Vascular Access: Maintaining Patency and Reducing Infection Risk

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For home infusion therapy patients, a vascular access device (VAD) represents a lifeline to treatment. Maintaining that lifeline to allow uninterrupted delivery of the prescribed therapy is a primary goal of home infusion providers. Proper VAD maintenance is essential to both patient safety and preservation of a patent line for the administration of needed IV therapies.

FLUSHING, LOCKING, AND HEPARIN

Flushing plays a critical role in catheter maintenance. The procedure serves three purposes; to assess catheter function, to maintain catheter patency, and to prevent contact between incompatible medications or fluids that could form a precipitate or cause an adverse reaction (see Exhibit 1). Typical IV drug administration protocols include flushing using the SASH technique, which calls for:[1]

Saline flush prior to drug administration to ensure patency of line and clear residual medication

Administration of the medication

Saline flush to ensure patency of the line and clear residual medication

Heparin (if required) to minimize the potential of a blood clot forming inside the catheter lumen

Flush solution is typically preservative-free 0.9% sodium chloride (normal saline, or NS). For medications not compatable with NS, flush solution is typically a similarly isotonic solution, such as 5% dextrose in water. A lock solution should be instilled as a final flush to maintain VAD patency. Using saline flushing and heparin locks is one of the most important strategies for maintaining catheter patency and preventing thrombus formation.[2]

THE EVOLUTION OF FLUSHING PROTOCOLS

Traditionally, heparin is the agent of choice for a lock solution. The standard of care is to instill at the lowest possible dose (10 units/mL). For larger VADs, such as pheresis and hemodialysis catheters, larger doses (up to 1,000 units/mL or more) may be required. It's important that higher concentration heparin is withdrawn from the catheter prior to the next VAD access rather than being flushed through the catheter into the patient's bloodstream.[3]

Health care providers realize that there are instances when heparin is contraindicated. In addition, heparin has also been associated with an increased risk of developing thrombocytopenia (see box below). These factors sparked the evolution of flushing practice and the development of new vascular access technology. Vascular access devices, such as valved catheters and positive displacement needleless connectors, have been designed to inhibit blood reflux into the catheter, minimizing the risk of catheter occlusion and catheter-related infection.

Exhibit 1
Infusion Therapy Standards of Practice

Standard 40. Flushing and Locking

40.1 Vascular access devices (VADs) are flushed and aspirated for a blood return prior to each infusion to assess catheter function and prevent complications.

40.2 VADs are flushed after each infusion to clear the infused medication from the catheter lumen, thereby reducing the risk of contact between incompatible medications.

40.3 The VAD is locked after the completion of the final flush to decrease the risk of intraluminal occlusion and catheter-related bloodstream infection (CRBSI), depending on the solution used.

Source: Infusion Therapy Standards of Practice, 2016

HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Annually, approximately 12 million people in the U.S. are exposed to some form of heparin.[4] The majority of these are patients in the acute care setting receiving heparin as part of their infusion therapy and catheter care. Heparin-induced thrombocytopenia (HIT) occurs in between 0.1-5% of patients; this adverse reaction can be severe with a mortality rate of 20-30%.[5] Any patient receiving heparin who develops a significant thrombocytopenia should be carefully monitored.

Being aware of the signs and symptoms as well as having a rudimentary knowledge of the pathophysiology of HIT is vital for clinicians caring for infusion therapy patients. HIT can be one of two types:

- **Type 1** - usually manifests itself within 48-96 hours of heparin exposure and is a benign, non-immune-mediated response. It can result in mild platelet aggregation and thrombocytopenia. The platelet count rarely falls below 100,000/uL and is self-correcting.
- **Type 2** - is an immune-mediated syndrome caused by antibodies to platelet factor 4 (PF4) complex that occurs 4-10 days following exposure. The antibodies are activated after heparin has been administered, which results in the formation of microparticles and generation of thrombin. From this comes thrombus formation and thromboembolic sequelae. Type 2 HIT can result in venous thromboembolism and less frequently in arterial thromboembolism and myocardial infarction and necessitates the immediate discontinuation of all heparin.[6] Once the antibodies are present, even after heparin has been discontinued, reintroducing heparin can result in a severe decrease in platelet count. Patients who develop Type 2 HIT should cease using heparin immediately and then be carefully monitored via laboratory tests and physical assessments.

Any patient receiving heparin who develops thrombocytopenia or has an unexplained thrombus formation 5-10 days after exposure should be evaluated for HIT. Some forms of thrombocytopenia result in bleeding issues; HIT does not give this appearance. The most common presentation can be seen in venous thromboembolism such as deep vein thrombosis or pulmonary embolism. Treatment commonly begins with heparin discontinuation and initiation of alternate anticoagulants if needed.

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To obtain this benefit, it is essential to follow the manufacturers' recommendations for the sequence of flush, clamp, and disconnect.[1]

Clinical procedures have improved as well. Flushing techniques such as "push-pause" or "pulsatile" flushing have demonstrated better catheter clearance than a single bolus flush of NS and positive displacement flush, which is recommended by the Infusion Therapy Standards of Practice (INS Standards), and has been shown to inhibit blood reflux and associated catheter occlusion.[1,3,7] The dynamics of fluid movement through a catheter, the flushing technique used, and sufficient volume of the flushing solution all contribute to the prevention of occlusions.[3]

The following are some other home infusion practices that have evolved as means of maintaining vascular access while minimizing the use of heparin.

NORMAL SALINE (NS) FOR PERIPHERAL VENOUS CATHETERS

Short peripheral catheters should be locked immediately following each use.[3] Various studies have proven the safety and efficacy of NS to maintain peripheral catheter patency when compared to heparinized solutions.[3,8] Past studies have shown that patency rates with heparin and NS were very similar.[3]

In 2012, the American Society of Health-System Pharmacists (ASHP) released a position statement on the use of NS for peripheral catheter patency as a safe and effective alternative to heparin.[9] However, the position statement was rather narrow in scope, noting a lack of evidence for the use of a saline only in the home and outpatient settings, pediatric patients (<1 year), and midline catheters. Despite these limitations, the position boosted acceptance of the practice of using NS as a locking solution for peripheral IVs.[9]

In addition, ITSP recommend using NS for locking in adults.[1] Outcomes data regarding neonates and pediatric patients is limited, so standard practice dictates that clinicians use heparin (0.5-10 units per mL) or NS to lock peripheral IVs in this patient population.[1,10] For short peripheral catheters that are not being used for intermittent infusion, consider locking once every 24 hours.

CENTRAL LINES AND HEPARIN

Central venous catheters (CVCs) are a mainstay in virtually all health care settings in the U.S., with more than five million CVCs placed annually.[7] Yet, the ideal flush solution for maintaining catheter patency remains unestablished. Researchers identify a lack of well-controlled studies, variances in terminology, and discrepancies in flush volume and technique as factors contributing to the failure to empirically identify the optimal flush protocol and establish standardized practice.[3,11]

To maintain patency of CVCs, NS and heparinized saline appear to have equal efficacy. However, researchers posit that for secondary concerns, such as prevention of catheter-related infections and thrombus development, heparinized saline has demonstrated higher efficacy over NS.[12] Additionally, INS Standards identify both NS and heparin as appropriate flush solutions, but note that use of heparin to maintain peripherally inserted central catheters (PICCs) should be considered in home care patients.[1]

For home care patients, whose catheters are not being routinely assessed or maintained by clinicians, occlusions can result in missed doses, delayed treatment completion, and increased risk of catheter-related infections.[11,13] CVC occlusions require additional (and typically unexpected) nursing hours to restore patency and resume therapy. In spite of the advances in technology and product development related to maintaining catheter patency, researchers and practitioners are still seeking definitive answers.

SODIUM CITRATE 4% SOLUTION FOR HEMODIALYSIS CATHETERS

The preferred VADs for hemodialysis are either arteriovenous (AV) fistulas or grafts; however, many patients use more conventional VADs for this therapy. Customarily, dialysis catheters have been locked with heparin. This solution (5,000-10,000 units/mL) is instilled in each lumen based on the internal volume needed and then withdrawn prior to the next treatment session. Heparin can have systemic anticoagulant effects, even when used only to fill a specific lumen with a certain volume.[3] Heparin-induced antibodies (HIA) can lead to a decreased platelet count and thrombocytopenia due to antibody stimulation.[14] HIA can also induce the formation of biofilm in the presence of *Staphylococcus aureus.*[15]

Because of recent cautions regarding the anticoagulant effects of heparin and risk of thrombocytopenia, clinicians have examined the use of sodium citrate 4% for hemodialysis catheters. Sodium citrate has been used for over 100 years as an anticoagulant to stabilize blood and blood products. It acts as a chelating agent to the calcium in blood, which prevents the activation of pro-coagulants which are calcium dependent. This solution has been proven to have similar efficacy to heparin with fewer incidences of catheter-related bloodstream infection (CRBSI).[16]

ANTIBIOTIC LOCK THERAPY (ALT)

Clinical practice guidelines for the treatment of CRBSI offered by the U.S. Centers for Disease Prevention and Control (CDC) and the Infectious Diseases Society of America (IDSA) both recommend antibiotic lock therapy (ALT) for treatment of CRBSI in certain situations.[17-20] ALT treatment of CRBSI allows the catheter to remain in place, avoiding the risks associated with line replacement while preserving veins for future use. Typically, when used to salvage a catheter, ALT is used as an adjunct to systemic antibiotic therapy.[4,17,20,21] The CDC and IDSA also recommend the use of ALT as prophylaxis in patients with long-term catheters who have a history of multiple CRBSI despite maximal adherence to aseptic technique.[18,22,23]

Exhibit 2
Considerations When Selecting Antibiotic Locking Solutions

- Compatibility with anticoagulants (when applicable)
- Spectrum of antimicrobial activity for suspected organism(s)
- Ability to penetrate biofilm either directly or with an additive
- Low side effect and/or adverse reaction profile
- Stability of the solution
- Low potential for resistance
- Cost and ability to get reimbursed

> *It must be noted that due to incompatibility heparin cannot be added to an ethanol lock solution or given immediately before or after locking.*

When making the decision as to which antibiotic to utlizie for the ALT, prescribers must evaluate the targeted organism, pick a compatible solution, evaluate the stability and clinical effectiveness of the solution and consider the patient's medication regimen. In addition to these decision points, ALT solutions must also have a variety of other characteristics (see Exhibit 2). ALT solutions consist of a highly concentrated—100-1000 times the minimum inhibitory concentration (MIC)—antibiotic plus an anticoagulant. The solution is instilled into the lumen of the catheter and "locked" in place while the catheter is not in use. The INS Standards recommend withdrawing the ALT solution prior to using the VAD to prevent antibiotic resistance and adverse effects.[1]

Current published literature has shown the effectiveness of the following antibiotics for ALT. See chart on pages 42 and 43 for specific use information.[8,19-23]

- ***Aminoglycosides (amikacin, gentamicin, tobramycin)*** – are a potent, clinically effective combination when paired with anticoagulants. Nurses and pharmacists need to be aware that the combination of an aminoglycoside plus heparin in a solution can result in cloudiness, which does not change the effectiveness of the solution. Aminoglycosides have been studied in combination with other antimicrobials, such as vancomycin, and are proven to be effective options for patients with polymicrobial infections.[17,20]

- ***Cephalosporins (cefazolin, cefotaxime, ceftazidime)*** – have been studied in treatment of CRBSI and found to be effective. However, due to the high rate of methicillin resistance in the staphylococcal species, they are not recommended as a prophylactic ALT therapy.[17,20]

- ***Glycopeptides (vancomycin, telavancin)*** – have been successfully used as ALTs. Vancomycin has been shown as effective and safe to use with heparin. Doses lower than 0.025 mg/mL may not be adequate to penetrate biofilm-embedded organisms so they are not recommended for use. Vancomycin has also been studied in combination with other antimicrobials, such as gentamicin, ciprofloxacin, and colistimethate. When used in combination it can be considered for patients with polymicrobial infections. There needs to be more data on the effectiveness of telavancin with heparin in ALT.[17, 20]

- ***Cyclic lipopeptides (daptomycin)*** - are calcium-dependent and therefore require a calcium-containing solution such as lactated Ringer's solution. This is a medication where cost-effectiveness needs to be considered.[17, 20]

- ***Fluoroquinolones (ciprofloxacin, levofloxacin)*** - should be set aside for gram-negative or multi-drug-resistant organisms. There is conflicting data on the compatibility of ciprofloxacin and heparin. Some studies have demonstrated long-term stability and some have shown only 72 hours. This has been shown to be concentration-dependent. As a result, use caution with this solution by monitoring for any precipitate formation. Levofloxacin with heparin should be avoided due to the physical incompatibilities of these two drugs.[17, 20]

- ***Lincosamides (clindamycin)*** - have been studied in home infusion patients receiving parenteral nutrition, with a heparinized saline solution. There were no reported compatibility issues. Clindamycin lock solutions can be effective against gram-positive organisms.[17, 20]

- ***Oxazolidinones (linezolid)*** - as a lock solution should be reserved for cases with limited treatment options. Although the stability of linezolid with heparin and sodium citrate has been established, there has not been enough published clinical use.[17, 20]

- ***Penicillins (ampicillin, piperacillin, ticarcillin-clavulanic acid)*** - lack substantial data in the use for ALT. Most of the available data is on the penicillin combination timentin (ticar-clav), which has been found to be 90% effective when stored mixed with heparin and refrigerated for up to 10 days. Penicillin is the best medication option when an extended-spectrum therapy is required or when treating a multi-drug-resistant organism.[14,17]

ETHANOL LOCK THERAPY FOR TREATING CRBSI

An alternative to ALT is the instillation of a 70% ethanol lock solution. Ethanol lock therapy (ELT) can be more cost-effective and require a shorter duration therapy compared to ALT.[24] One study demonstrated ethanol locks using a 70% solution with dwell times as short as 4-6 hours, used in conjunction with routine intravenous antibiotics was 92% effective in clearing the infection, with a 72% catheter salvage rate.[25] A 2018 met-analysis showed that ELT significantly decreased the incidences of CRBSI, especially in patients who are immunocompromised and have hematological diseases.[24]

When using ethanol lock therapy, the catheter material needs to be assessed for compatibility. Because VADs are subject to continuous upgrades and technical improvements, the prudent measure is to check compatibility with the manufacturer. It must be noted that due to incompatibility heparin cannot be added to an ethanol lock solution or given immediately before or after locking. Additional considerations for the use of ELT are listed in Exhibit 3. Nursing education on ELT should address the installation procedure, locking in place, and the withdrawal of the solution prior to medication administration.

CONCLUSION

Maintaining vascular access is critical to a successful home infusion plan and achieving optimal outcomes. Heparinized saline has been the gold standard for maintaining catheter patency and inhibiting the associated risks of catheter-related infections and thrombotic complications. However, as adverse events are identified and research outcomes expand our knowledge, it is critical that nursing practice evolves as well. Determining the best solution for catheter maintenance is an area that warrants additional study and it will be essential for clinicians and prescribers to evaluate the evidence to facilitate best practice.

Exhibit 3
Situations When Ethanol Lock Therapy May Not Be Appropriate

- For patients under age of six months or weighing less than 6kg due to concern of systemic alcohol exposure
- Catheters other than CVCs
- In patients with a history of liver disease
- In situations where religious concerns are expressed over exposure to alcohol

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Exhibit 3
Most Commonly Used Antibiotics for Antibiotic Lock Therapy

Drug	Drug Concentration	Additive + Concentration	Stability
Gentamicin			
	0.1 mg/mL	Heparin 5000 units/mL	At 4 ° C, compatible and stable for up to 4 weeks
	5 mg/mL	Heparin 5000 units/mL	In CVCs, 92% of gentamicin concentration retained at 72 hours
	2.5 mg/mL	Trisodium Citrate (TSC) 40 mg/mL	At 37 °C, no decrease in gentamicin or TSC concentration at 96 hours; at room temperature, 100% of gentamicin and 101.3% TSC retained for 112 days
Cefazolin			
	0.5 mg/mL	Heparin 100 units/mL	At 25°C and 37°C, compatible and stable for up to 10 days
	10 mg/mL	Heparin 5000 units/mL	At 37°C, <10% change in absorbance at 72 hours in glass tubes; 27.3% change in absorbance at 72 hours in polyurethane catheter
Ceftazidime			
	0.5 mg/mL	Heparin 100 units/mL	At 25 and 37°C, compatible and stable for up to 7 days
	2 mg/mL	Heparin 100 units/mL	Compatible and stable up to 15 days
	10 mg/mL	Heparin 5000 units/mL	At 37°C, 12.9% change in absorbance at 72 hours in glass tubes; 40.2% change in absorbance at 72 hours in polyurethane catheters
Vancomycin			
	0.025 mg/mL	Heparin 9.75 units/mL	At 4 or 25°C, stable for 40 days
	0.025 mg/mL	Heparin 100 units/mL	At 4°C, vancomycin concentration stable for 14 days; at 37°C concentration reduced by 15-37% at 24 hours
	0.025 mg/mL	Heparin 5000 units/mL	At 4 and 27°C compatible and stable for 72 hours; at 40°C vancomycin concentration reduced by 19% at 72 hours
	0.1 mg/mL	Heparin 5000 units/mL	At 4°C, compatible and stable for up to 4 weeks
	0.5 mg/mL	Heparin 100 units/mL	At 25 and 37°C, vancomycin concentration reduced by <10% at 10 days
	2 mg/mL	Heparin 100 units/mL	Vancomycin concentration of ≥130 mg/mL retained up to 28 days
	2 mg/mL	Heparin 2500 units/mL	At 37°C, compatible and stable for at least 72 hours; at 37°C vancomycin concentration reduced by <10% over 72 hours

Drug	Drug Concentration	Additive + Concentration	Stability
Vancomycin (continued)			
	10 mg/mL	Heparin 5000 units/mL	At 37°C, no change in vancomycin concentration at 72 hours in glass test tubes; 29.7% decrease in concentration at 72 hours in CVCs
	1 and 3 mg/mL	TSC 40 mg/mL	At 4, 25, or 37°C, vancomycin concentration reduced by <8% at 72 hours in PVC syringes of HD catheters
	2 mg/mL	TSC 22 mg/mL	At 37°C, initial precipitation, but precipitation noted after 10 minutes of incubation; vancomycin concentration reduced by <10% over 72 hours
	2 mg/mL	TSC 40 mg/mL	At 37°C, vancomycin concentration reduced by <10% over 72 hours
	5 mg/mL	TSC 22 mg/mL	At 37°C, initial precipitation, but precipitation noted after 10 minutes of incubation; vancomycin concentration reduced by <10% over 72 hours
	5 mg/mL	TSC 40 mg/mL	At 37°C, vancomycin concentration reduced by <10% over 72 hours
Daptomycin			
	1 mg/mL	Heparin 100 units/mL plus LR	At 25°C, daptomycin concentration reduced by 0.6% at 72 hours and reduced by 17.9% at 96 hours
	1 mg/mL	Heparin 1000 units/mL plus LR	At 25°C, daptomycin concentration reduced by 1.7% at 72 hours and reduced by 16% at 96 hours
	5 mg/mL	Heparin 5, 500, or 5000 units/mL plus LR	At 37°C, daptomycin concentration reduced by ≤10% at 24 hours
	1 mg/mL	TSC 28 mg/mL plus LR	At 25°C, daptomycin concentration reduced by 6.7% at 96 hours
Ciprofloxacin			
	0.125 mg/mL	Heparin 100 units/mL	At 25 and 37°C, compatible and stable for up to 10 days
	1 mg/mL	Heparin 2500 units/mL	At 37°C, compatible and stable for up to 72 hours
Ticarcillin/Clavulanic Acid			
	0.5 mg/mL	Heparin 100 units/mL	At 25 and 37°C, compatible and stable for up to 10 days

Sources: Justo AJ, Bookstaver PB. Antibiotic lock therapy: Review of techniques and logistical challenges. *Inf and Drug Resist* 2014;(7):343-363 and Bookstaver PB, Rokas, K, Norris, L, Edwards J, Sherertz R. Stability and compatibility of antimicrobial lock solutions. *Am J Health-Syst Pharm*.2013;70(24):2185-98.