

Central Venous Catheters: Saline or Heparin for Locking?

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Patent peripheral and central venous catheters, the goal for all healthcare settings, will flush easily without resistance; produce a brisk, free-flowing blood return on aspiration; and allow for unimpeded fluid flow through the catheter. Lack of patency is a common and confusing problem. Resistance when the catheter is flushed or failure to obtain the required brisk blood return before catheter use indicates a non-functioning catheter. Fluid flow by gravity may be extremely slow, or the infusion pump could present occlusion alarms. This problem disrupts patient care, threatens attainment of treatment goals, adds to the burden of limited nursing resources, increases the risk of additional complications such as infiltration or extravasation, and increases cost of care.^{1,2}

Catheter occlusion may be categorized as partial or complete occlusion. Partial occlusion means that although the nurse flushes or infuses through the catheter, it does not yield the brisk blood return required for complete assessment of catheter patency. Complete occlusion is defined as the inability to flush, infuse, and aspirate from the catheter. Catheter occlusion can be caused by drug precipitates and several mechanical issues, although intraluminal thrombosis is thought to be the most common factor. Many factors cause blood to move into the catheter lumen from many sources (Table 1). Catheter patency is also affected by fibrin and thrombosis development inside the vein around the catheter tip, where the flushing solution or technique will have no effect. This discussion will be limited to intraluminal causes of thrombotic occlusion, focusing specifically on solutions used to flush and lock the catheter.

Dilute heparin is used as a standard flush to lock most central venous catheters. The exceptions are valved catheters and needleless connectors that are indicated to be used with saline only.³ However, numerous issues regarding the use of heparin have led to serious concerns in recent years. These issues drive the many questions about the continued use of heparin for catheter-locking procedures, including technology changes, cultural concerns, impact on coagulation laboratory values, drug compatibility, biofilm growth, heparin-induced thrombocytopenia, and medication errors.

Overview of Catheter Flushing

Flushing procedures are necessary before and after the administration of intermittent medications through a capped catheter lumen; before and after blood sampling or the infusion of blood products; before and after the administration of incompatible medications; and when converting a catheter from a continuous to an intermittent infusion. The healthcare setting also influences the frequency of flushing. For instance, a hospitalized patient will usually receive flushes after each use and at least every 8 or 12 hours. Patients in home care or an ambulatory infusion clinic will have the catheter flushed daily or after each infusion, which could be less frequent than every day.

The concept of intermittent use of an intravenous (I.V.) catheter began in the early 1970s, when a stopcock was added to plastic tubing on a winged needle infusion

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Table 1. Factors Causing Blood Reflux Into Catheter Lumen		
Action	Explanation	Intervention
Catheter flushing with a traditional syringe	The gasket on the plunger rod is compressed when syringe is emptied. Release of the force on the plunger rod causes expansion of the gasket and draws blood into the catheter lumen	<ul style="list-style-type: none"> • Leave 0.5 to 1 mL of fluid in syringe to avoid gasket compression • Use a prefilled syringe for catheter flushing that is designed to prevent this problem
Disconnecting the syringe from the needleless connector	Many needleless connectors produce negative displacement of blood into the catheter lumen upon disconnection of the syringe or administration set	<ul style="list-style-type: none"> • Know the type of needleless connector being used and corresponding flushing technique • Negative displacement connector requires positive pressure flushing technique <ul style="list-style-type: none"> • Flushing, clamp, then disconnect • Positive displacement connector requires <ul style="list-style-type: none"> • Flushing, disconnection, then clamping • Neutral displacement connector can be clamped before or after disconnection
I.V. fluid container hangs after it has emptied	<ul style="list-style-type: none"> • The pressure from an empty container is lower than venous pressure, causing blood to move into the catheter lumen • Most needleless connectors remain an open conduit while the administration set remains connected • Positive or neutral displacement ONLY occurs upon disconnection of the set or syringe from the connector • The exception to this are the devices that function by pressure, which include PASV® catheters from Navilyst Medical (Natick, MA) and TKO add-on devices from Hospira (Lake Forest, IL) 	<ul style="list-style-type: none"> • All intermittent fluids must be disconnected immediately. Use the proper flushing and clamping sequence described above • Disconnect and flush immediately when medication is infused • Piggyback all intermittent medications into a “carrier” fluid (eg, normal saline) that will continue to flow after the medication has finished
Increases in intrathoracic venous pressure	<ul style="list-style-type: none"> • Coughing, vomiting, sneezing, or congestive heart failure increases venous pressure that can cause blood to move into catheter lumen • Normal heart contractions can also cause blood reflux because there is no valve at the junction of the superior vena cava and right atrium 	<ul style="list-style-type: none"> • Adequately lock the catheter lumen with fluid between infusions • Make sure that infusion pressure is always greater than venous pressure
Compression or manipulation of the catheter, forcing the locking fluid into the bloodstream and causing reflux when the force is	<ul style="list-style-type: none"> • Manipulation of the external catheter segment by pinching or folding • Excessive use of the arm with a PICC produces strong muscle contractions that can compress the catheter 	<ul style="list-style-type: none"> • Teach your patient to perform normal activities of daily living and to avoid excessive or repetitive physical activity or heavy lifting with a PICC • If this is not possible, choose another type of central venous catheter • Avoid inserting central venous catheters in areas where compression is possible, such as the fold of the antecubital fossa and the medial aspect of the subclavian vein • Use a manufactured catheter stabilization device and avoid sutures and tape that can lead to compression • Secure the extension set and needleless connector. Teach your patient to avoid unnecessary manipulation of the external catheter segment (ie, Twiddler’s syndrome)

I.V., intravenous; PICC, peripherally inserted central catheter.

set used in patients with cystic fibrosis. A diluted unfractionated heparin (UFH) solution was instilled into the lumen to ensure it remained patent between uses. Within a short time, manufacturers made commercial products with preattached injection caps or separate injection caps that could be added to any catheter.⁴ The concept of intermittent home parenteral nutrition originated in Seattle in 1970 with the use of a tunneled, cuffed central venous catheter. A report of successful long-term infusion of parenteral nutrition in children was reported in 1979 with the use of silicone central venous catheters that were heparin locked during the daytime.⁵ By 1978, the intermittent infusion of antibiotics through peripheral heparin-locked catheters had moved into the home.⁶

UFH, a potent anticoagulant agent, does not break down existing blood clots but allows the body’s natural fibrinolytic system to act. It prevents additional clots from forming and existing clots from growing larger. Pharmaceutical-grade heparin is most often obtained from porcine intestine or bovine lung. Heparin is one of the oldest drugs in clinical use and actually predates the existence of the FDA.

UFH interacts with antithrombin III, causing the inactivation of several normal clotting factors; interacts with platelets and endothelial cells; increases vascular permeability; restrains the proliferation of smooth muscle cells; and promotes bone loss by suppressing osteoblast formation. The average half-life of heparin is between 30

to 150 minutes, with larger doses producing a longer half-life. The reason for this dose-dependent difference is thought to be caused by large amounts of the drug binding to endothelial cell receptors and macrophages.⁷ The drug's half-life pertains to the dose entering the bloodstream and is not a factor for the dose residing inside the catheter lumen. The therapeutic effect of heparin is measured by the activated partial thromboplastin time (aPTT); values between 1.5 to 2.5 are considered the traditional therapeutic range.⁷ However, patients receiving dilute heparin only for catheter patency do not usually have this blood test performed on a regular basis.

Low molecular weight heparins (LMWH) are made from unfractionated heparin and have superior pharmacokinetic properties. European studies have used LMWH for catheter locking. In the United States, these drugs are given by the subcutaneous route, are not labeled for I.V. use, and are not used for any catheter maintenance procedures.

The past events with heparin contamination have caused the US Pharmacopeia to require additional testing of heparin products. Additionally this new standard requires a change from measurement with the USP unit to the international unit (IU), resulting in a possible decrease in potency by about 10%. This is not anticipated to result in any clinical changes for heparin lock solutions, however therapeutic doses may be affected.

Instillation of dilute heparin into catheters prompted many questions from the inception of its use, and we are still struggling with many of these issues today. Improvements in the design of peripheral and central venous catheters and numerous changes to the catheter-capping devices have introduced additional confusion. There is also growing concern about the use of heparin and its ability to produce or contribute to other catheter complications.

Currently, there are no commercially available alternatives in the United States to heparin lock solution. Ongoing clinical research with alternative solutions may bring about practice changes; however, we must understand the current issues with heparin and the factors that must be considered before heparin is eliminated from catheter maintenance protocols.

Current Guidelines

The Infusion Nursing Standards of Practice establishes the national standard for all infusion therapy.¹ This standard on flushing emphasizes the goals of maintaining patency and preventing contact between heparin and incompatible solutions. The standard incorporates the concepts of catheter flushing and locking. Flushing assesses catheter patency and functionality and removes the previously infused medication. Locking the catheter creates a closed column of fluid inside the catheter lumen intended to prevent blood from moving into the lumen.

Normal Saline

Flushing is accomplished with 0.9% sodium chloride or normal saline. The saline-filled syringe is attached to the catheter hub to determine if blood can be successfully aspirated indicating that nothing is obstructing the catheter's tip. When blood aspiration is not possible with a short peripheral catheter, several factors may be involved. The catheter tip may have punctured the posterior wall of the vein and lie within the subcutaneous tissue. Additionally, the vein wall or a venous valve may be pulled over the catheter lumen, preventing blood backflow. This is possible in patients with anatomical changes caused by diseases or aging. The skin, vein walls, and subcutaneous tissue of geriatric patients become thinner, allowing the vein wall to easily occlude the catheter lumen. Dehydration or fluid volume deficit reduces the volume of blood flow and may allow the vein wall to occlude the catheter. Failure to aspirate blood from a central venous catheter is related to the catheter's tip location, the tip's position relative to the vein wall, the site of in-

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sertion, fibrin or thrombus development inside the catheter lumen and/or in the vein around the catheter tip, or catheter damage. All of these situations have the potential to produce serious problems for the patient.

Flushing is used to clear the catheter lumen of any medication that was previously instilled or infused. Medication incompatibility can produce drug precipitate that occludes the catheter lumen. Flushing with normal saline between each medication can prevent contact between incompatible drugs and prevent the formation of this occluding precipitate. This concern about drug incompatibility extends to heparin lock solution.

Normal saline is available in multi- and single-dose containers. Multidose vials of bacteriostatic normal saline contain benzyl alcohol as the preservative. One animal study recommends no more than 30 mL in 24 hours for adults⁸ and is contraindicated in infants.⁹ The purpose of the preservative is to allow multiple entries into the vial and is not intended to have an impact on catheter-related infection. This preservative produces a bacteriostatic effect by simply inhibiting the growth of organisms. It does not have the ability to actually kill organisms. There have been multiple outbreaks of infection associated with multiple dose vials of saline and heparin used for catheter flushing.¹⁰ For this reason, single-dose containers of preservative-free normal saline are recommended, including single-dose vials and prefilled syringes.¹¹

The volume of normal saline used to flush catheters depends on the type of catheter and the kind of therapy being infused. The Infusion Nurses Society (INS) recently released a set of recommendations on quantities of flush solution.³ A short peripheral catheter is commonly flushed with a minimum of 2 mL, although a larger volume may be required to assess patency when a vesicant medication must be given. A central venous catheter is longer than a peripheral catheter, requiring a minimum of 5 mL for flushing. Blood sampling from the catheter or blood transfusion through the catheter requires a minimum of 10 mL, although 20 mL is often used.

Normal saline is commonly used to lock short peripheral catheters. Two meta-analyses published in 1991 confirmed that there was no difference in peripheral catheter patency when they were flushed with saline only.^{12,13} Practice quickly changed to eliminate the use of heparin solution in these catheters.

The use of normal saline as the locking solution for a central venous catheter depends on the specific brand of catheter or needleless connector being used. Catheters designed with an integral valve were introduced in the mid-1980s and now include valves on the internal (Groshong[®], Bard Access Systems, Salt Lake City, UT; LifeValve, AngioDynamics, Queensbury, NY) and the external (PASV[®], Navilyst Medical, Natick, MA; SoloPICC[®], Bard Access Systems, Salt Lake City) ends of the catheter. These brands have instructions that allow for saline-only flushing. Because the opening pressure for the valve is greater than normal intrathoracic venous pressure, these valves remain closed until pressure is applied for infusion or aspiration.

Catheters with the valve located in the bloodstream may be affected by the fibrin and thrombosis that attach to all catheters. This can impact the function of the valve and is often referred to as persistent withdrawal occlusion (PWO). Clinical outcomes were compared between a group of 28 Groshong tunneled catheters flushed with 5 mL of normal saline and a group of 23 Groshong tunneled catheters flushed with 2.5 mL of heparin 100 units per mL. This nonrandomized study found that PWO occurred less frequently in the heparin group. All saline-flushed catheters displayed intraluminal adherent clots, whereas none in the heparin group had intraluminal clots on explantation. The authors recommended the use of heparin in this valved catheter to decrease clot formation and improve catheter functionality¹⁴ (Table 2).

A randomized study compared a nonvalved peripherally inserted central catheter

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(PICC) with the PASV PICC in 362 patients. The nonvalved catheters were locked with 10 units per mL of heparin and the valved catheters were locked with normal saline. All catheters were flushed after each use or every 8 hours with the valved catheter flushed with saline, producing a lower rate of occlusion¹⁵ (Table 2).

Several brands of needleless connectors also include instructions for saline-only flushing when these devices are attached to the catheter hub. These instructions are based on the design of the connector that overcomes blood reflux from disconnection of the administration set or syringe, commonly known as a positive displacement mechanical valve. Not all brands of these connectors include instructions for saline locking, making it imperative that each nurse understand the specific type of connector being used and the associated instructions.

Heparin

Dilute heparin is recommended as the solution to lock most central venous catheters in the absence of a valved catheter or needleless connector with saline-only instructions. The concentration and volume of heparin locking solution varies greatly; however, the INS Flushing Protocol recommendations provide some guidance. Based on expert consensus and a review of primarily descriptive literature, this protocol recommends the use of 10 units per mL of heparin for locking most central venous catheters. The only indication for heparin at a dose of 100 units per mL is for implanted ports.³ Many port manufacturers have historically recommended use of 100 units per mL of heparin for monthly flushing, and there is a dearth of published studies using lower concentrations. Because of concern about frequent use of higher-concentration heparin to maintain patency of central venous catheters, the lower, 10-unit heparin concentration has evolved over the years as standard practice.

The volume of heparin required to properly lock the catheter depends on the priming volume of the catheter plus any add-on devices. The Infusion Nursing Standards of Practice call for the minimum volume to be equal to twice the internal volume of the catheter system. The INS Flushing Protocol recommends a minimum of 5 mL for central venous catheters to ensure meeting this standard. This overflow should allow for properly filling the entire system, but the excess may have negative aspects.

Published studies assessing the use of catheter flushing and locking solutions have numerous variations, such as patient populations, volume and concentration of solutions used, method of data collection, type of healthcare setting, and study end points¹⁶⁻¹⁸ (Table 2). For these reasons, it is very difficult to pool data for a meaningful analysis. One study assessed flushing and locking procedures with PICCs; however, the majority of the catheters had tip locations in the midclavicular location, which is known for a higher rate of vein thrombosis.¹⁶ Vein thrombosis presents with signs very similar to lumen occlusion, making it difficult to distinguish between the two conditions.

A multicenter German study assessed for the presence of vein thrombosis when various doses of subcutaneous LMWH were given. The study also reported that patients receiving a flushing protocol using fewer than 250 units per mL of heparin were associated with greater rates of thrombosis than patients receiving a flushing protocol using more than 500 units per mL of heparin.¹⁹ Other studies have assessed the patency of venous and arterial catheters with the continuous infusion of saline versus saline with 1 unit per mL of heparin but provide no useful information about the question of locking catheters.^{20,21}

Changes in technology drive the increasing questions about the elimination of heparin lock solution and total reliance on normal saline for locking catheters. Catheters with an integral valve are routinely flushed and locked with normal saline; however, the valve does not contraindicate the use of heparin locking solution.

Based on expert consensus and a review of primarily descriptive literature, this protocol recommends the use of 10 units per mL of heparin for locking most central venous catheters.

Table 2. Studies on Catheter Flushing and Locking				
Author/Year	Type of Study	Type of Catheter	Number and ages of patients	Results
Anderson & Holland, 1992 (ref 15)	Retrospective data analysis, followed by prospective data collection from multiple locations of a national home care company	PICCs, however the tip location was actually midclavicular, not superior vena cava.	Retrospective – 20 patients receiving heparin 100 units per mL; 26 patients receiving heparin 10 units per mL. Prospective – 1 patient receiving heparin 100 units per mL	65 patients receiving 10 units per mL 10 units per mL – 7/21 (33%) completed therapy; 2 (9%) clotted catheters 100 units per mL – 43/91 47% completed treatment; 6 (6%) clotted catheters Authors concluded that 10 units per mL was equally as effective as 100 units per mL
Stephens, et.al., 1997	Descriptive study using sequential cohorts	Apheresis catheters used for stem cell transplantation	Non-heparin group - 29 women, mean age 44 years receiving 10-20 mL saline flush only after each procedure Heparin group – 49 mean and women, mean age of 46 years receiving 10-20 mL saline followed by 5 mL of heparin 100 units per mL after each procedure	Study endpoints included apheresis flow rates less than 50 mL per min, urokinase use for thrombolysis, and radiographic evidence of catheter thrombosis. No significant differences between groups, suggesting that saline may be as effective as heparin
Buswell and Beyea, 1998	Literature review of 6 studies with multiple study designs	Tunneled central venous catheters	More than 1400, adults and pediatric oncology patients	Recommended 5 mL of heparin 10 units per mL once or twice weekly but emphasized the need for prospective randomized studies
Mayo, et.al.1996 (Ref. 13)	Nonrandomized, historical control group of patients compared to prospective data on the experimental group	Groshong double-lumen tunneled catheters flushed and locked weekly with 5 mL saline in the control group compared to a group with the same catheter flushed weekly with heparin 100 units per mL, 2.5 mL	Inpatients and outpatients at a cancer research center: 28 flushed weekly with saline 23 flushed weekly with heparin mean age 48 years, range from 34-66 years	Control group flushed with saline had 94 instillations of a thrombolytic agent over 3420 catheter days, (1 every 36 days) Experimental group flushed with heparin had 14 instillations over 3095 days (1 every 221 days)
Hoffer, et.al.1999 (Ref 14)	Randomized controlled trial in 362 patients	Non-valved 5 Fr open-ended PICC locked with heparin 10 units per mL compared to PASV PICC 5 Fr locked with saline.	182 non-valved catheters and 180 valved catheters; mean patient age was 46 with a range from 18 to 80 years; antibiotics was the primary reason for the catheter placement in both groups	Non-valved group: ● 13 catheter related infections ● 13 catheter occlusions ● 2 phlebitis ● 2 catheter fractures Valved group: ● 6 catheter related infections ● 6 catheter occlusions ● 3 phlebitis ● 3 catheter fracture
Jacobs, et.al. 2004 (Ref 19)	Nonrandomized prospective study in 2 sequential cohorts; 153 pediatric patients	Nontunneled central, PICCs and tunneled catheters with 312 lumens	Group 1- 151 lumens with a split septum needleless connector with heparin flush (concentration not provided) Group 2- 161 lumens with a positive displacement mechanical valve with saline only flushing	Group 1 ● Total and partial occlusion – 23 (15.2%) ● Catheter infection 8.8 per 1000 Group 2 ● Total and partial occlusion 19 (11.8%) ● Catheter infection 15.5 per 1000 catheter days
Schilling, et.al. 2006 (Ref 20)	Nonrandomized prospective study in 360 pediatric patients in sequential cohorts	Nontunneled central, PICC and tunneled catheters with 599 catheter lumens for analysis	Group 1 150 lumens with split septum connector and heparin 10 units per mL Group 2 149 lumens with negative displacement mechanical Group 3 150 lumens with positive displacement mechanical valve and heparin 10 units per mL Group 4 150 lumens with positive	Group 1 ● Total and partial occlusion rate – 26 or 17.3% (20.1 per 1000 catheter days) ● Catheter related infections – 5 or 5.3 per 1000 catheter days Group 2 ● Total and partial occlusion – 13 or 8.7% (2.7 per 1000 catheter days) ● Catheter related infections – 3 or 4.1 per 1000 catheter days Group 3 ● Total and partial occlusion – 11 or 7.3% (8 per 1000 catheter days) ● Catheter related infections 3 or 4.8 per 1000 catheter days Group 4 ● Total or partial occlusion – 12 or 8% (9.3 per 1000 catheter days) ● Catheter related infection – 7 or 10.9 per 1000 catheter days
Bowers, et.al. 2008 (Ref 21)	Randomized controlled trial of 102 patients in general inpatient population	Newly inserted single lumen PICCs for intermittent use with average age of 54	Saline group – Positive displacement mechanical valve needleless connector with saline only flushes Heparin group – Positive displacement mechanical valve needleless connector with heparin 100 units	Saline group – 3 occlusions or 6% Heparin group – 0 occlusions Not statistically significant; but authors emphasized the economic significance of treating 6% of PICCs for occlusion
Cesaro, et.al 2009	Randomized controlled trial in 203 pediatric oncology patients	Newly placed tunneled, cuffed catheters; 102 in control group flushed with saline and heparin 200 units per mL twice weekly using a standard catheter cap; 101 in experimental group flushed with saline only at least weekly using a positive displacement needleless connector	102 in control group 101 in experimental group ages 0 to 17 years, malignant and nonmalignant hematologic oncologic disease	CVC occlusion was most common complication and most frequent in the experimental group 83/101 in experimental vs 41/102 in control group Bacteremia/fungemia 24/101 in experimental group 9/102 in control group Catheter survival rates were comparable for both groups and premature removal was not associated with flush solution or connector.

Needleless connectors introduce more confusion. These devices now include split septum systems and mechanical valve systems. The split septum group is divided into those that require a blunt cannula and those that will accept the male luer end of a syringe or administration set. Mechanical valves have numerous internal designs, including compressible sleeves and collapsing bellows or springs. Some, but not all, needleless connectors have instructions for saline-only flushing and locking. Published research has provided very little information regarding the issue of the most effective locking solution.

Few published studies are available that compare different locking solutions for central venous catheters. Two studies in a pediatric population used sequential cohorts to compare different types of needleless connectors and a variety of locking solutions.^{22,23} One small, randomized prospective study used a positive displacement mechanical valve on all patients with peripherally inserted central catheters and compared flushing with heparin and flushing with saline only. The authors rejected the saline-only locking procedure, citing the cost of the declogging procedure on 6% of their PICCs annually²⁴ (Table 2).

A recent randomized prospective study compared a twice-weekly flush of heparin (concentration and volume not reported) using a “standard CVC cap” with a weekly flush of normal saline using a positive displacement mechanical valve²⁵ (Table 2).

Patient age is another factor in the concern about catheter flushing. A 2009 policy recommendation from the American Society of Health-System Pharmacists concluded, “The data are conflicting and insufficient to support the recommendation of a preferred solution for line maintenance in neonatal patients at this time.” They went on to emphasize the need for decreasing practice variations through standardized concentrations of heparin and the recommended the use of “manufacturer-prepackaged products” as the best method to provide safe care for neonates.²⁶ This recommendation suggests that prefilled syringes for catheter flushing could eliminate the risk associated with preparing syringes on the nursing unit.

The value of using normal saline exclusively for maintaining catheter patency has not been well established. The use of add-on needleless connectors with instructions for saline-only flushing and locking procedures adds greater confusion; however, there is a trend toward greater complications with saline-only flushing. There are limited studies on valved catheters, and they have conflicting results based on where the valve is located.

Clinical Issues With Heparin

Numerous issues regarding the use of heparin have led to serious concerns in recent years. These issues drive the many questions about the continued use of heparin for catheter locking procedures.

Cultural Concerns

Heparin is primarily derived from pork, possibly indicating that its use in Muslim and Jewish patients would be prohibited. Islamic medical scholars issued a letter to the World Health Organization in 2001 stating that the process of making many medications transformed the substance from impure and prohibited to pure and acceptable. Jewish leaders have also issued a similar statement about non-oral medications derived from pork.²⁷

Impact on Coagulation Laboratory Values

Two clinical situations generate concerns about heparin and its effect on coagulation: locking hemodialysis catheters with very large doses of heparin and obtaining blood samples for coagulation laboratory values from any catheter that has been exposed to heparin.

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Hemodialysis catheters may be locked with very large doses of heparin, frequently as high as 5000 units per lumen. The volume of heparin instilled may be larger than the priming volume of the catheter lumen, resulting in overspill of heparin into the bloodstream. Additionally, some hemodialysis catheters have multiple side holes, causing the locking solution to leak out of the lumen and into the bloodstream. Although the common recommendation is to withdraw this heparin locking solution from the catheter lumen before dialysis, this step may be overlooked, resulting in the entire quantity being injected into the bloodstream.^{28,29} A French study of hemodialysis catheters found normal aPTT values immediately after dialysis, yet all patients had elevated aPTT values 10 minutes after locking each lumen with 2 mL containing 5000 units of heparin, a total of 10,000 units of heparin.³⁰ The American Society for Diagnostic and Interventional Nephrology (ASDIN) now recommends the use of 1000 units per mL of heparin for hemodialysis catheters. The use of higher doses should be reserved for patients who have experienced catheter lumen occlusion or thrombosis.³¹

Several studies have assessed the accuracy of various coagulation laboratory values when the sample was taken from a catheter exposed to heparin. Significant differences in prothrombin time (PT) and aPTT were reported from a small study in oncology patients. Samples were taken from peripheral veins and compared with samples taken from central venous catheters locked with 100 units per mL of heparin. Blood equal to 6 times the interval volume of the catheter was discarded before the laboratory sample was drawn.³² A similar study found that 25 mL of blood must be discarded before obtaining the laboratory sample for coagulation studies. This large discard volume results in clinically useful PTs and fibrinogen levels in all samples and 95% of the aPTTs.³³ Another study reported that discard volumes of 6 mL, 9 mL, and 12 mL were not sufficient to obtain correct values for PT, fibrinogen levels, and aPTT. Although there were statistical differences for all three blood tests, clinical experts thought that there was enough difference in the aPTT values to wrongly influence clinical decisions.³⁴ Requirements for withdrawing and discarding relatively large volumes of the patient's blood from a central venous catheter causes serious concern about the impact on total circulating blood volume, especially in acute-care patients who may have already lost blood from other sources.

Drug Compatibility

Heparin is incompatible with numerous other medications; however, there have been very few studies assessing compatibility between a medication inside the catheter lumen that is followed by a heparin locking solution. Trissel's Handbook of Injectable Drugs reports precipitate formation when meperidine, promethazine, hydroxyzine HCl, gentamicin sulfate, tobramycin sulfate, metilmicin sulfate, and amikacin sulfate are administered into a heparinized catheter.³⁵ If data were available for all I.V. medications, this list would possibly be much longer. In the absence of data confirming that 2 drugs are compatible, one must always assume incompatibility. To assure that the I.V. drug does not come into contact with the heparin lock solution, saline should always be used to flush the residual drug from the catheter's lumen prior to locking with heparin.

Influence on Biofilm Growth

There are several reports stating that the presence of heparin inside the catheter lumen has a beneficial effect on reducing catheter-related bloodstream infections. As early as 1949, reports about the bacteriostatic nature of heparin appeared in the literature.³⁶ A meta-analysis of randomized trials using heparin as a low-dose infusion, a locking solution, and heparin-bonded catheters concluded that all uses of heparin showed a strong trend toward reducing catheter-related thrombosis and bacterial colonization of the catheters.³⁷ In vitro studies have focused on the preservative in the heparin lock solutions as the agent that provides the antimicrobial activity and therefore would reduce catheter-related infection.³⁶ Two reports of clinical studies revealed a trend toward reduction of catheter-related bloodstream infection when catheters were locked with heparin, although there were limitations due to varying

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definitions of catheter-related infections and other issues with study design.

In 2005, *in vitro* studies reported that heparin actually stimulated the growth of biofilm, the polysaccharide matrix known to be the most important factor in the pathogenesis of catheter-related bloodstream infections. Heparin concentrations ranging from 0.1 unit per mL to 1000 units per mL were shown to cause *Staphylococcus* adhesion and biofilm formation when tested in a polystyrene microtiter plate. The researchers reported that increased cell–cell interactions after primary attachment appeared to be the mechanism for heparin-stimulated biofilm growth.³⁸ A subsequent *in vitro* study compared the formation of biofilm on polystyrene, polyurethane, and silicone elastomer after each material was exposed to lepirudin, LMWH, tissue plasminogen activator, sodium citrate, sodium citrate with gentamicin, and sodium ethylene diamine tetra-acetic acid (EDTA). LMWH was shown to stimulate the growth of biofilm.³⁹

There is strong clinical evidence of *Pseudomonas fluorescens* bloodstream infections after patients were exposed to contaminated heparin flush solution in prefilled syringes. A multistate outbreak of *P fluorescens* bloodstream infections, first reported in March 2005, resulted in voluntary recall by the manufacturer. *P fluorescens* was obtained from catheter and/or blood cultures and confirmed by pulsed-field gel electrophoresis to be the same organisms as that in the contaminated heparin. Scanning electron microscopy confirmed the presence of *P fluorescens* biofilm in explanted catheter segments. Many of these bloodstream infections were delayed from 84 to 421 days after exposure to the contaminated heparin solution. Delay of the signs and symptoms were related to the colonization of existing biofilm or formation of new biofilm from the contaminated solution with subsequent flushes using uncontaminated flush solution, disturbing the biofilm and flushing it into the bloodstream.⁴⁰

Another outbreak of *Pseudomonas putida* and *Stenotrophomonas maltophilia* was confirmed in heparin lock syringes prepared by a compounding pharmacy. Of 48 patients with a central venous catheter flushed with this solution, 41 were found to have a bloodstream infection with one of these organisms.⁴¹ Given this diversity of information, the actual impact of heparin on the development of catheter-related bloodstream infections requires additional study.

Side Effects of Heparin Lock Solution

Bleeding

Leakage or spillage of the locking fluid from the catheter lumen is a factor with all catheters, but the greatest concern is associated with hemodialysis catheters, in which the instilled heparin may be as many as 5000 units of heparin. In such situations, bleeding from excessive anticoagulation has been reported. This is another reason for the position taken by ASDIN on limiting the heparin lock solution to 1000 units per mL.³¹

Leakage has been demonstrated to occur immediately following the locking procedure and late during the locked period between uses. Leakage of the locking solution in the late period is associated with gravity; internal compression of the catheter, such as pinch-off syndrome between the clavicle and first rib or the muscle pump action that causes normal venous compression; viscosity of the locking solution; and the number of holes in the catheters. Manufacturers could also have imprecise priming volumes of catheter lumens in specific product literature, thus adding to the volume that spills from the catheter during the locking procedure.

Using the equivalent of a catheter's priming volume, multiple brands of hemodialysis catheters were filled with 5000 units per mL of heparin. Early leakage was calculated to range between 2900 units and 6550 units of heparin and late leakage was calculated to range between 5350 units and 6850 units. These doses would be

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enough to cause bleeding in many patients.⁴²

Although leakage from hemodialysis catheters locked with high doses of heparin is known to lead to bleeding episodes, infusion catheters do not produce similar outcomes due to the much lower concentrations of heparin being used. However, leakage of locking solution from any catheter is not a desirable situation. Locking fluid moving out of the catheter lumen is replaced with blood and may increase the risk of lumen occlusion.

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT), a severe immunologic drug reaction known to cause arterial and venous thrombosis, raises serious concern regarding the use of heparin. Platelet factor 4 (PF4) is released when platelets are activated, with some PF4 binding to the injected heparin. This combination stimulates the development of immunoglobulin antibodies, known currently as HIT-IgG, whereas older studies used the term "heparin-associated antiplatelet antibodies."^{43,44} Platelet counts drop by at least 50% from the baseline value. HIT-IgG activates the clotting cascade, causing formation of thrombosis within 5 to 10 days after heparin exposure begins. Delayed reactions have been reported, with thrombocytopenia and thrombosis occurring as late as 40 days after the heparin has been discontinued.⁴⁴

The true incidence of HIT caused by heparin lock solution is unknown, but studies have attributed its occurrence to exposure to this small dose of heparin. This indicates that the pathophysiology does not depend on the dose of heparin. A 1999 study reported 3 cases and found 29 previously reported cases in the literature.⁴⁵ A 2006 study reported that heparin exposure from catheter flushing was the most common cause in 210 of 2046 antibody-positive patients.⁴⁶ Several other case reports of HIT have associated its occurrence with catheter flushing procedures, and there is 1 report associated with heparin-coated catheters.⁴⁷⁻⁵⁰

A study using argatroban to treat HIT analyzed the multicenter data to identify 23 patients whose only heparin exposure was from catheter flushing procedures. The median heparin dose was 400 units, ranging from 10 to 13,000 units. Catheters were flushed for a mean of 8.1 days, with a range 3 to 16 days, before HIT diagnosis. These authors emphasized that heparin used for catheter flushing may be undocumented in the medical record and therefore may be overlooked as the cause of the problem.⁵¹

Those at greatest risk for HIT include those receiving any form of UFH, those receiving treatment with UFH for more than 1 week, surgical patients, and female patients. A scoring system places patients in the moderate-risk group when they are postoperative patients receiving UFH catheter flushes for more than 4 days. This group is estimated to have a risk of 0.1% to 1%. The recommendation for platelet counts in this moderate-risk group is every 2 to 3 days from day 4 to day 14 or until heparin is stopped, whichever is first. This recommendation emphasizes this frequency when practical, realizing that many postoperative patients may be discharged from the hospital prior to the end of this period. Medical patients receiving only heparin lock solution are in the low-risk group, and routine platelet counts are not recommended.⁴⁴

Medication Errors

The most critical medication errors involving heparin lock solution have resulted in the deaths of at least 3 neonates and put at least 20 others at serious risk for injury. The deaths occurred in an Indiana hospital in 2006 when vials of heparin 10,000 units per mL instead of heparin 10 units per mL were placed in the storage area on the nursing unit. The same error was repeated in California in 2007, although no deaths occurred. In 2008, a medication mixing error in a Texas hospital pharmacy resulted in 17 infants receiving doses of heparin as much as 100 times the intended dose.⁵²

Heparin-induced thrombocytopenia (HIT), a severe immunologic drug reaction known to cause arterial and venous thrombosis, raises serious concern regarding the use of heparin.

These errors occurred because vials of heparin may have similar appearances, although the dosages are very different. Confirmation bias causes such errors. When nurses look at a label on a vial taken from its customary place, they may see what they anticipate will be on the label rather than what actually is written there.⁵³ They are expecting to see a label of heparin 10 units per mL and do not realize that it actually states heparin 10,000 units per mL.

The Institute for Safe Medication Practices (ISMP) has also received reports of at least 2 deaths and other injury from the mistaken use of insulin instead of heparin to flush central venous catheters.⁵⁴

Another form of medication error involves the incorrect use of multidose vials. Reports of outbreaks of hepatitis B and C and HIV have been documented as a result of contaminated vials of heparin and normal saline used for catheter flushing. This usually occurs when a contaminated syringe and/or needle is used to withdraw a second dose of solution from the vial. Changing the needle alone is not sufficient to prevent such contamination. Subsequent use of the same vial exposes other patients to this contaminated medication.⁵⁵⁻⁶¹

The ISMP makes strong recommendations for preventing such errors, including standardizing the stock of heparin dosages to a limited number, thus preventing confusion associated with many concentrations; separating the storage of heparin and insulin vials in all areas such as countertops, drug carts, and under the laminar flow hood in the pharmacy; performing independent double checks by 2 professionals when heparin must be drawn from a vial; using bar coding for all medication dispensing and administration; and using prefilled syringes for all catheter flushing procedures, preventing the need for syringe preparation by pharmacy or nursing staff.⁵²⁻⁵⁴

Costs

Obviously, elimination of one step in the catheter flushing and locking procedure would reduce costs. Using normal saline alone and dispensing with the use of heparin would eliminate the costs of either prefilled syringes or vials, syringes, and nursing time required to properly fill and label the syringe. Cost was a major factor in the decision to eliminate heparin from the flushing procedure for short peripheral catheters. Studies showed no clinical difference in the patency of peripheral catheters flushed with saline alone versus those flushed with saline and locked with heparin. A 1991 meta-analysis estimated an annual cost savings of more than \$218 million, a figure that would be much higher by today's standards.¹²

The same analysis cannot be made for flushing central venous catheters with saline only. As discussed, the use of add-on needleless connectors with instructions for saline-only flushing does not produce the same outcomes as saline for flushing followed by locking with heparin. Bowers et al reported an annual savings of almost \$23,000 from the continued use of heparin for locking PICCs. This dollar amount is based on patient charges rather than on operational costs. Cesaro et al reported higher complication rates in tunneled catheters with the saline-only flushing protocol and one of the positive displacement needleless connectors.²⁵

Management of complications associated with saline-only flushing must be considered in the cost analysis, but no additional published resources are available. Ideally, this analysis should focus on operational costs rather than on patient charges; however, cost figures may be more difficult to obtain. The operational cost of PICC insertion is approximately \$200, whereas the costs of surgically inserted central venous catheters exceeds \$1500.⁶² The analysis should also include the cost of saline flushes and the add-on needleless connector compared with the costs of saline and heparin with a more conventional needleless connector, the costs of treating lumen occlusion with a thrombolytic agent and bloodstream infections with antibiotics,

When nurses look at a label on a vial taken from its customary place, they may see what they anticipate will be on the label rather than what actually is written there.⁵³

and the costs of removal and replacement of the catheter if treatment is unsuccessful.

Potential Alternative Locking Solutions

One strategy to improve catheter performance and reduce the risk of catheter-related bloodstream infections (CRBSI) is to use different locking solutions. Much research has been published about substitutes for heparin lock solutions, yet no alternative solutions are commercially available in the United States at the present. The locking solutions discussed below are only available from a compounding pharmacy.

Combinations of various antibiotics and heparin, known as antibiotic lock therapy (ALT), have been suggested as a means to treat existing CRBSI. Although this has been reported as a successful treatment for the salvage of infected catheters, the use of ALT as a routine prophylactic flushing or locking solution remains controversial. There is growing concern about the development of drug resistance when ALT is routinely used. Because these questions do not address the fundamental issue of alternatives to heparin, ALT is not included in this discussion.

The published literature contains two major trends—improving catheter flow rates in hemodialysis patients and reducing catheter-related bloodstream infection in all types of central venous catheters. The criteria for an alternative locking solution should focus on the following key points:

- The required length of time the solution must remain in the catheter lumen to be effective. An extended period (ie, 20-24 hours) would make the solution inappropriate for critical-care patients receiving frequent doses of medication.
- The absence of adverse reactions when the locking solution is flushed through the catheter. It would be virtually impossible to ensure that every nurse would remember to aspirate and discard the locking solution rather than the current practice of flushing it into the bloodstream
- The effectiveness for ensuring catheter patency
- The effectiveness of reducing or preventing the development of intraluminal biofilm and subsequent CRBSI
- The impact of the locking solution on the integrity of the catheter material
- The compatibility of the locking solution with other fluids and medications infused through the catheter

Ethylenediaminetetraacetate (EDTA) was suggested as an alternative locking solution approximately 20 years ago because it has anticoagulant properties and kills *Staphylococcus* and *Candida*. Disodium EDTA combined with minocycline has been shown to reduce fresh and mature biofilm in animal, in vitro, and ex vivo studies.⁶³⁻⁶⁵ Tetrasodium EDTA is now the focus of research.^{66,67}

Ethanol has been used for more than 20 years for the treatment of catheters occluded with fat emulsion, yet there has always been concern about the use of all alcohol solutions in catheters made of polyurethane. There are three types of polyurethane used in the manufacturer of catheters. The oldest is an organic compound in an open chain structure. This type has the potential for stress cracking. The catheter surface can feel tacky after exposure to alcohol because the material absorbs the alcohol and swells but does not return to its original size when dry. The second generation of polyurethane material is more chemically stable because of changes in the organic structure. The most recent formulation has the greatest chemical tolerance with the lowest risk of stress cracking. In vitro testing by exposing the second generation of polyurethane to 70% ethanol has demonstrated no changes in the force required to break a catheter segment or the maximum elongation and strain before breakage.⁶⁸ It is imperative to know the catheter manufacturer's instructions before exposing it to any form of alcohol, as these instructions would be based on

Much research has been published about substitutes for heparin lock solutions, yet no alternative solutions are commercially available in the United States at the present

the specific type of polyurethane being used.

Ethanol as a locking solution has been successfully used to treat catheter-related bloodstream infection. Ethanol concentrations in these studies ranged from 25% to 74%, and catheters were locked for 12, 20, and 24 hours. A randomized animal study locked tunneled catheters contaminated with *Staphylococcus epidermidis* with either 70% ethanol or heparinized saline for one 3-hour treatment. Intraluminal and extraluminal catheter surfaces were then cultured with more catheters in the ethanol group, producing no growth.⁶⁹ Another randomized study compared locking tunneled cuffed catheters in hematology patients. All catheter lumens were locked with heparin lock solution or 70% ethanol for 2 hours each day. The solution was then aspirated and all lumens were locked with heparin lock solution for the remainder of the day. Three patients in the ethanol group and 11 in the heparin group developed a bloodstream infection.⁷⁰

Sodium citrate acts as an anticoagulant by binding to calcium and removing it from the coagulation cascade. It is also antibacterial in hypertonic concentrations. Studies have included 4%, 10%, 30%, and 47% concentrations of sodium citrate.⁷¹⁻⁷⁵

Taurolidine is a derivative of the amino acid taurine, which inhibits and kills a wide range of organisms. Randomized and nonrandomized studies of dialysis catheters have compared combinations of citrate and taurolidine with heparin and found favorable results.⁷⁶

An in vitro study examined the effects of 4% citrate and 30% ethanol on the newest formulations of polyurethane. Although the force required to elongate and break the catheters was lower with citrate/ethanol than with catheters exposed to heparin, the authors thought this difference was not significant in clinical applications.⁷⁷ Biofilm reduction was demonstrated in another in vitro study of hemodialysis catheters.⁷⁸

Another in vitro study found that a combination of 7% sodium citrate, methylene blue, and parabens showed positive benefits as a locking solution compared with heparin plus preservative. This combination is effective against free-floating and attached biofilm.⁷⁹

Tissue plasminogen activator as a catheter-locking solution has been compared with heparin locking in hemodialysis catheters and was shown to produce greater flow rates and fewer complications.^{80,81} A study comparing 3 mL of lepirudin 100 micrograms per mL with 3 mL of heparin 100 units per mL in catheters used for bone marrow transplantation showed lepirudin to be no more effective than heparin. There is also concern about anaphylactic reactions to lepirudin.⁸² A literature review of 5 randomized trials comparing heparin locking with urokinase locking found that the methodology of those trials prevented a recommendation of one solution versus the other.⁸³

Clinical Decisions

This review provides many aspects of heparin use as a locking solution that require consideration; however, there are no concrete answers about the numerous issues associated with heparin. The goal among many healthcare professionals appears to be the elimination of heparin as a catheter locking solution, but this decision requires careful assessment of many factors. Based on the data presented, saline alone is not a reliable solution for ensuring catheter patency regardless of the type of needleless connector being used. To minimize complications, the data suggest that some form of anticoagulation is needed for central venous catheters. The alternative solutions will provide the added benefit of reducing CRBSI as well, but there are no commercially available alternative solutions on the US market. These solutions must be prepared in a compounding pharmacy.

Ethanol as a locking solution has been successfully used to treat catheter-related bloodstream infection.

While we wait for clearance by the FDA, we must make careful decisions about catheter lock solutions. Rapid elimination of heparin lock solutions may not be the best alternative. These decisions must be based on an assessment of many factors in each facility. All facilities currently using one of the technologies with instructions for heparin elimination should be documenting outcomes with the use of the catheter or needleless connector. These outcomes should include

- frequency of catheter lumen occlusion;
- quantity of thrombolytic agents and declotting procedures required in the patient population;
- rate of CRBSI in the facility with changes in this rate correlated to recent product change; and
- rate of heparin-induced complications in the patient population.

Patient safety is foremost in all healthcare practice settings today, followed closely by cost containment. The elimination of heparin lock solutions for central venous catheters requires a careful assessment of the evidence by a collaborative, multidisciplinary team of professionals. Does the risk of heparin elimination (eg, loss of catheter patency, diagnosis, treatment, and possible catheter replacement) outweigh the benefits derived from using saline only as a locking solution for central venous catheters? These and many other questions require careful evaluation. Heparin remains the recommended locking solution for intermittent central venous catheters.¹ However, research on alternative solutions is ongoing and ideally will allow for practice changes in the future.

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