



PROVINCIAL STANDARDS & GUIDELINES



Alteplase Use for Occluded Hemodialysis Catheters

May 2017

Developed by the BCPRA Hemodialysis Committee

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IMPORTANT INFORMATION

This BCPRA guideline/resource was developed to support equitable, best practice care for patients with chronic kidney disease living in BC. The guideline/resource promotes standardized practices and is intended to assist renal programs in providing care that is reflected in quality patient outcome measurements. Based on the best information available at the time of publication, this guideline/resource relies on evidence and avoids opinion-based statements where possible; refer to www.bcrenalagency.ca for the most recent version.

For information about the use and referencing of BCPRA provincial guidelines/resources, refer to <http://bit.ly/28SFr4n>.



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Alteplase Use for Occluded Hemodialysis Catheters

This guideline is intended for adults and for children weighing over 10 kilograms. For children weighing less than or equal to 10 kilograms, the concentration and dosage need to be adjusted.

1.0 Scope of Guideline

This guideline provides recommendations for the use of thrombolytic alteplase (Cathflo®) to maintain catheter patency.

A well functioning vascular access is a prerequisite for hemodialysis (HD). To be consistent with national and international standards, the BCPRA HD Committee has identified the preferred form of HD vascular access as the native arteriovenous fistula (AVF), followed by the artificial arteriovenous graft (AVG) and lastly the central venous catheter (CVC).

Despite all best efforts for patients undergoing HD to have an AVF (preferred) or AVG (2nd choice), there will always be patients that receive HD by CVC on a temporary or permanent basis. The most common complications of CVCs are thrombosis and infection (Develter, 2005 and Little, 2001). Even with care, fewer than half the CVCs placed as “long-term accesses” are in use a year after placement (Ponikvar, 2005) and about a third are removed because they fail to deliver adequate blood flow (K/DOQI 2006).

The initial approach to treatment of a dysfunctional or blocked CVC is conservative — rule out mechanical issues

such as machine problems or kinks in the CVC and forcefully flush the lines with normal saline. If conservative measures fail, the administration of thrombolytic agents may be required.

2.0 Summary of the Literature

Use of recombinant tissue plasminogen activators (rtPAs) (alteplase, reteplase or tenecteplase)

Mokrzycki and Lok (2010) reviewed the literature on the use of rtPAs (alteplase, reteplase or tenecteplase) for the treatment of thrombosis in CVCs between 1993 and 2010. The short-term success rate ranged from 40% to 92% in the 18 studies reviewed. None of the trials compared the effects between the three different rtPAs.

Mokrzycki and Lok stratified the 18 studies according to method of instillation: push/pause method, dwell (short and long-term) and/or infusion. They noted that:

- Methods of instillation were not compared in the studies.
- Dwell time did not significantly impact short-term or 2-week patency rates in the two trials where this was studied (Nguyen, 2004 and MacRae, 2005).
- The success rate diminished with each subsequent dose of rtPA.

Success rates by method of instillation

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were as follows:

Push/pause method (4 studies):

- Short-term: 59% to 92%.
- Long-term: 60% patency at 30 days.

Short dwell (6 clinical trials; dwell time \leq 60 min):

- Short-term: 69% to 97%; 22% to 97% if Tumlin's tenecteplase study (2010) is included.
- Long-term: median time to next intervention: 12.5 to 30 days.

Long-dwell (7 studies; dwell time 2 to 72 hrs):

- Short-term: 79% to 100%; 22% to 100% if Tumlin's tenecteplase study (2010) is included.
- Long-term: median patency after rtPA was 14 to 30 days.

Infusion (3 studies):

- Short-term: 84% to 91%.
- Long-term: 55% patency at 30 days.

Another systematic review by Hilleman & Campbell (2011), on the safety and efficacy of alteplase, tenecteplase and reteplase for clearing HD CVCs included literature published between 1975 to 2010. The success rate was highest with reteplase ($88 \pm 4\%$), followed by alteplase ($81 \pm 37\%$) and tenecteplase ($41 \pm 5\%$).

Use of Alteplase

Alteplase is used for CVC thrombosis in HD centres in BC. It is the only thrombolytic agent approved for CVC clearance and studies suggest a higher success rate

with alteplase compared to tenecteplase. Reteplase is no longer available in Canada.

Below is a summary of the results from 16 clinical trials on the use of alteplase for the treatment of thrombosis in CVCs:

Success rates:

- Definitions of "success" differed between studies. Common definitions included:
- Short-term success: blood pump speeds of 250 to 300 mL/min and/or the ability to initiate HD.
- Long-term success: the time from the first course to the next course of alteplase treatment and/or CVC patency and/or survival.
- Short-term success rates ranged from 59% to 100%.
- The time from the first course to the next course of alteplase ranged from 12.5 to 30 days. Patency rates ranged from 54% to 60% at 30 days.

Method of instillation:

- There was no obvious correlation between method of instillation and success.
- This finding was similar to that reported in two systematic review articles (Mokrzycki and Lok, 2010 and Lok, 2006).

Dosages:

- For the push/pause and dwell methods, dosages ranged from 1 to 2 mg/lumen. There was no obvious correlation

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between dosage and success.

- For the infusion methods, the dosage ranged from 4 to 10 mg. Again, there was no obvious correlation between dosage and success.
- The observed lack of correlation between dosages and success was similar to that reported in two systematic review articles (Mokrzycki and Lok, 2010 and Lok, 2006).
- Two studies reported a cost savings from the use of a lower dosage (Hamond, 2005 and Nguyen, 2004).

Refer to Appendix 2 for a summary of the results of the 16 clinical trials on the use of alteplase for the treatment of thrombosis in CVCs (study design, dose, protocol, population, definitions of “success” and short and long-term success rates).

Prevention of Catheter Lumen Occlusion with rtPA versus heparin (Pre-Clot) Study

- The Pre-Clot study was a randomized controlled trial evaluating the effectiveness of weekly alteplase lock for the prevention of HD CVC malfunction. Patients from 14 centres across Canada were randomized to the treatment arm received alteplase 1 mg/lumen once per week, with heparin 5,000 units/mL as a CVC locking solution for the remaining two sessions. Patients randomized to the control arm received heparin 5,000 units/mL as a CVC locking solution after each HD.
- Results suggested that patients in the alteplase arm had significantly fewer CVC malfunctions 20 vs. 24.8% HR

1.91 (95% CI 1.13 to 3.22, $p = 0.02$) and fewer episodes of bacteremia 4.5% vs. 13% HR 3.3 (95% CI, 1.18 to 9.22, $p = 0.02$) There were no significant differences in bleeding.

This is the first large, well-designed trial that has evaluated the routine prophylactic use of alteplase lock in HD CVCs. It has not yet been replicated in other trials.

In summary, alteplase and other rtPA medications appear to be effective as a short-term option for treating thrombosis-related dysfunctional CVCs. While many studies do not support the use of rtPA in preventing thrombosis, the results of the more recent Pre-Clot study does provide some evidence for the use of alteplase. However, until cost-effectiveness of this strategy has been proven and similar results have been replicated in other trials, the use of alteplase to prevent thrombosis is recommended only in specific circumstances in BC (refer to recommendation #5).

3.0 Recommendations & Rationale

Recommendation 1:

Prevent and/or reduce incidences of CVC-related thrombosis by:

- **Regularly assessing HD performance and early recognition of problems (see next point for signs of CVC dysfunction).**
- **Forceful flushing with normal saline pre- and post-HD and capping the CVC pre- and post-HD with heparin**

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or citrate.

- Regularly reversing the flows (e.g., once per week) if using Palindrome catheters (opinion). Not recommended with any other CVC
- Using newer CVCs that are capable of achieving rates of ≥ 400 mL/min when properly placed.
- Using needle-free connectors for HD lines.

Signs of CVC dysfunction include (K/DOQI, 2006):

- Blood pump flow rate < 300 mL/min
- Arterial pressure (< -250 mmHg) or venous pressure (> 250 mmHg)
- Ratio of blood pump flow to the absolute value of pre-pump pressure (conductance) (< 1.2)
- Urea reduction ratio (URR) progressively $< 65\%$ (or $Kt/V < 1.2$)
- Unable to aspirate blood freely (late manifestation)
- Frequent pressure alarms—not responsive to patient repositioning or CVC flushing
- Trend analysis of changes in access flow is the best predictor of access patency and risk for thrombosis.

Recommendation 2:

If CVC dysfunction is identified, rule out causes other than thrombosis as the source of the dysfunction.

Causes of CVC dysfunction other than thrombosis includes mechanical reasons such as kinks (angulation in tunnel), misplaced sutures, CVC migration, drug precipitation (some antibiotic locks or IV

IgG), hypovolemia, patient position, CVC integrity, holes and cracks (KDOQI, 2006). Such causes need to be ruled out prior to the use of thrombolytics.

Recommendation 3:

If CVC dysfunction is related to thrombosis, administer alteplase as per prescriber's orders, using the algorithm (section 4.0) and pre-printed orders (section 5.0) as a guideline.

After mechanical reasons, thrombotic occlusion (partial or total) is the most common cause of CVC dysfunction and/or occlusion. Common sites of thrombus formation are the CVC lumen (intraluminal), along the CVC and vein wall (mural), the CVC tip (fibrin tail) and along the external surface of the CVC (fibrin sheath).

Alteplase is the thrombolytic agent of choice for treating occluded HD CVCs. Alteplase works by binding to fibrin in a thrombus, then converting the entrapped plasminogen to plasmin which results in local fibrinolysis (i.e. digests fibrin and dissolves blood clot).

While alteplase has proven to be useful in the management of CVC-related thrombotic occlusions, little published evidence exists addressing the most effective method(s) of administration. Guidelines are provided in this document for the three most commonly used methods: push/pause, dwell (short and long) and infusion (simultaneous infusion method via arterial and venous lumens prior to initiating HD and single lumen method during HD). Selection of

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the method will depend on individual circumstances including the severity of the occlusion and the timing and urgency of the need for HD.

Alteplase is an expensive medication (2 mg = \$65; 4 mg = \$130). It is important that its use and dosage be limited to that which is absolutely necessary. Generally speaking, a graduated dosing scheme is recommended, starting with a lower dose and increasing to a higher dose if the lower dose is not effective. This guideline provides a range of dosages to allow for this practice.

Recommendation 4:

Notify the physician if one or both lumens are still “sticky” or blocked after administering alteplase more than twice on two separate occasions in a 2-week period.

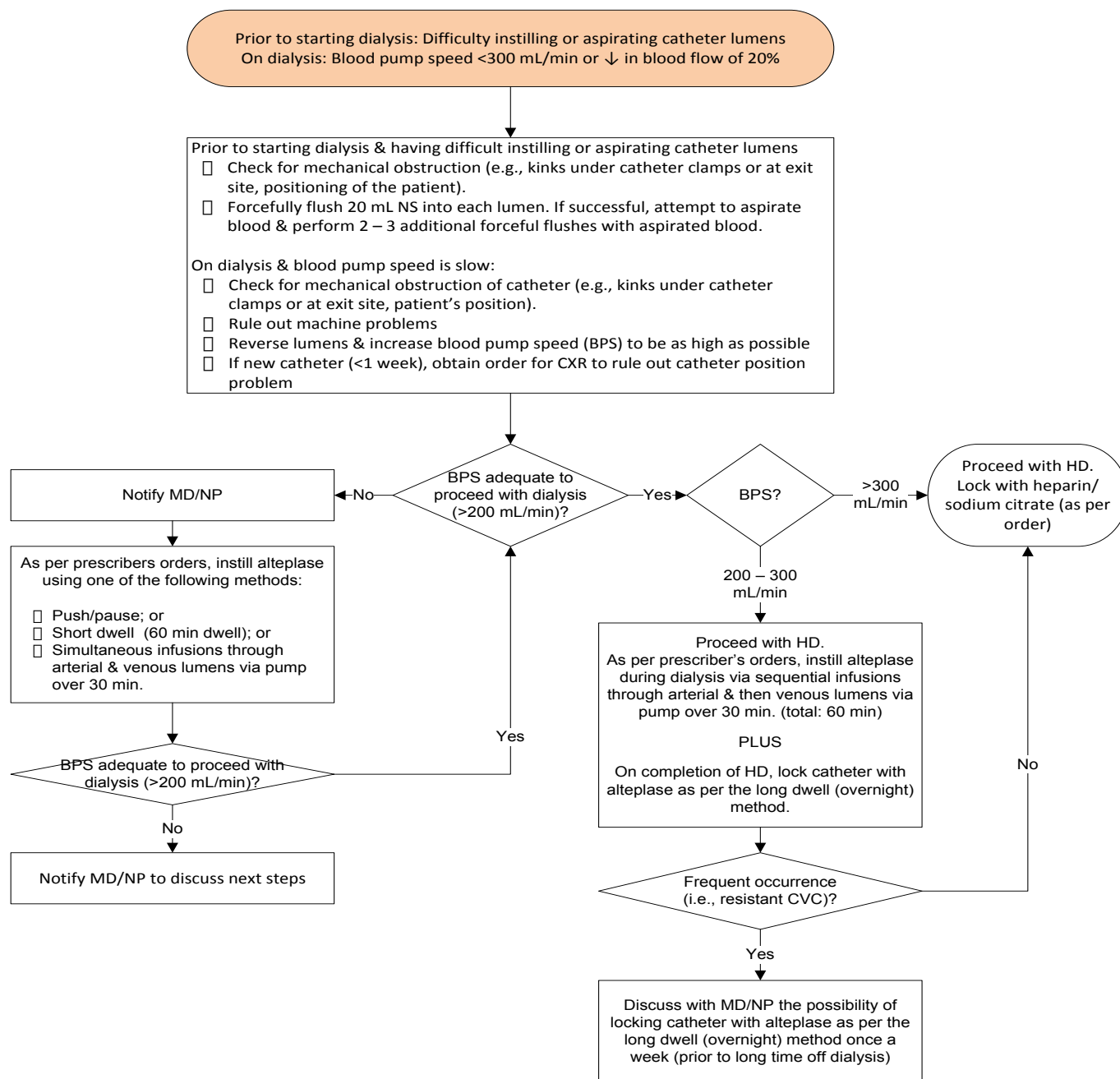
Recommendation 5:

Chronic use of alteplase is recommended in specific circumstances, namely resistant CVCs where:

- **Substituting one weekly dose of alteplase might be a more effective long-term solution than providing regular, intermittent doses; OR**
- **A CVC is the patient’s last option for HD access AND the patient is unable to tolerate further CVC replacements.**

Alteplase Use for Occluded Hemodialysis Catheters

4.0 Algorithm to Guide Nurses in the Use of Alteplase in Occluded HD CVCs



Note re transonics:

- ☐ If recirculation is >10% & arterial or venous pressures are increasing, this suggests the catheter dysfunction is increasing.
- ☐ Call MD/NP to discuss an alteplase intervention to prevent further dysfunction.

Note re alteplase:

- ☐ Alteplase is expensive (2 mg = \$65, 4 mg = \$130).
- ☐ Use of alteplase & dosage should be limited to that which is absolutely necessary.
- ☐ A graduated dosing scheme is recommended. Start with the lower dose in the range & increase to the higher dose if not effective.

Alteplase Use for Occluded Hemodialysis Catheters

5.0 Prescriber's Orders for Alteplase Use for Occluded HD Catheters (Sample)

See [Appendix 1](#) for a sample Prescriber's Order and Reconstitution Instructions (intended to be printed on the back of the Prescriber's Order).

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7.0 Sponsors

This BCPRA guideline/resource was developed to support equitable, best practice care for patients with chronic kidney disease living in BC. The guideline/resource promotes standardized practices and is intended to assist renal programs in providing care that is reflected in quality patient outcome measurements. Based on the best information available at the time of publication, this guideline/resource relies on evidence and avoids opinion-based statements where possible; refer to www.bcrenalagency.ca for the most recent version.

Developed by:

- Vascular Access Educator's Group of BC, with significant input from a pharmacy leader (BCPRA and Fraser Health Authority)

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Reviewed by:

- BCPRA Pharmacy and Formulary Committee

Approved by:

- BCPRA Hemodialysis Committee
- BCPRA Medical Advisory Committee (2011 version was approved; changes in this current version were mostly editorial/clarification and were not resubmitted for approval).

For information about the use and referencing of BCPRA provincial guidelines/resources, refer to www.bcrenalagency.ca.

8.0 Effective Date

- May 2017
- Refer to www.bcrenalagency.ca for most recent version.


9.0 Appendices

[Appendix 1: Alteplase Prescriber's Order and Reconstitution Instructions](#)

[Appendix 2: Alteplase Use for Occluded CVCs \(Sample Procedure\)](#)

[Appendix 3: Summary of the Studies on the Use of Alteplase in the Treatment of HD Catheter Thrombosis](#)

Appendix 1: Alteplase Prescriber's Order and Reconstitution Instructions



BCRenal
an agency of the Provincial Health Services Authority

ALTEPLASE PROTOCOL
For Occluded Hemodialysis Catheters

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PATIENT INFORMATION

Name: _____

Address: _____

Phone: _____

PHN: _____

Mandatory **Optional:** Prescriber check (✓) to initiate, cross out and initial any orders not indicated.

Prior to administering alteplase:

- Rule out mechanical obstruction of catheter and/or machine problems.
- Forcefully flush lines with 20 mL NS (without preservative) into each lumen. If flush is successful, attempt to aspirate blood and perform 2 to 3 additional forceful flushes with aspirated blood; ALTEPLASE is not required.

Dose (a graduated dosing scheme is recommended):

- ALTEPLASE 1 mg (recommended starting dose for all instillation methods, except sequential infusions)
- ALTEPLASE 2 mg (recommended starting dose for sequential infusions, or if 1 mg failed with other methods)
- ALTEPLASE 4 mg (recommended only for sequential infusions, when a 2 mg dose has previously failed)

DIRECTIONS:

If there is no flow or the blood pump speed is less than 200 mL/min

Push/pause method:

- Instill **ALTEPLASE** into each lumen, then instill NS to fill the internal volume plus 0.2 mL for overflow.
- Wait 10 min, then gently push NS into each lumen: 0.3 mL for larger volume catheters (greater than 1.5 mL) and 0.2 mL for low volume catheters (less than 1.5 mL). Wait 10 min and then repeat this step x 1.
- After waiting another 10 min, aspirate clot(s) using a 10 mL syringe and discard. If unable to withdrawal, may push remaining **ALTEPLASE**. Lastly, forcefully flush each lumen with NS.
- If a 1 mg dose was used and it was ineffective, may repeat above with a 2 mg dose.

Short dwell method:

- Instill **ALTEPLASE** into each lumen, then instill NS to fill the internal volume plus 0.2 mL for overflow.
- Leave **ALTEPLASE** in situ for a minimum of 30 min and a maximum of 120 min (note: success may increase with longer durations), then withdrawal the solution and clot(s). If unable to withdrawal, may push remaining **ALTEPLASE**. Lastly, forcefully flush each lumen with NS.
- If a 1 mg dose was used and it was ineffective, may repeat above with a 2 mg dose.

Simultaneous infusion method (prior to initiating hemodialysis):

- Add **ALTEPLASE** into 50 mL NS and infuse into each lumen over 30 min.

If blood pump speed is greater than 200 mL/min but less than 300 mL/min:

Sequential infusion method (one lumen at a time) during hemodialysis

- Add **ALTEPLASE** into 100 mL NS and infuse into each lumen, one at a time, over 60 min.

Overnight dwell method

- Instill **ALTEPLASE** into each lumen, then instill NS to fill the internal volume plus 0.2 mL for overflow.
- Leave **ALTEPLASE** in situ until the next hemodialysis run.
- Aspirate **ALTEPLASE** immediately prior to the next hemodialysis run; if unable to withdrawal, may push remaining **ALTEPLASE**. Lastly, forcefully flush each lumen with NS.
- If a 1 mg dose was used and it was ineffective, may repeat above with a 2 mg dose.

Resistant catheters:

- Instill **ALTEPLASE** once weekly as per overnight dwell method (prior to long stretch off dialysis)

NOTE: Do not premix reconstituted alteplase with NS in the same syringe. See reconstitution instructions on back.

| DATE (DD/MM/YYYY) | PRESCRIBER NAME (PRINTED) | PRESCRIBER SIGNATURE | COLLEGE ID | CONTACT NUMBER |
|-------------------|---------------------------|----------------------|------------|----------------|
| | | | | |

This communication is intended only for the use of the BC Provincial Renal Agency. It may contain information that is confidential. If you receive this communication in error, please notify us immediately at (604) 875-7366.

Appendix 1: Alteplase Prescriber's Order and Reconstitution Instructions

RECONSTITUTION INSTRUCTIONS FOR ALTEPLASE



- Reconstitute immediately before use, as there is no preservative in the vials. The solution may be used within 8 hours following reconstitution when stored at 3 to 30°C.

Reconstitution instructions for **push/pause** and **dwelling instillation** methods:

To prepare **ALTEPLASE** to a final concentration of **1 mg/mL**:

1. Use aseptic technique to withdraw 2.2 mL of SWI. Do not use bacteriostatic water for injection for reconstitution, as it has not been studied.
2. Inject the 2.2 mL of SWI into the **ALTEPLASE** 2 mg vial, directing the diluent stream into the powder. Slight foaming is not unusual; let the vial stand undisturbed to allow large bubbles to dissipate.
3. Mix by gently swirling until the contents are completely dissolved.

Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

1.0 Practice Standard

Skill Level (Nursing): Specialized

Registered nurses and Licensed Practical Nurses who have completed the required hemodialysis (HD) specialty education and who provide care in a BC In-Centre and/or Community Renal Program may perform this procedure, upon the order of a physician.

Need to Know

1. Use of alteplase in occluded hemodialysis (HD) central venous catheters (CVCs) requires a prescriber's order.
2. Blocked or dysfunctional CVCs are identified by: difficulty instilling or aspirating CVC lumens, a blood pump speed of < 300 mL/min and/or a decrease in blood flow of 20% during HD.
3. Low-dose alteplase is the thrombolytic of choice for treatment of a blocked or dysfunctional HD CVC.
4. Alteplase may be instilled using one of three methods: push/pause, dwell (short and long) and infusion (sequential infusion via one lumen or simultaneous infusion via two lumens).
5. If no flow or blood pump speed < 200 mL/min, instill alteplase as per orders using one of the following:
 - Push/pause method; or
 - Short dwell method (60 minutes); or
 - Simultaneous infusions through arterial & venous lumens via pump (prior to initiating HD).
6. If blood pump speed is between 200 and 300 mL/min, instill alteplase as per orders:
 - Sequential infusions through arterial and then venous lumens via pump over 30 minutes (total 60 minutes); PLUS
 - Long dwell method (overnight).
7. Notify the physician if one or both lumens are still “sticky” or blocked after administering alteplase twice on two separate occasions in a two week period.
8. The physician may prescribe an ongoing alteplase order for patients who have problematic HD CVCs that repeatedly become occluded or function poorly (resistant CVC).
9. Alteplase is a thrombolytic agent that works by binding to fibrin in a thrombus, then converting the entrapped plasminogen to plasmin which results in local fibrinolysis (i.e. digests fibrin and dissolves blood clot).
10. Alteplase vials need to be protected from light and kept in their original box until needed. Alteplase vials do not contain antibacterial preservatives and should be stored in a refrigerator at a temperature between 2 and 8°C and reconstituted **immediately** before use. The solution must be used within 8 hours following reconstitution.
11. Alteplase must be reconstituted with Sterile Water for injection. Do not shake vial to dissolve.
12. Heparin and sodium citrate are incompatible when mixed with alteplase; therefore, if heparin or sodium citrate is used to lock the CVC, the solution must be aspirated or flushed from the CVC lumens prior to the instillation of alteplase.

Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

13. Common sites of thrombus formation; CVC lumen, site where CVC enters the vein, CVC tip and along the external surface of the CVC.

2.0 Definitions & Abbreviations

Cathflo®

Alteplase

rtPA

Recombinant tissue plasminogen activator (alteplase, reteplase or tenecteplase)

CVC

Central venous catheter

HD

Hemodialysis

3.0 Equipment

Push/pause and dwell methods:

- 1 or 2 vials of alteplase with 2 mg/vial
- 1 or 2 vials of sterile water for injection (do not use bacteriostatic water for injection)
- 4 x 3 mL luer lock syringes with needles (2 for alteplase and 2 for sodium chloride 0.9%)
- 2 x 10 mL luer lock syringes (to withdrawal old anticoagulant and clot from lumens)
- 4 x 10 mL or 2 x 20 mL luer lock syringes with sodium chloride 0.9% (to flush lumens)
- 2 luer lock caps (to cap off lumens)
- 2 medication labels
- Chlorhexidine gluconate 2% aqueous or antiseptic solution per unit protocol

IV infusion method:

- 1 or 2 vials of alteplase with 2 mg/vial
- 1 or 2 vials of sterile water for injection (do

not use bacteriostatic water for injection) 2 or 3 x 3 mL luer lock syringes

- 1 or 2 x 18 g needles
- Chlorhexidine gluconate 2% aqueous or antiseptic solution per unit protocol
- 1 or 2 medication labels
- 1 or 2 minibags containing sodium chloride 0.9% (50 mL or 100 mL)
- 1 or 2 volumetric infusion pumps and tubing
- Y” luer lock adaptor

4.0 Assessment & Interventions

Separate sub-procedures are identified for each of the three methods of administration:

1. Dwell (short & long);
2. Push/pause; and
3. Infusion (sequential infusion via one lumen or simultaneous infusion via two lumens).

4.1 Preparation for All Administration Methods

1. Prior to initiating each HD treatment, attempt to aspirate the heparin or sodium citrate from each lumen of the CVC with a 10 mL syringe using aseptic technique.
2. If aspiration is unsuccessful, attempt to forcefully flush each lumen as follows:
 - a. Draw sodium chloride 0.9% in 2 x 10 mL or 1 x 20 mL luer-lock syringe(s) for each CVC lumen.
 - b. Flush each CVC port with a total of 20 mL sodium chloride 0.9% using maximum force.
3. If flush is successful, attempt to aspirate blood and perform 2 to 3 additional forceful flushes with aspirated blood.

Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

4. If flush is unsuccessful, repeat step 2; if still unsuccessful, contact the physician
5. Prepare alteplase as per physician order, the product monograph and the reconstitution procedure on the reverse side of the pre-printed orders.

4.2 Alteplase Administration

4.2.1 Dwell (Short & Long) Method

1. Follow steps 1 to 5 under “Preparation for All Administration Methods.”
2. Clean stopper with alcohol swab. Using 3 mL syringes with needles, withdraw the alteplase solution.
 - a. If using alteplase **1 mg** per lumen, draw 1 mL of alteplase 1 mg/mL solution into each of two 3 mL syringes (label carefully). Fill two additional 3 mL syringes with sufficient sodium chloride 0.9% to fill the internal volume of each CVC lumen plus 0.2 mL overfill (e.g., if CVC volume is 2.2 mL per lumen, draw 1 mL of alteplase 1 mg/mL and 1.4 mL sodium chloride 0.9% for each lumen).
 - b. If using alteplase 2 mg per lumen and CVC lumen volume is **2 mL or greater**, draw up 2 mL of alteplase 1 mg/mL solution into each of two 3 mL syringes (label carefully). Fill two additional 3 mL syringes with sufficient sodium chloride 0.9% to fill the internal volume of each CVC lumen plus 0.2 mL overfill (e.g., if dose is 2 mg alteplase per lumen and CVC volume is 2.2 mL per lumen, draw 2 mL of alteplase 1 mg/mL and 0.4 mL sodium chloride 0.9% for each lumen).

- c. If using alteplase **2 mg** per lumen and CVC lumen volume is **less than 2 mL**, draw up 1 mL of alteplase **2 mg/mL** solution into each of two 3 mL syringes (label carefully). Fill two additional 3 mL syringes with sufficient sodium chloride 0.9% to fill the internal volume of each CVC lumen plus 0.2 mL overfill (e.g., if dose is 2 mg alteplase per lumen and CVC volume is 1.3 mL per lumen, draw 1 mL of alteplase 2 mg/mL and 0.5 mL sodium chloride 0.9% for each lumen).

3. Clamp both lumens and then attach the 3 mL syringe(s) filled with alteplase to the occluded CVC port(s).
4. Instill alteplase as per order into the each of the arterial and venous lumens of the CVC then add sodium chloride 0.9% without preservative to fill the internal volume of each lumen plus 0.2 mL overfill
5. Clamp both lumens.

For Short (Pre-HD) Dwells:

- a. Leave the alteplase solution instilled in the CVC for at least 30 minutes to a maximum of 120 minutes, unless otherwise ordered by the physician.
- b. Withdraw the alteplase solution and residual clot from each lumen and discard. If unable to withdraw alteplase solution, try to re-position the CVC or patient to aid in the withdrawal. May push remaining alteplase if unable to withdraw.
- c. Attempt to flush the CVC with sodium chloride 0.9% using the forceful flush

Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

protocol described under “Preparation for All Administration Methods”.

d. If one or both lumens are still “sticky” or blocked, repeat administration of alteplase. If still “sticky” or blocked after administering alteplase twice on two separate occasions within a two week period, notify the physician for further orders.

For Long (Overnight) Dwells:

a. Remove the emptied 3 mL alteplase or sodium chloride 0.9% syringe from each lumen and secure a luer lock cap.

b. When patient returns for the next HD treatment:

- Withdraw the alteplase solution and residual clot from both lumens and discard. If unable to withdraw alteplase solution, try to re-position the CVC or patient to aid in the withdrawal. May push remaining alteplase if unable to withdraw.
- Attempt to flush the CVC with sodium chloride 0.9% using the forceful flush protocol described under “Preparation for All Administration Methods”.
- If one or both lumens are still “sticky” or blocked, repeat administration of alteplase. If still “sticky” or blocked after administering alteplase twice on two separate occasions within a two week period, notify the physician for further orders.

4.2.2 Push/Pause Method

1. Follow steps 1 to 5 under “Preparation for All Administration Methods” and step 2 under the instructions for dwell (short & long) method for drawing up the syringes
2. Clamp both lumens and then attach the 3 mL syringe(s) filled with alteplase to the occluded CVC port(s).
3. Instill alteplase as per order into each CVC lumen then add sodium chloride 0.9% without preservative to fill the internal volume of each lumen plus 0.2 mL overfill.
4. Attach a 3 mL syringe filled with sodium chloride 0.9% without preservative to each lumen.
5. Wait 10 minutes, then gently push sodium chloride 0.9%: 0.3 mL for larger volume CVCs (> 1.5 mL) and 0.2 mL for low volume CVCs (< 1.5 mL)
6. Wait another 10 minutes, then repeat sodium chloride 0.9% push as above.
7. Wait another 10 minutes, then use a 10 mL syringe to aspirate any clots and discard. May push remaining alteplase if unable to withdraw. Forcefully flush each CVC lumen as per protocol.
8. If one or both lumens are still “sticky” or blocked, repeat administration of alteplase. If still “sticky” or blocked after administering alteplase twice on two

Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

separate occasions within a two week period, notify the physician for further orders.

4.2.3 Infusion Method

For Sequential Infusion of Alteplase through a Single Lumen During HD

Scenario:

- One CVC lumen provides a minimum blood flow of 200 mL/min.
 - One CVC lumen does not provide adequate blood flow, however, alteplase can be administered through this lumen.
1. Follow steps 1 to 5 under “Preparation for All Administration Methods.”
 2. Prepare alteplase infusion:
 - a) Add alteplase in the amount ordered by the physician to the 100 mL sodium chloride 0.9% minibag for infusion and label the minibag.
 - b) Connect the infusion tubing to one limb of the “Y” adapter.
 - c) Prime the infusion pump tubing and “Y” adapter.
 3. Connect arterial blood-line to the CVC lumen that provides adequate blood flow. Prime circuit with blood as per procedure to initiate HD.
 4. Connect the venous blood-line to the “Y” adapter and then connect the male end of the “Y” adapter to the problematic lumen of the CVC blood-line
 5. Initiate HD as per routine.

6. Commence alteplase infusion to run over 1 hour.
7. Monitor and document q 15 min: vital signs and signs and symptoms of adverse complications (e.g., bleeding or allergic reaction).
8. After 30 min of alteplase infusion, consider switching lines to prophylactically administer alteplase through the opposite lumen as follows:
 - Stop blood pump and infusion pump.
 - Using aseptic technique, disconnect and switch arterial blood-line and “Y” adapter with venous blood-line.

If lines are not switched, continue infusion into the same line for 60 minutes.
9. Restart blood pump and infusion pump.
10. Observe and document blood pump speed and arterial and venous pressures. Continue HD treatment. Key point: A blood pump speed of 300 mL or more per minute with corresponding arterial and venous pressures is an indication of successful fibrinolysis.
11. In the event that adequate blood pump speeds are not attainable after switching the lines (i.e., more than 300 mL per minute), stop blood pump and infusion pump. Using aseptic technique, switch the arterial blood-line and “Y” adapter with the venous blood-line to resume the alteplase infusion through the problematic lumen. Repeat vital signs. Continue HD treatment.
12. When infusion is complete, if unable to

Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

attain blood pump speeds of greater than 300 mL/min, notify the physician.

For Simultaneous Infusions of Alteplase into the Arterial and Venous Lumens Prior to Initiating HD

Scenario:

- One CVC lumen provides a blood flow of less than 200 mL/min
 - Unable to initiate HD due to inadequate blood flow
 - Unable to aspirate from either lumen, however, can administer alteplase through both lumens
1. Follow steps 1 to 5 under “Preparation for All Administration Methods.”
 2. Prepare alteplase infusion:
 - a) Add alteplase in the amount ordered by the physician to the 50 mL sodium chloride 0.9% minibag for infusion and label the minibag.
 - b) Prime both infusion pump tubing sets and load onto pumps.
 3. Connect pump infusion tubing directly to arterial & venous ports on central line. Open clamps on arterial & venous ports.
 4. Commence alteplase infusions to run over 30 minutes (simultaneously infuse alteplase into both ports).
 5. Monitor and document q 15 min: vital signs and signs and symptoms of adverse complications (e.g., bleeding or allergic reaction).
 6. After completion of alteplase infusion, perform procedure to initiate HD.
 7. Observe and document blood pump speed and arterial and venous pressures. Continue HD treatment.

8. If unable to aspirate blood from lumens, notify physician.
9. If unable to attain blood pump speed of greater than 300 mL/min, continue treatment and notify physician. Key point: A blood pump speed of 300 mL or more per minute with corresponding arterial and venous pressures is an indication of successful fibrinolysis.

5.0 Documentation

1. Document according to unit protocol:
 - a) Pre, intra and post assessments of patient and catheter function.
 - b) Interventions: MD notification, additional monitoring and procedures performed.
 - c) Alteplase dose and method of delivery.
2. Enter the dose of alteplase, the method of delivery, and the outcome in the HD access module in PROMIS.

6.0 References

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Appendix 2: Alteplase Use for Occluded CVCs (Sample Procedure)

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Appendix 3: Summary of the Studies on the Use of Alteplase in the Treatment of HD Catheter Thrombosis

The literature review was last updated in September 2010; thus, a new search was conducted in PubMed, MEDLINE and EMBASE for articles published between Sept 1, 2010 and July 18, 2015. There were no new studies published since 2014.

| Study | Design | Dose | Protocol | Pop'n | Defn of Success | Short-term Success | Long-term Success | Author's Conclusions |
|---|--|---|--|--|--|--|--|---|
| Ragsdale et al. (2014) | Retrospective case series | 0.1 mg/kg (max 2 mg) in 25 mL NS Variable doses for dwells | Infusion over 3 hrs Dwell for 0.5 to 2 hrs | (≤ 18 years old) 88 infusion events and 66 dwell events were reviewed | Ability to withdraw blood at the conclusion of infusion or dwell | 1 st infusion = 85% (781/84), 2 nd increased to 86% 1 st dwell = 77% (51/66), 2 nd increased to 80% | Not specified | Both alteplase infusions and dwells are safe and effective in critically ill pediatric patients |
| Mendes et al. (2013) | Prospective cohort study | 1 mg/lumen | Short dwell (40 min), may repeat immediately x 1 | 152 CVCs for HD | Ability to instill fluid and withdraw blood from the device | 82.8% (147/179 attempts) with 1 st dose 97.9% after 2 nd consecutive dose | Not specified | Alteplase is safe and effective in the clearance of CVCs for HD patients |
| Peng et al. (2011) | Retrospective case series | Varied from: 0.5 or 2 mg per 2 mL or 2 mg per 3 mL | Duration varied from < 2 hrs to > 4 hrs | 87 CVCs | Restoration of CVC patency upon aspiration of alteplase | 68.5% after 1 dose - 78.7% after 2 nd dose | Survival for all CVCs treated with alteplase: 64% at 3 months 57% at 6 months 47% at 12 months | Alteplase is safe and effective in extending the life of occluded CVCs |
| Hemmelgarn et al. (2011) PRECLOT study | Prospective, single-blinded, randomized controlled trial 6 month duration | 1 mg/lumen | Once weekly as a locking solution at the midweek session instead of heparin 5,000 unit/mL, full luminal volume, which was still given as a lock on other HD days. This was compared to heparin 5,000 unit/mL 3 times weekly. | 225 newly inserted CVCs with Qb > 300 mL/min <u>110 patients received alteplase</u> <u>There was a ~50% drop out in each group</u> | CVC malfunction (1 ^o outcome): • Peak Qb ≤ 200 mL/min for 30 min • Mean Qb ≤ 250 mL/min for 2 consecutive sessions • Inability to initiate HD Bacteremia (2 ^o outcome) | N/A | Primary outcome: 20% vs. 34.8% HR 1.91 (95% CI, 1.13 to 3.22, p = 0.02) Secondary outcome: 4.5% vs. 13% HR 3.3 (95% CI, 1.18 to 9.22, p = 0.02) | Alteplase 1mg/lumen once weekly as a locking solution reduces incidence of CVC malfunction and bacteremia |

continued...

Appendix 3: Summary of the Studies on the Use of Alteplase in the Treatment of HD Catheter Thrombosis

| Study | Design | Dose | Protocol | Pop'n | Defn of Success | Short-term Success | Long-term Success | Author's Conclusions |
|---|--|--|--|------------------------|--|---|--|---|
| Haymond, Shalansky & Jastrzebski (2005) | Prospective, nonrandom, open-label, consecutive patients with dysfunctional CVCs | 1 mg/lumen (previously used 2 mg/lumen) | 60 min dwell (only 3 patients); repeat once if necessary or overnight dwell between HD sessions (large majority of patients) | 50 patients 50 CVCs | Qb \geq 300 mL/min for at least 3/4s of HD and patient had to finish session at or above that rate. Reduced costs when compared to costs 11 months prior to implementation of new protocol. | 1st dose 72% (36/50). 2nd dose: 83%. Financial savings: \$22,000 (compared costs 11 mos prior to & after implementation of new protocol) | 62% required a subsequent alteplase treatment with a median time to next course of 14 days. 38% had radiological interventions within 4 mos of initial dose; 8 CVCs were replaced, 7 were stripped. | 1 mg/lumen successfully treated CVC occlusions, with a resulting cost reduction. |
| MacRae et al (2005) | Prospective, randomized, non-blinded | 1 mg/ml, volume determined by lumen size | Short (1 hr) vs long (> 48 hrs) dwell | 60 patients 60 CVCs | Qb > 250 mL/min at next HD run and no CVC dysfunction for 2 weeks | Short dwell: • Next HD: 77% (20/26) • 2 wks: 42% (11/26) Long dwell: • Next HD: 79% (27/34) • 2 wks: 53% (18/34) No statistically significant difference in patency with short vs long dwell groups at subsequent HD run or at 2 weeks. | Median days to next CVC event: • Short dwell: 14 • Long dwell: 18 | Either short or long alteplase dwell time achieves patency for the next HD run but neither is reliable for long-term patency. Use of alteplase for CVC dysfunction is temporary and provides a 2 week window to employ more definitive therapies. |

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Appendix 3: Summary of the Studies on the Use of Alteplase in the Treatment of HD Catheter Thrombosis

| Study | Design | Dose | Protocol | Pop'n | Defn of Success | Short-term Success | Long-term Success | Author's Conclusions |
|-----------------------|--|--|---|---|---|---|---|---|
| Nguyen & Dikun (2004) | Non-randomized case series | 1.5 mg/lumen | Gp A: 1.5 mg/lumen x 30 min if unable to initiate HD Gp B: 1.5 mg/lumen x 30 min at start of HD if last session Qb < 300 mL/min Gp C: 1.5 mg/lumen as 48 hr dwell if last session Qb < 300 mL/min | Number of patients not specified, 52 episodes | Qb > 300 mL/min | Overall success: 94% • Gp A: 97% (22/23) • Gp B: 84% (18/21) • Gp C: 100% (8/8) Cost savings: \$45 for 1.5 mg vs \$77 for 2 mg alteplase (\$3,354 over 6 mos) | Not specified | 1.5 mg alteplase effective in treating occluded HD CVCs with lumen volumes ranging from 1 to 2.5 mL. Cost savings were also realized. |
| Dowling et al (2004) | Retrospective case studies | 2.5 mg/hr/lumen (total 10 mg) | Infusion over 2 hrs while pts were off HD. | 25 patients 25 CVCs | Qb ≥ 250 mL/min CVC patency (Qb ≥ 250 mL/min), immediately after infusion, at 30 days and at 45 days | Immediately after infusion: 100%, with 84% after 1st dose and 100% after the 2nd dose | 54% at 30 days 33% at 45 days | Alteplase is a safe & effective means of clearing blocked tunnelled CVCs |
| Davies et al (2004) | Retrospective case studies | 1 or 2 mg/hr x 4 hrs (1 mg if partial obstruction and 2 mg if total) | Infusion over 4 hrs | 20 patients 57 infusions | Qb ≥ 250 mL/min for > 4 hrs after infusion | Completely blocked lines: 85% with 2 mg infusion Partially blocked: 88% with 1 mg infusion | Not specified | Alteplase 2 mg/hr for blocked lines & 1 mg/hr for sluggish lines effectively restores HD CVC patency. |
| O'Mara et al (2003) | Prospective, non-randomized consecutive CVCs | 1 mg/ml, volume determined by lumen size | Dwell 30 min and a 2nd additional dose over 30 min if needed | 25 patients 30 CVCs and 62 episodes | Success: Qb ≥ 300 mL/min Partial: Qb ≥ 200 to < 300 mL/min (min 50 mL/min increase required) | Complete or partial responses combined: 69% (43/62) | 50% (15/30) received more than 1 dose: mean time from 1 st to 2 nd dose was 12.5 days | Alteplase 1 mg/mL was effective for restoring patency in HD CVCs |

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Appendix 3: Summary of the Studies on the Use of Alteplase in the Treatment of HD Catheter Thrombosis

| Study | Design | Dose | Protocol | Pop'n | Defn of Success | Short-term Success | Long-term Success | Author's Conclusions |
|------------------------|---|---|---|--|--|--|--|--|
| Zacharias et al (2003) | Prospective, nonrandomized case series | 1 mg/mL to fill lumen volume | Push protocol of 0.3 mL NS at 2 x 10 min intervals; aspirate CVC at 30 min mark (30 min dwell) | 30 patients, 66 CVCs, 116 doses | Qb > 200 mL/min for remainder of HD session | 92% for partially occluded CVCs and 85% for completely occluded CVCs | 60% patency rate 30 days after 1 alteplase treatment | Alteplase 30 min push-protocol is effective at restoring HD CVC patency. |
| Little & Walshe (2002) | Prospective study, all consecutive CVCs inserted over a 3 year period | 1 mg/mL, dose determined by lumen volume | Dwell: left in 2 to 8 hrs Alteplase used if Qb < 250 mL/min & likely related to thrombosis | Total: 336 patients, 570 CVCs Alteplase: 196 CVCs 614 doses | CVC survival | Alteplase required in 2.77 CVCs/100 HD sessions 10% (62/570) of CVCs required alteplase in > 10% of HD sessions; this subgroup accounted for 47% of alteplase use | 34% 1 yr primary patency rate (insertion to 1 st episode of thrombosis/CVC failure) Median survival to 2 nd intervention: 27 days; decreased to < 20 days for each additional episode | Very little benefit to repetitive alteplase treatments |
| Eyrich et al (2002) | Retrospective review | Alteplase 1 mg or 5000 units of urokinase in each port, then filled with NS to lumen volume | Push protocol of 0.2 mL NS at 20 min intervals. Duration: 60 min | Alteplase: 27 patients received 43 doses Urokinase: 10 patients received 20 doses | Qb > 300 mL/min maintained for at least 30 min during HD session | Alteplase: average Qb increased from 110 to 291 mL/min. 70% achieved Qb > 300 mL/min. Urokinase: average Qb increased from 63 to 203 mL/min. 35% achieved Qb > 300 mL/min | Alteplase: 86% functioned at next HD session Urokinase: 65% functioned at next HD treatment | HD blood flow rates increased after either alteplase or urokinase. Alteplase was more likely than urokinase to result in a HD blood flow rate of > 300 mL/min. |

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Appendix 3: Summary of the Studies on the Use of Alteplase in the Treatment of HD Catheter Thrombosis

| Study | Design | Dose | Protocol | Pop'n | Defn of Success | Short-term Success | Long-term Success | Author's Conclusions |
|--------------------------|--|--|--|---|---|---|--|---|
| Savader (2001) | Prospective, non-randomized | 2.5 mg/lumen infused over 3 hrs | Infusion over 3 hrs | 55 patients 55 CVCs | Effortless manual aspiration and infusion capability from both ports followed by at least one successful HD session | 91%. | 1° patency: 55% at 30 days 36% at 60 days 25% at 90 days 15% at 120 days 2° patency: 70% at 60 days 46% at 120 days 30% at 180 days 27% at 240 days | Alteplase 2.5 mg infusion is safe and effective. Immediate return of CVC function is achieved in most patients. 1° patency rates are relatively short, but CVCs that fail can be retreated, resulting in significantly improved 2° rates. |
| Spry (2001) | Prospective, non-randomized, open label | 1 mg/mL, dose determined by lumen volume | Push 0.3 mL of alteplase q10 min to exhaust syringe volume | 44 patients 117 episodes (113 evaluable) | Qb > 300 mL/min during next attempted HD session | 59% achieved Qb > 300 mL/min (91% of patients could "resume HD") | Not specified | Unable to access original article |
| Daeihagh, P et al (2000) | Prospective, consecutive non-functional CVCs | 2 mg/lumen | Dwell time 2 to 96 hrs | 22 patients 56 episodes | Qb ≥ 200 mL/min during the next attempted HD session | 87.5% | | Alteplase is as effective as urokinase. |
| Meers et al (1999) | Non-randomized case series | 1 mg/lumen; filled to lumen volume with NS | 0.2 mL NS pushed into lumen at mid-point (20 min or 40 min) in 14 cases or a 48 hr dwell post HD in 26 cases | 17 patients 21 CVCs 40 doses | Ability to dialyze pts at current or next session who previously had CVC malfunction causing frequent alarms | Results combined for the push and dwell protocols: 39/40 with "restored function" Average Qb = 148.5 increased to 238.7 mL/min | Primary patency (time from treatment to next intervention required) was a mean of 29.7 days +/- 27 days | Alteplase can safely and effectively restore blood flow and extend patency in HD CVCs. |