove CVC/IVD and treat with systemic antifungals per Infectious Disease	No-low success rate		

4.3 ALT Treatment Regimens by Organism

4.3.1Candida: salvage is almost never justified due to high risk of endocarditis or other metastatic complications

- Ethanol 50% **in silicone catheters only** . Note: *not compatible with heparin* – see section 5.0
- Hemodialysis – remove catheter

4.3.2 Staphylococcus aureus (MRSA) salvage is almost never justified due to high risk of endocarditis or other metastatic complications

- Ethanol 50% **in silicone catheters only**. Note: *not compatible with heparin* – see section 5.0.
- Hemodialysis – remove catheter

4.3.3 Coagulase negative staphylococcus

Listed concentrations for anti-infective(s) and heparin are **final concentration per mL** of admixed solution:

- Vancomycin 2 milligrams in 20 units heparin/mL¹²
- Vancomycin 2 milligrams in 100 units heparin/mL¹³
- Vancomycin 5 milligram in 5000 units heparin/mL¹⁹
- Vancomycin 1 milligram in 4% sodium citrate/mL (may be used in hemodialysis and non-hemodialysis catheters)²¹
- Vancomycin 3 milligram in 4% sodium citrate/mL (may be used in hemodialysis and non-hemodialysis catheters)²¹
- Ethanol 50% **in silicone catheters only** . Note: *not compatible with heparin* – see section 5.0
- Hemodialysis only (due to heparin concentration);
 - Vancomycin 2.5 milligram in 2500 units heparin/mL¹¹
 - Vancomycin 5 milligram in 5000 units heparin/mL¹⁹Although the standard concentration of heparin used for dialysis is 1000uit/mL, the clinical trials used a higher concentration of heparin. Lower concentrations of heparin need to be validated prior to use.

When vancomycin is used for treatment, the concentration of the lock solution should be 1000 times the MIC of the organism.¹⁹

4.3.4 Gram negative organisms:

Listed concentrations for anti-infective(s) and heparin are **final concentration per mL** of admixed solution:

- Ceftazidime 2 milligram in 100 units heparin/mL¹³
- Ciprofloxacin 2 milligram /mL (no anticoagulant)¹²
- Gentamicin 2.5 milligram in 4% sodium citrate/mL (may be used in hemodialysis and non-hemodialysis catheters)²⁰
- Ethanol 50% **in silicone catheters only**. Note: *not compatible with heparin* – see section 5.0
- Hemodialysis only (due to heparin concentration):
 - Ceftazidime 10 milligram in 5000 units heparin/mL¹⁴
 - Gentamicin 1 milligram in 2500units heparin/mL.¹¹Although the standard concentration of heparin used for dialysis is 1000uit/mL, the clinical trials used a higher concentration of heparin. Lower concentrations of heparin need to be validated prior to use.

4.4.4 Dwell Times¹⁹

- 4.4.4.1 **Dwell time: the length of time the antibiotic lock solution dwells within the catheter lumen.**
- 4.4.4.2 Dwell times will be specified by the Infectious Disease physician when the order is initiated.
- 4.4.4.3 At the end of the dwell time, the anti-infective lock solution is removed from the catheter lumen prior to instillation of fresh solution.
- 4.4.4.4 Hemodialysis catheters: fresh lock solution is instilled into the catheter after each dialysis session.
- 4.4.4.5 Dwell times for non-hemodialysis catheters should generally not exceed 48 hours before reinstallation of a new antibiotic lock solution.
- 4.4.4.6 Dwell times for non-hemodialysis catheters in ambulatory patients with femoral catheters should preferably not exceed 24 hours.

5.0 Stability and compatibility^{7,15,16,17}

- 5.1 Combinations of anti-infectives should not be used without evidence of stability or compatibility or studies showing clinical outcomes of the combination.
- 5.2 Anti-infective concentrations ordered should be limited to concentrations with evidence of stability and efficacy either alone or in combination with other anti-infectives and anticoagulants.
 - 5.2.1 Gentamicin
 - 5.2.1.1 Gentamicin and heparin admixtures show *inhibition* of bactericidal activity at gentamicin concentrations less than 1 mg/mL.¹¹
 - 5.2.1.2 Gentamicin precipitates in heparin at a concentration of 10mg/mL or higher¹¹
 - 5.2.1.3 Gentamicin 40mg/mL intradialytic dwell produced *detectable* pre-dialysis gentamicin concentrations (median 2.8 mcg/mL).¹⁸
 - 5.2.1.4 Gentamicin 5mg/mL intradialytic dwell produced less than 0.2mcg/mL gentamicin pre-dialysis concentrations.¹¹
 - 5.2.1.5 Arbitrarily changing concentration of gentamicin or heparin concentrations may result in precipitation.
 - 5.2.1.6 Gentamicin 2.5mg in 4% sodium citrate is stable in HD catheters at 37 degrees for at least 96 hours with no degradation²⁰
- 5.3 Ethanol
 - 5.3.1 Ethanol **is not compatible** with heparin. The ethanol lock should dwell for the 60 minutes, then remove ethanol and flush the with *0.9% sodium chloride*. Heparin can then be instilled into the CVC/ID.
 - 5.3.2 Ethanol locks should be limited to silicone catheters only until sufficient data are available to ensure no effect on catheter integrity.^{6,15,16}
 - 5.3.3 Ethanol 50% is not a commercially available product. The compounded ethanol 50% (v/v) product is stable in syringes at room temperature for up to 28 days (unprotected from light).¹⁷
- 5.4 Ciprofloxacin
 - 5.4.1 Ciprofloxacin 2mg has been reported to be stable with heparin 20 units/mL¹² In our experience, this combination exhibits variable stability in heparin. Ciprofloxacin 2 mg/mL will be available as a lock without any anticoagulant.

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