PROVINCIAL STANDARDS & GUIDELINES

BCRenal
Provincial Health Services Authority

Use of Alteplase for Dysfunctional Hemodialysis Catheters

Approved July 2006; Last Updated March 2021
Approved by the BC Renal Hemodialysis Committee

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IMPORTANT INFORMATION

This BC Renal 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 BC Renal guidelines/resources, refer to http://bit.ly/28SFr4n.

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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

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). Consistent with national and international standards, the BC Renal HD Committee acknowledges that the preferred form of HD vascular access (as appropriate to the patient) is 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), cuffed, tunneled, dual-lumen CVCs have become an acceptable form of HD access when an AVF or AVG is not suitable or available, despite the associated high complication rates and mortality risk (Lok et al., 2020; Ravani et al., 2017; Solid & Foley, 2012).

Maintenance of CVC patency is important to providing adequate HD in patients requiring CVCs on either a temporary or long-term basis. A common complication of the CVC is CVC dysfunction, which is associated with reduced dialysis adequacy, increased risk of catheter related bloodstream infection (Hemmelgarn et al., 2011) and mortality. The most recent KDOQI guideline (2020) defines CVC dysfunction as failure to maintain the prescribed extracorporeal blood flow required for adequate HD without lengthening the prescribed HD treatment (Lok et al., 2020).

The initial approach to treatment of a dysfunctional or blocked CVC is conservative – check for mechanical obstruction (e.g., kinks under catheter clamps at exit site, positioning of patient) and forcefully flush the lumens with normal saline. If conservative measures fail, the administration of a thrombolytic agent to restore function of a dysfunctional CVC due to thrombosis may be required. Alteplase is the thrombolytic agent used to treat CVC dysfunction in BC HD units.

2.0 Summary of the Literature

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

Mokrzycki and Lok (Mokrzycki & 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:

- Dwell time did not significantly impact short-term or 2-week patency rates in the two trials where this was studied ((Macrae et al., 2005; Nguyen & Dikun, 2004).
- The success rate diminished with each subsequent dose of rTPA.

Success rates by method of instillation were as follows:

Push/pause method (4 studies):

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

Short dwell (7 clinical trials; dwell time < 60 min):

- Short-term: 69% to 97%; 22% to 97% if Tumlin's tenecteplase study (Tumlin et al., 2010) is included.
- Long-term: median days to next event: 14 days (alteplase).

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

- Short-term: 79% to 100%; 22% to 100% if Tumlin's tenecteplase study (Tumlin et al., 2010) is included.
- Long-term: median days to next event: 13 – 27 days (alteplase).

Infusion (4 studies, not part of Mokrzycki and Lok review- refer to literature review in the Appendix of this document):

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

Another systematic review by Hilleman & Campbell (Hilleman & Campbell, 2011), on the safety and efficacy of alteplase, tenectaplase and reteplase for clearing HD CVCs included literature published between 1975 to 2010. The success rate was highest with reteplase (88 ± 4%), followed by alteplase (81 ± 37%) and tenecteplase (41 ± 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 tenectaplase. Reteplase is no longer available in Canada.

Below is a summary of the results from 20 clinical trials on the use of alteplase for the treatment of thrombosis in CVCs. Refer to literature review in the Appendix of this document for details.

Success rates:

- Definitions of "success" differed between studies. Common definitions included:
  - Short-term success: blood pump speeds of >280 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.
- One prospective randomized study by Vercaigne et al (Vercaigne, Zacharias, & Bernstein, 2012) compared an alteplase dwell over 30 minutes to the 30-minute push/pause method. The study showed in their 82 patients that the push/pause protocol was superior to achieving blood flows ≥ 300mL/min, although the results were not statistically significant despite a 17% higher point estimate.
- This finding was similar to that reported in two systematic review articles (Lok, Thomas, Vercaigne, & Canadian Hemodialysis Catheter Working Group, 2006; Mokrzycki & Lok, 2010).

Dosages:

- For the push/pause and dwell methods, dosages ranged from 1 to 2 mg/lumen.
- 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 which referenced both short and long dwell methods (Lok et al., 2006; Mokrzycki & Lok, 2010).
- A retrospective analysis of 1 mg vs 2 mg 30 min dwell found 2 mg to be superior to 1 mg

in improving catheter survival time (Yaseen et al., 2013). However, when the same authors conducted a prospective randomized controlled trial in 48 patients comparing the 2 doses in a similar manner, they found alteplase 1 mg to be as effective as 2 mg in restoring catheter patency and found no difference in catheter survival time (El-Masri et al., 2020)
- Two studies reported a cost savings from the use of a lower dosage of 1 to 1.5 mg/lumen for overnight and short-term dwells (Haymond, Shalansky, & Jastrzebski, 2005; Nguyen & Dikun, 2004).

Refer to Appendix 3 for a summary of the results of the 20 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 (Hemmelgarn et al., 2011) 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.

The Pre-Clot study was the first large, well-designed trial that evaluated the routine prophylactic use of alteplase lock in HD CVCs. The authors subsequently repeated a similar study in 3 sites as a cohort study with high risk catheters and found similar results (Hemmelgarn 2018).

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 Pre-Clot and subsequent follow-up studies does provide some evidence for the use of weekly alteplase. However, until cost-effectiveness of this strategy improves, 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 citrate or heparin.**
- **Using needle-free connectors for HD lines.**

Signs of CVC dysfunction include:

- Blood pump speed <300 mL/min or trend towards reduction in blood pump speed over multiple runs.
- At prescribed pump speed, arterial pressure (< –250 mmHg) or venous pressure (> 250 mmHg)
- Urea reduction ratio (URR) progressively < 65% (or Kt/V < 1.2)
- Frequent pressure alarms—not responsive to patient repositioning or CVC flushing
- If recirculation is present within the catheter and arterial or venous pressures are increasing, this may be an indicator of dysfunction.

- Unable to aspirate blood freely (late manifestation)
- Signs &/or symptoms of inadequate dialysis

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 include mechanical obstruction (e.g., kinks under catheter clamps or at exit site, positioning of patient, CVC migration) and patient factors (blood pressure drop, interdialytic weight gain, higher levels of hemoglobin). Such causes need to be ruled out prior to the use of thrombolytics (KDOQI, 2019).

Recommendation 3: If CVC dysfunction is suspected to be thrombosis-related, administer alteplase as per prescriber's orders, using the algorithm (section 4.0) and pre-printed orders (section 5.0 and Appendix 1) 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 dysfunctional 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 (on and off dialysis). Selection of the method will depend on individual circumstances including the severity of the occlusion and the timing and urgency of the need for HD.

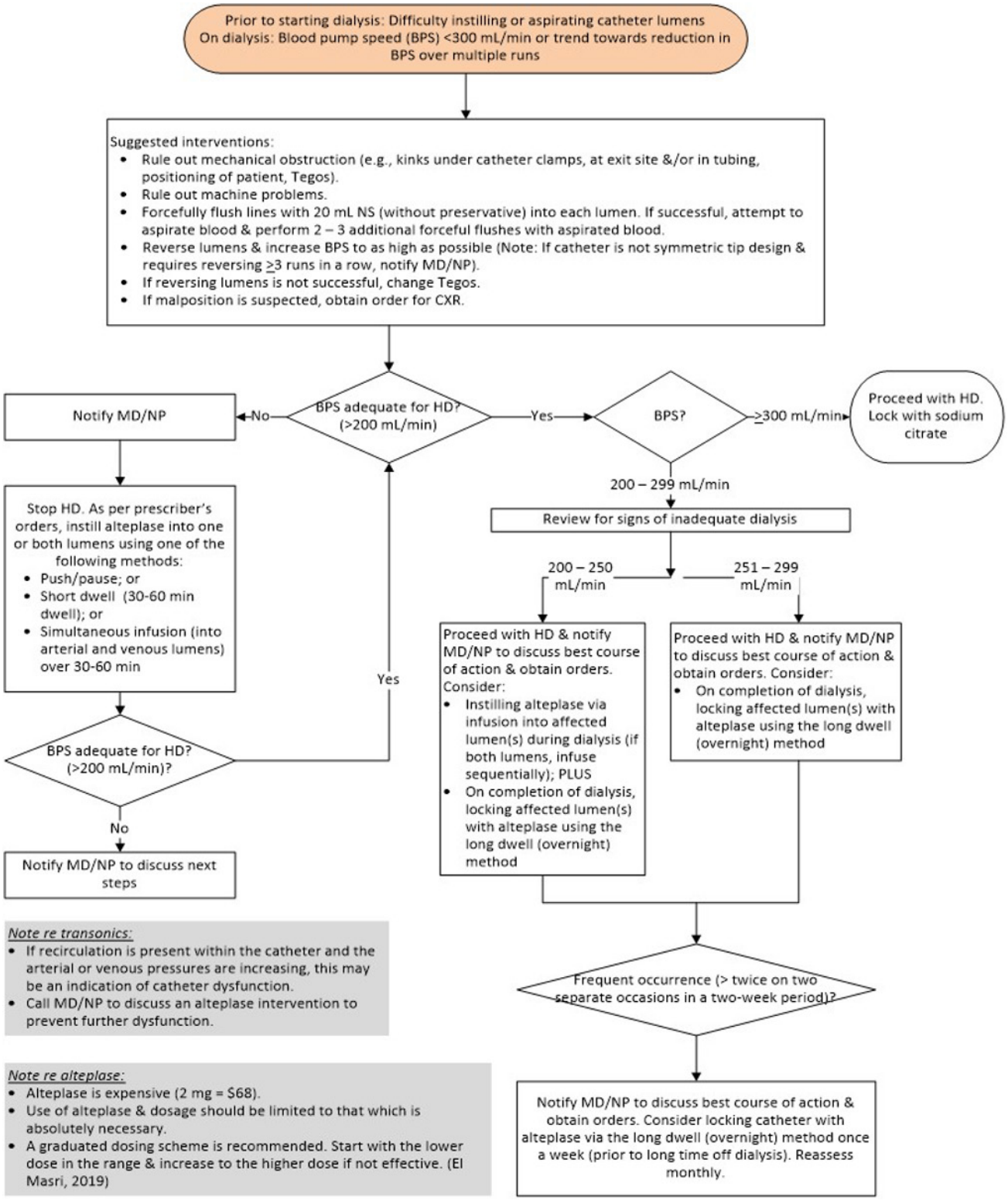
Alteplase is an expensive medication (2 mg = $68; 4 mg = $130). It is important that its use and dosage be limited to that which is absolutely necessary. Generally speaking, a graduated dosing scheme is recommended, starting with a lower dose (1 mg/lumen) and increasing to a higher dose (2 mg/lumen) if the lower dose is not effective. This guideline provides a range of dosages to allow for this practice (El-Masri et al., 2020).

Recommendation 4: Notify the MD/NP 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, unless identified otherwise by the MD/NP.

Recommendation 5:

- **Chronic use of alteplase is recommended in specific circumstances, namely resistant CVCs where:**
  - **Substituting one weekly dose with 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 unlikely or unable to tolerate further CVC replacements.**
- **Reassess the continued need for alteplase monthly.**

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



5.0 Prescriber's Orders for Alteplase Use for Dysfunctional HD Catheters

See Appendix 1 for a **sample** Prescriber's Order and Reconstitution Instructions (for printing on the back of the Prescriber's Order).

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7.0 Sponsors

Developed by:

- Vascular Access Educator's Group of BC: Original version developed in 2006; updated regularly since 2006; most recent update July 2021
- BC Renal Pharmacy and Formulary Committee: Original version developed in 2006; updated regularly since 2006; most recent update July 2021

Reviewed by:

- Ad hoc group of nephrologists, pharmacists and vascular access nurses: Jan 26, 2021
- BC Renal Educators Group (REG): Feb 2, 2021

Approved by:

- BC Renal Hemodialysis Committee: Jun 24, 2020; Mar 10, 2021
- BC Renal Medical Advisory Committee: Original 2006 version was approved; changes since have been mostly editorial/clarification and updated versions have not been submitted for approval.

8.0 Appendices

Appendix 1:
Alteplase Prescriber's Order and Reconstitution Instructions (Sample)

Appendix 2:
Use of Alteplase for Dysfunctional 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 (Sample)

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:
☐ **ALTEPLASE** 1 mg per lumen
☐ **ALTEPLASE** 2 mg per lumen
☐ **ALTEPLASE** 2 mg into affected lumen only (other lumen locked with sodium citrate 4%)
☐ **ALTEPLASE** 2 mg in 50 mL NS for simultaneous infusion off dialysis (2 mg/lumen = 4 mg total); OR single lumen infusion during dialysis (2 mg total)
☐ **ALTEPLASE** 4 mg in 100 mL NS for sequential infusion into both lumens during dialysis

Directions:
If blood pump speed is 200-299 mL/min:
☐ **Overnight dwell method (if using Tego needless connector, add extra 0.1 mL for priming):**
- Instill **ALTEPLASE** 1 mg into each lumen or 2 mg into affected lumen, then instill NS to fill the internal volume plus 0.2 mL for overfill. If instilled into 1 lumen only, lock the other lumen with sodium citrate 4%.
- 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** through catheter. Lastly, forcefully flush each lumen with NS.
- If a 1 mg/lumen dose was used and it was ineffective, may repeat these steps with a 2 mg/lumen dose.

If the blood pump speed is 200 to 250 mL/min:
☐ **Infusion method (during dialysis):**
Both Arterial AND Venous lumen dysfunction
- Sequential infusion: Add **ALTEPLASE** 4 mg into 100 mL NS. Connect venous bloodline to one of the catheter ports and infuse 2 mg (50 mL) over 30 to 60 minutes via Y-connector. Switch venous bloodline to the other port and infuse remaining 2 mg (50 mL) over 30 to 60 minutes.

Single Arterial OR Venous lumen dysfunction
- Add **ALTEPLASE** 2 mg into 50 mL NS and infuse into affected lumen over 30 to 60 minutes.

If there is no flow or the blood pump speed is less than 200 mL/min:
☐ **Push/pause method:**
- Instill **ALTEPLASE** 1 mg into affected lumen(s), then instill NS to fill the internal volume plus 0.2 mL for overfill.
- Wait 10 min, then gently push NS into lumen(s): 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** through catheter. Lastly, forcefully flush lumen(s) with NS.
- If a 1 mg dose was used and it was ineffective, may repeat these steps with a 2 mg dose.

☐ **Short dwell method: (if using Tego, add extra 0.1 mL for priming)**
- Instill **ALTEPLASE** 1 mg into each lumen, then instill NS to fill the internal volume plus 0.2 mL for overfill.
- Leave **ALTEPLASE** *in situ* for 30 to 60 minutes, withdraw the solution. If unable to withdraw, may push remaining **ALTEPLASE** through catheter. Lastly, forcefully flush lumen(s) with NS (longer dwell time preferred).
- If a 1 mg dose was used and it was ineffective, may repeat these steps with a 2 mg dose.

☐ **Simultaneous Infusion method (off dialysis):**
☐ Add ALTEPLASE 2 mg/50 mL NS x 2 minibags (2 mg/lumen = 4 mg total) and infuse simultaneously into both arterial and venous lumens over 30 to 60 minutes.

Resistant catheters (if alteplase administered more than twice on two separate occasions in a 2-week period, and line change not feasible)
☐ Instill **ALTEPLASE** 1 mg per lumen once weekly as per overnight dwell method (prior to long stretch off dialysis). Reassess monthly.

NOTE: Do not premix reconstituted alteplase with NS in the same syringe for 1 mg/lumen doses. See reconstitution instructions on back.

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 room temperature or in refrigerator.

Reconstitution instructions for **push/pause** and **dwell 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. **Do not shake**. The reconstituted preparation results in a colorless to pale yellow transparent solution containing **ALTEPLASE** 1 mg/mL.
4. Withdraw prescribed amount of **ALTEPLASE** 1 mg (1 mL) or 2 mg (2 mL) from the reconstituted vial.

Reconstitution instructions for **infusion** method:

To prepare **ALTEPLASE** for infusion of a **2 mg/50 mL**:
1. Perform steps 1 to 3 as per push/pause and dwell instillation methods.
2. Withdraw 2 mg (2 mL) of solution from the reconstituted vial and inject into 50 mL NS.

To prepare **ALTEPLASE** for infusion of a **4 mg/100 mL**:
- Perform steps 1 to 3 as per push/pause and dwell instillation methods. Repeat x 1 to prepare a second reconstituted vial.
- Withdraw 4 mg (4 mL) of solution from the reconstituted vials and inject into 100 mL NS.

Appendix 2: Use of Alteplase for Dysfunctional 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 Dialysis Unit may perform this procedure, upon the order of a physician/nurse practitioner (NP).

Need to Know

1. Use of alteplase in dysfunctional hemodialysis (HD) central venous catheters (CVCs) requires a prescriber's order.
2. Blocked or dysfunctional CVCs are identified by:
    - Prior to starting dialysis: Difficulty instilling or aspirating CVC lumens.
    - On dialysis: Blood pump speed of <300 mL/min and/or a trend towards reduction in blood pump speed over multiple runs during dialysis.
3. Low dose alteplase is the thrombolytic of choice for treatment of a blocked or dysfunctional HD CVC.
4. Alteplase is a thrombolytic agent and it 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). Common sites of thrombus formation: CVC lumen, site where CVC enters the vein, CVC tip and along the external surface of the CVC.
5. Alteplase vials need to be protected from light and kept in their original box until needed. Alteplase vials do not contain preservatives and should be reconstituted immediately before use. The solution may be used within 8 hours following reconstitution when stored at room temperature or in the refrigerator.
6. Alteplase must be reconstituted with Sterile Water for Injection (SWI). Do not shake vial to dissolve.
7. 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.
8. If using needleless connector, add priming volume as per pre-printed orders (Appendix 1).
9. Alteplase may be instilled using one of three methods: push/pause, dwell (short and long) and infusion.
10. Notify the MD/NP if one or both lumens are still "sticky" or blocked after administering alteplase twice on two separate occasions in a two-week period.
11. The MD/NP may prescribe an ongoing alteplase order for patients who have problematic HD CVCs that repeatedly become occluded or function poorly (resistant 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 syringes with needles (2 for alteplase and 2 for sodium chloride 0.9% (NS))
- 2 x 10 mL syringes (to withdrawal old anticoagulant and clot from lumens)
- 4 x 10 mL or 2 x 20 mL syringes with NS (to flush lumens)
- 2 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 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 NS (50 mL or 100 mL)
- 1 or 2 volumetric infusion pumps and tubing
- "Y" adaptor

4.0 Assessment & Interventions

Sub-procedures identified in this section:
1. Steps Prior to Alteplase Preparation and Administration for All Methods
2. Alteplase Preparation and Administration
    a. Dwell method (short & overnight/long)
    b. Push/pause method
    c. Infusion method:
        i. Off Dialysis: Simultaneous infusions into both arterial and venous Lumens
        ii. During Dialysis: Sequential infusion through arterial AND venous lumens (one lumen at a time)
        iii. During Dialysis: Single infusion through arterial OR venous lumen (one lumen only)

4.1 Steps Prior to Alteplase Preparation and Administration for All Methods

1. Prior to initiating each HD treatment, attempt to aspirate the sodium citrate (or heparin) from each lumen of the CVC with a 10 mL syringe using aseptic technique.
2. If aspiration is unsuccessful OR if during dialysis, the blood pump speed (BPS) is <300 mL/min (or trending towards a reduced BPS over multiple runs), follow the interventions suggested on the algorithm (section 4.0):
    a. Rule out mechanical obstruction (e.g., kinks under catheter clamps, at exit site and/or in tubing, positioning of patient, Tegos).
    b. Rule out machine problems.
    c. Attempt to forcefully flush lumens:
        i. Use a pre-filled sterile NS syringe(s) (2x10 mL or 1 x 20 mL) for each lumen).
        i. Flush each lumen with a total of 20 mL sterile NS using maximum force.
        ii. If flush is successful, attempt to aspirate blood and perform 2 to 3 additional forceful flushes with aspirated blood.
    d. Reverse lumens and increase blood pump speed to as high as possible (note: if catheter is not symmetric tip

design and requires reversing >3 runs in a row, notify MD/NP).
e. If reversing lumens is not successful, change Tegos.
f. If malposition is suspected, obtain order for chest x-ray.

3. If the above steps are unsuccessful, contact the MD/NP. Refer to algorithm (section 4.0) for suggested interventions.
4. Prepare alteplase as per MD/NP order, the product monograph and the reconstitution instructions on the reverse side of the pre-printed orders (Appendix 1).

4.2 Alteplase Preparation and Administration[1]

4.2.1 Dwell Method (Short & Overnight/Long)

1. Follow steps 1 to 5 under "Steps Prior to Alteplase Preparation and Administration for all 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 NS to fill the internal volume of each CVC lumen plus 0.2 mL overfill. If using Tego, add extra 0.1 mL for priming (0.3 mL total). Do not premix alteplase together with NS prior to administration.

   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) plus add sufficient NS to fill the internal volume of each CVC lumen plus 0.2 mL overfill. If using Tego, add extra 0.1 mL for priming (0.3 mL total). Do not premix alteplase together with NS prior to administration.

   c. If using alteplase **2 mg** per lumen and CVC lumen volume is **less than 2 mL**, draw up sufficient volume of alteplase plus 0. 2 mL into each of two 3 mL syringes (label carefully). For example, if dose is 2 mg alteplase per lumen and CVC volume is 1.6 mL per lumen, draw 1.8 mL of alteplase (i.e., patient only receiving alteplase 1.9 mg/lumen). If using Tego, add extra 0.1 mL for priming (0.3 mL total).

3. Clamp both lumens and then attach the 3 mL syringe(s) filled with alteplase to the occluded CVC port(s).

4. Slowly instill alteplase as per order into the each of the arterial and venous lumens, then add NS, if required, to fill the internal volume of each lumen plus 0.2 mL overfill. If using Tego, add extra 0.1 mL for priming (0.3 mL total).

5. Clamp both lumens.

   For Short Dwells:

   a. Leave the alteplase solution instilled in the lumens for 30 to 60 minutes, unless otherwise ordered.

   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 through catheter if unable to withdraw.

   c. Attempt to flush the CVC with NS using the forceful flush protocol described under "Steps Prior to Alteplase Preparation and Administration for all Methods."

   d. If one or both lumens are still "sticky" or blocked, consult MD/NP re further direction.

[1] Instructions in this guideline are for instilling alteplase into both lumens. If only one lumen is affected, adjust instructions accordingly.

For Overnight (Long) Dwells:

a. Remove the empty 3 mL syringe from the Tego or secure with a luer lock cap. Leave the alteplase solution instilled in the CVC until the next dialysis run.

b. When patient returns for the next HD treatment:

   i. 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 through catheter if unable to withdraw.

   ii. Attempt to flush the CVC with NS using the forceful flush protocol described under "Steps Prior to Alteplase Preparation and Administration for All Methods."

   iii. 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 MD/NP for further orders.

4.2.2 Push/Pause Method

1. Follow steps 1 and 2 under the instructions for section 4.2.1 "Dwell method (short & overnight/long)."
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 NS to fill the internal volume of each lumen plus 0.2 mL overfill. If using Tego, add extra 0.1 mL for priming (0.3 mL total).
4. Attach a 3 mL syringe filled with NS to each lumen.
5. Wait 10 minutes, then gently push NS: 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 NS and push as above.
7. Wait another 10 minutes, then use a 10 mL syringe to aspirate any clots and discard. May push remaining alteplase through catheter if unable to withdraw. Forcefully flush each CVC lumen as per protocol.
8. If one or both lumens are still "sticky" or blocked, consult MD/NP re further direction.

4.2.3 Infusion Method

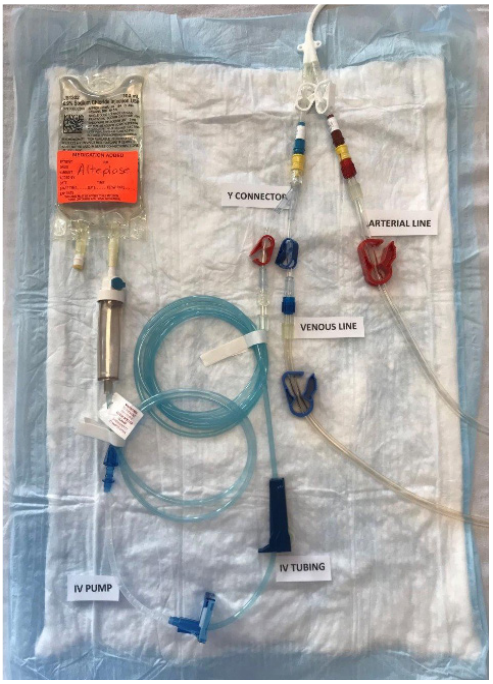
Off Dialysis: Simultaneous infusions into both arterial and venous lumens

1. Prepare alteplase infusion:
   - Add 2 mg of reconstituted alteplase to each of two 50 mL NS minibags (2 mg/lumen = 4 mg total), as per reconstitution instructions for **infusions.**
   - Prime both infusion tubing sets and load onto pumps.
2. Connect tubing directly to arterial & venous lumens on central line. Open clamps.
3. Commence alteplase infusions to run over 30 to 60 minutes (simultaneously infuse alteplase into both lumens
4. Monitor and document q 15 min: vital signs and signs and symptoms of adverse complications (e.g., bleeding or allergic reaction).

5. After completion of alteplase infusion, check blood flow is adequate. If still unable to aspirate blood from either lumen, notify MD/NP.
6. Initiate HD. Observe and document blood pump speed and arterial and venous pressures.
7. If unable to attain blood pump speed of greater than 300 mL/min, notify MD/NP. If MD/NP orders, lock catheter lumens after completing dialysis with alteplase using the long dwell (overnight) method.

During Dialysis: Sequential infusion through arterial AND venous lumens (one lumen at a time)

1. Prepare alteplase infusion:



- Add 4 mg of reconstituted alteplase to 100 mL NS minibag as per reconstitution instructions for **infusions**.
- Prime the infusion tubing and "Y" adapter.

2. Connect arterial bloodline to the CVC lumen that provides the best blood flow.
3. Connect the venous bloodline to the "Y" adapter and then connect the male end of the "Y" adapter to the problematic lumen of the CVC bloodline.
4. Commence alteplase infusion to run 2 mg (50 mL) over 30 to 60 minutes, then switch lines to administer the remaining alteplase 2 mg (50 mL) over 30 to 60 minutes through the opposite lumen as follows:

- Stop blood pump and infusion pump, close clamps on bloodlines
- Using aseptic technique, disconnect and switch arterial blood line and "Y" adapter.

5. Monitor and document q 15 min: vital signs and signs and symptoms of adverse complications (e.g., bleeding or allergic reaction).
6. Observe and document blood pump speed and arterial and venous pressures.
7. If ordered (and as per algorithm– section 4.0), lock affected catheter lumen(s) with alteplase after dialysis using the long dwell (overnight) method.

During Dialysis: Single infusion through arterial OR venous lumen (one lumen only)

1. Prepare alteplase infusion:
   - Add 2 mg of reconstituted alteplase to 50 mL MS minibag, as per reconstitution instructions for **infusions.**
   - Prime the infusion tubing and "Y" adapter.
   - Connect the venous bloodline to the "Y" adapter and then connect the male end of the "Y" adapter to the problematic lumen of the CVC bloodline.
2. Commence alteplase infusion into the problematic lumen to run over 30 – 60 minutes.

3. Monitor and document q 15 min: vital signs and signs and symptoms of adverse complications (e.g., bleeding or allergic reaction).
4. Observe and document blood pump speed and arterial and venous pressures.
5. If ordered (and as per algorithm), lock affected catheter lumen(s) with alteplase after dialysis using the long dwell (overnight) method.

5.0 Documentation

1. Document according to unit protocol:
   - Pre, intra and post assessments of patient and catheter function.
   - Interventions: MD notification, additional monitoring and procedures performed.
   - Alteplase dose and method of delivery.

2. Enter the dose of alteplase, the method of delivery, and the outcome in the HD vascular access module (under procedures) in PROMIS.

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

This literature review was initially completed in September 2010 and was updated in July 2019. The update included a new search of articles published in PubMed, MEDLINE and EMBASE between Sept 1, 2010 and July 18, 2019.

Study	Design	Dose	Protocol	Pop'n	Defn of Success	Short-term Success	Long-term Success	Author's Conclusions
El-Masri MM et al (2020)	Prospective, randomized, double-blind single Centre	Alteplase 2 mg / lumen vs 1 mg/ lumen	30-minute dwell into occluded lumen; may repeat x 2 until line patent; otherwise refer to radiology for stripping	48 HD patients with 252 catheter occlusion events	Rate of clot resolution, mean catheter survival time	Catheter Resolution: 85.7% (2 mg/lumen) vs 84.9% (1 mg/ lumen) (p=0.5) Median time of resolution after alteplase management for first occlusion: 192 days (2 mg) vs 120 day (1 mg) (p=0.48)	Catheter survival was similar in the 2 groups (HR = 0.72; 95% CI 0.4-1.29)	Alteplase 1 mg was as effective as 2 mg in restoring catheter occlusion.
Hemmelgarn et al (2018)	Prospective multicenter	1mg/lumen	Weekly lock then standard locking solution the rest of the week	374 patients	Rate of rt-PA use for catheter malfunction	Rate of rTPA usage declined from 18.4 days per 1000 catheter to 10.1 days Unadjusted incidence rate ratio 0.33 (95% CI 0.24 to 0.44)	Not specified	A reduction in rate of treatment with rt-PA was noted with weekly rt-PA locking; however, no change in bacteremia or catheter stripping/removal rates and overall use was 5 times higher with incremental cost of $962CAD per enrollment
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	1st infusion = 85% (781/84), 2nd increased to 86% 1st dwell = 77% (51/66), 2nd 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 1st dose 97.9% after 2nd consecutive dose	Not specified	Alteplase is safe and effective in the clearance of CVCs for HD patients

Study	Design	Dose	Protocol	Pop'n	Defn of Success	Short-term Success	Long-term Success	Author's Conclusions
Yaseen O et al (2013)	Retro-spective chart review	2 mg/ lumen vs 1 mg/ lumen	Dwell time 30 mins	129 patients (2mg) 108 patients (1 mg)	Time to catheter removal		Catheter removal: 19.4% (2mg) vs 10.2 % (1mg) p= 0.05 Time to catheter removal longer in the 2 mg vs 1 mg group (p=0.019)	Alteplase 2mg was superior to 1 mg dwells for treatment of dysfunctional catheters
Ver-caigne LM et al (2012	Prospec-tive ran-domized multi-center	2mg/ lumen	Dwell 30 mins with ability to increase to 90 mins Push: instill for 10 mins then 0.3mL NS pushed repeat once for another 10 mins. Pro-cedure took 30 mins	83 CVCs	Post thrombolytic blood flow ≥ 300mL/min	65% (28/43) in dwell versus 82% (32/39) in push (p=0.084)	Duration to next cath-eter 59.3d (dwell) vs 65.5d (push) (p=0.766)	Alteplase push was effective and safe and more practical than 2 hour dwell
Hem-melgarn et al. (2011) PRE-CLOT study	Prospec-tive, sin-gle-blind-ed, random-ized 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 lumi-nal 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 110 patients received alteplase There was a ~50% drop out in each group	CVC mal-function (1o outcome): • Peak Qb ≤ 200 mL/min for 30 min • Mean Qb ≤ 250 mL/min for 2 con-sec-utive ses-sions • Inabil-ity to initiate HD Bacteremia (2° out-come)	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

Study	Design	Dose	Protocol	Pop'n	Defn of Success	Short-term Success	Long-term Success	Author's Conclusions
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 2nd 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
Haymond et al (2005)	Prospective, non-random, 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 > 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.
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

Study	Design	Dose	Protocol	Pop'n	Defn of Success	Short-term Success	Long-term Success	Author's Conclusions
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.
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.
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 1st to 2nd dose was 12.5 days	Alteplase 1 mg/mL was effective for restoring patency in HD CVCs
Zacharias et al (2003)	Prospective, non-randomized 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.
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.

Study	Design	Dose	Protocol	Pop'n	Defn of Success	Short-term Success	Long-term Success	Author's Conclusions
Little & Walshe (2001)	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 1st episode of thrombosis/CVC failure) Median survival to 2nd intervention: 27 days; decreased to < 20 days for each additional episode	Very little benefit to repetitive alteplase treatments
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%.	1º patency: 55% at 30 days 36% at 60 days 25% at 90 days 15% at 120 days 2º 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. 10 patency rates are relatively short, but CVCs that fail can be retreated, resulting in significantly improved 2^0 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 midpoint (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.