Alteplase Site-directed Thrombolytic Therapy

**Background:** Thrombolytic agents are a class of drugs known as plasminogen activators that convert plasminogen into plasmin. Plasmin enzymatically cleaves the fibrin strands, which bind the platelets and red blood cells together within the thrombus, leading to clot dissolution. T-PA is a naturally occurring serine protease. T-PA is endogenously secreted by the vascular endothelium and helps maintain, along with other hematologic components, a balance between hemostasis and fibrinolysis. In the early 1980s, the ability to purify and express the human gene sequence for t-PA with use of recombinant DNA techniques was achieved, allowing sufficient quantities of drug (rt-PA; alteplase) to be produced for clinical applications. Alteplase was approved by the Food and Drug Administration in 1987 and is indicated for the treatment of acute myocardial infarction, pulmonary embolism, and acute ischemic stroke. Alteplase is a potent activator of plasminogen, has a higher affinity for fibrin-bound plasminogen, and has a low affinity for free circulating plasminogen. Alteplase acts by rapidly binding to fibrin within the clot to convert the entrapped plasminogen to plasmin. In the presence of fibrin, plasminogen activation by alteplase increases 400-fold. Simultaneously, α2-antiplasmin, a naturally circulating inhibitor of plasmin, tends to preferentially bind to fibrin instead of plasmin and allows fibrinolysis to occur essentially unopposed. In the absence of fibrin, there is minimal alteplase conversion of plasminogen and plasmin production is readily inhibited by α2-antiplasmin. Plasma clearance of alteplase is mediated primarily via the liver. The free circulating half-life of alteplase is approximately 5 minutes, and 80% of unbound alteplase is cleared within 10 minutes. Despite the short time for plasma clearance, the pharmacodynamic effects of alteplase persist for up to 1 hour at the site of fibrin-bound plasminogen. As alteplase dissolves the acute gelatinous clot, new sites on fibrin become available for alteplase binding.

Deep venous thrombosis (DVT) of the lower extremities is routinely treated with anticoagulants; additional therapy with thrombolytics should be considered in patients with significant thrombosis involving major vessels. Early experience suggests that site-directed thrombolytic therapy may reduce long-term sequelae of deep vein thrombosis (post thrombotic syndrome). Site directed thrombolysis, particularly combined with mechanical thrombectomy, may also be also be considered for the treatment of life or limb threatening arterial thrombosis, although there are no large or randomized studies in children.

Catheter directed thrombolytic therapy with alteplase is initiated in interventional radiology or in the cardiac catheterization laboratory. The treatment may also include mechanical disruption of the thrombus by balloon angioplasty or a thrombectomy device. All patients being considered for this therapy should have a hematology consult prior to initiation of site directed thrombolysis, when clinical status allows. (See P&T Policy V-144 Medications Restricted by Location or Service).
Inclusion Criteria:
1. Patients with significant thrombosis documented by imaging to involve the inferior vena cava, deep veins of the pelvis and/or a lower extremity proximal to the calf veins (i.e., the popliteal vein or above) or of the major veins in the chest and upper extremity (i.e. superior vena cava, subclavian, or brachiocephalic veins.)
2. Patients with limb or life threatening arterial thrombosis
3. Patients with congenital heart disease and life threatening thrombosis (e.g. thrombosis within an arteriopulmonary shunt)

Contraindications to Thrombolytic Therapy:

A. Absolute Contraindications

1. Pregnant patients are not eligible, although postpartum mothers over 10 days from delivery are eligible if they refrain from breast feeding their infants for 24 hours after each study with x-ray contrast material.
2. Any current bleeding diathesis not attributable to heparin or warfarin.
3. Fibrinogen less than 100 mg/dL. Any patient with a prolonged prothrombin time or prolonged aPTT, should be evaluated by hematology.
4. A platelet count less than 100,000/µL is a contraindication for thrombolytic therapy unless the platelet count can be raised to greater than 100,000 by platelet transfusion or other therapy as per hematology recommendations prior to undergoing thrombolysis.
5. Uncontrolled systolic blood pressure greater than 180 mm Hg or diastolic greater than 100 mm Hg (for children: systolic and diastolic blood pressure > 95th percentile for age and gender.)
6. History of anaphylactic reactions to contrast media.

B. Relative Contraindications

1. Serum creatinine greater than 2 mg/dL.
2. Within the previous 10 days: major surgery or trauma, puncture of a noncompressible vessel, organ biopsy, or cardiopulmonary resuscitation.
3. Within the previous 2 months: cerebrovascular infarction or hemorrhage, or intracranial or intraspinal surgery or trauma.
4. Within the previous 6 months: major internal bleeding.
5. Active intracranial disease (aneurysm, vascular malformation, neoplasm).
6. Atrial fibrillation, unless a cardiac echocardiogram excludes the presence of intracardiac thrombus.
7. Known right-to-left intracardiac shunt.
8. Known pericarditis, infective endocarditis.
9. History of heparin-induced thrombocytopenia within 6 months or the presence of persistent anti-heparin antibodies by ELISA. Anticoagulation with argatroban should be used in place of heparin.
If a female adolescent patient is menstruating, consultation with gynecology and cessation of menstrual bleeding is recommended prior to alteplase therapy.

**Precautions During Thrombolytic Therapy:**
1. No intramuscular injections during therapy.
2. Minimal manipulation of the patient (e.g. no chest physiotherapy).
3. Avoid concurrent use of oral anticoagulant therapy, such as warfarin sodium (Coumadin®), oral direct thrombin inhibitors such as dabigatran (Pradaxa®), oral factor Xa inhibitors such as apixaban (Eliquis) or rivaroxaban (Xarelto®) or antiplatelet agents (i.e., aspirin, dipyridamole, non-steroidal anti-inflammatory medications, etc.).
4. No urinary catheterization, rectal temperatures, nasogastric tube placement or arterial punctures.
5. Blood samples should be obtained from a superficial vein or indwelling catheter.
6. Cranial imaging is recommended prior to and after therapy in children < 3 months of age. Consider head imaging prior to and after thrombolysis in any patient at high risk for ischemic or hemorrhagic stroke regardless of age.
7. Send blood type and screen before starting thrombolytic therapy.

**Alteplase Handling and Storage (General Guidelines)**
The use of continuous infusion alteplase is restricted to the ED, PICU, CICU, NICU, OR, Interventional Radiology and the Cardiac Catheterization Lab at CCHMC. A hematology consult is required prior to starting the infusion, except in emergent cases where a hematology consult should be obtained as soon as possible. (CCHMC P&T Policy V-144 Medications Restricted by Location or Service)

**Reconstitution**
Alteplase is available as a sterile, preservative-free, lyophilized powder in 2 mg vials (Cath-Flo Activase®) as well as 50- and 100-mg vials (Activase®) supplied with a 50- or 100-mL vial of sterile water for injection USP, respectively.
- To reconstitute the 2 mg vial, 2.2 mL of preservative-free sterile water for injection USP is mixed. Complete dissolution occurs within 3 minutes. The final concentration is 1 mg/mL.
- To reconstitute the 50 mg vial, 50 mL of preservative-free sterile water for injection USP is mixed with the 50-mg vial of alteplase under sterile conditions to produce a final concentration of 1 mg/mL.
- To reconstitute the 100 mg vial, 100 mL of preservative-free sterile water for injection USP is mixed with the 100-mg vial of alteplase under sterile conditions to produce a final concentration of 1 mg/mL.
**Stability**
Alteplase is preservative-free and is theoretically susceptible to bacterial contamination and biochemical degradation when left at room temperature for more than 8 hours. Although the manufacturer recommends changing the solution after 24 hours, *in vitro* data suggest that the drug should be physically and chemically stable for 24 hours.

**Alteplase is incompatible and may precipitate when mixed directly with unfractionated heparin; concomitant heparin should be given through a separate intravenous line.** An opaque diluent indicates precipitation of drug and may be associated with decreased efficacy. Visual inspection of the solution for precipitates is recommended after dilution and before administration. To minimize the risk of precipitate formation from excessive dilution in cases in which large volumes of normal saline or higher rates of infusion are necessary, the alteplase solution should be piggybacked into a normal saline infusion just before entering the infusion catheter.

**Alteplase Use in Interventional Radiology for Thrombolysis:**

**Bolus Dose Preparation in Interventional Radiology:** Obtain 10 vials of 2 mg alteplase from the pharmacy. Reconstitute the required number of vials needed for the specific case (maximum of 10 mg for procedure). [Add 2.2 ml of preservative-free sterile water for injection USP to each 2 mg vial. Complete dissolution occurs within 3 minutes. The final concentration is 1 mg/ml.]

**Dilution**
Reconstituted alteplase should be diluted with non-heparinized NS (D5W is also acceptable).

For pulse-spray or bolus dose during interventional radiology or interventional cardiology procedure, dilute 10 mg alteplase in 100 ml saline (or 0.1 mg/ml).

The usual alteplase dose for a procedure is 6 to 10 mg in 100 ml NS. All of the 100 ml alteplase/NS dilution will be used during the procedure.

**Alteplase Preparation for Post-Procedure Infusions**
Alteplase infusions for the post-op period should be ordered through the Epic Order Set, “Procedure Orders - Alteplase Thrombolysis”

Pharmacy will prepare all alteplase infusions in the main pharmacy, under sterile conditions.
Alteplase: A standard concentration of 0.01 mg/ml in Sodium chloride will be used for all post-procedure alteplase infusions. (The standard dilution will be 10 mg alteplase in 1000 ml NS.)

The usual dose ranges from 0.01 to 0.03 mg/kg/hr (maximum 1 to 2 mg/hr with the adult maximum of 20 to 40 mg per day), depending on the thrombus burden identified during the procedure.

Site-Directed Clot Lysis Procedure:

1. Full dose heparinization should be started prior to the procedure and continued during thrombolysis. Monitor full dose heparinization as per the CCHMC Unfractionated Heparin Clinical Guidelines. For patients at higher risk of bleeding consider heparin infusion at 50% of usual therapeutic dose. Heparin administered at <15 units/kg/hr does not require monitoring of UFH levels. For low-risk patients in whom low-dose t-PA is used, enoxaparin at therapeutic dosage every 12 hours may be considered. All patients receiving tPA infusion need to be monitored in the ICU.

2. Catheter directed thrombolytic therapy with alteplase is initiated in interventional radiology or in the cardiac catheterization laboratory. The treatment may also include mechanical disruption of the thrombus by balloon angioplasty, stent angioplasty, ultrasound accelerated thrombolysis or a use of a thrombectomy device.

3. If extensive thrombus exists or a pulmonary embolism is present, consider the insertion of a temporary vena cava filter prior to thrombolytic therapy to decrease the possibility of massive pulmonary embolus. Temporary vena cava filters should generally be removed within one month after insertion.

4. During pharmaco-mechanical site-directed thrombolysis, alteplase may be administered as a bolus or by pulse-spray (as delivered by the AngioJet (Possis Medical, Minneapolis, Minn) by the interventional radiologist. Alteplase pulse-spray boluses may be administered to the thrombus with a maximum of 2-10 mg (0.1 - 0.3 mg/kg) per 24 hours in the attempt to shorten the overall treatment period.

5. In the case of arteriopulmonary shunt thrombosis in the cardiac catheterization laboratory, pharmaco-mechanical site-directed thrombolysis using alteplase may be undertaken with catheter directed bolus administration into the thrombosed shunt. Alteplase catheter directed boluses may be administered to the thrombus in an initial dose of 0.1 - 0.3 mg/kg. This bolus dose may be repeated every 20 minutes, with a maximum of 3 total bolus doses delivered (maximum cumulative dose 10 mg).

6. If pharmaco-mechanical site-directed thrombolysis is not complete after the first attempt, the patient may be returned to the ICU for continuous alteplase and heparin administration overnight.

7. The recommended dose of alteplase for continuous infusion is 0.01 to 0.03 mg/kg/hr with an adult maximum of 1 to 2 mg/hr (20-40 mg/24 hr), dependent on the size of the
thrombus. Alteplase should be administered into the infusion catheter access used to perfuse the clotted segment of vein.

8. The interventional radiologist may elect to infuse heparin into the access sheath. The usual dose of heparin delivered into the access sheath is 0.5 units/kg/hr (Dilute 1000 units heparin in 500 ml NS) NOTE: This heparin infusion is in addition to the standard heparin infusion listed below in #8. (Patients may have 2 heparin infusions running simultaneously.)

9. During infusion of alteplase, continue heparin infusion at full heparinization rate. In individual patients the heparin infusion may be modified to half the usual therapeutic dose. Monitoring of the UFH anti-Xa level is not necessary if heparin infusion is <15 units/kg/hr.

10. Infuse heparin through a dedicated I.V. DO NOT interrupt the heparin infusion or use this I.V. site for the infusion of any other products. Heparin should be diluted as 100 units/mL in D5W.

11. The patient will return to interventional radiology for reimagining and further attempts at pharmaco-mechanical thrombolysis/mechanical thrombectomy at the interventional radiologist’s discretion.

12. Because of the relatively prolonged duration of pharmacologic activity for alteplase and/or heparin, the infusions should be terminated at least 1 hour before removal of arterial sheaths if manual compression of an arterial access site is used.

13. An aPTT, fibrinogen level and CBC should be obtained every 12 hours during alteplase infusion. ALERT: DURING ALTEPLASE CONTINUOUS INFUSION THE APTT MAY BE MARKEDLY PROLONGED. THIS PROLONGATION OF THE APTT MAY NOT BE RELATED TO THE HEPARIN LEVEL. THE UFH LEVEL IS THE PREFERRED METHOD FOR FOLLOWING HEPARIN LEVELS DURING ALTEPLASE. THE UFH LEVEL SHOULD BE ORDERED AS “UFH LEVEL” NOT “LMWH LEVEL.”

14. After completion of the procedure and the patient is deemed ready for transfer out of the ICU, administer the therapeutic enoxaparin dose and discontinue the heparin infusion. Overlapping the heparin infusion and enoxaparin for 4 hours will help maintain therapeutic heparin effect (peak anti-Xa levels are reached at 3 to 5 hours after subcutaneous enoxaparin administration.)

**Adjunctive Use of Heparin**

Unfractionated heparin infusion should be started prior to transfer of the patient to Interventional Radiology. Use a standard concentration of heparin for infusion of 100 units heparin/mL D5W. For patients receiving alteplase infusion, ONE-HALF TO FULL DOSE HEPARIN therapy is recommended throughout the alteplase infusion and during the mechanical thrombolytic procedure. It is recommended that a dedicated heparin I.V. be inserted. NO OTHER AGENTS SHOULD BE GIVEN THROUGH THE HEPARIN CATHETER. DO NOT INTERRUPT HEPARIN THERAPY. If heparin therapy is interrupted for any reason for more than two hours, a repeat bolus is recommended. A lapse in the heparin infusion may cause rapid re-thrombosis of the vessel. Contact the IR attending physician if the heparin infusion is stopped for any reason.
To initiate an unfractionated heparin infusion, administer a loading dose of 75 units/kg IV over 10 minutes (maximum 5,000 units). If the patient has been on enoxaparin and the last dose of enoxaparin was less than 6 hours previously, no loading dose of heparin is necessary. If the time from the last dose of enoxaparin was greater than 6 hours, administer a loading dose of unfractionated heparin. After the loading dose, begin a continuous infusion maintenance dose.

**Initial maintenance dose:**
Infants ≤ 1 year of age: 28 units/kg/hour

<table>
<thead>
<tr>
<th>UFH Level (units/mL)</th>
<th>Bolus (units/kg)</th>
<th>Hold (minutes)</th>
<th>Rate Change (units/kg/hour)</th>
<th>Repeat UFH Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.2</td>
<td>50</td>
<td>0</td>
<td>Increase by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>0.2 – 0.29</td>
<td>0</td>
<td>0</td>
<td>Increase by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>0.3 – 0.7</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>24 hours</td>
</tr>
<tr>
<td>0.71 – 0.8</td>
<td>0</td>
<td>0</td>
<td>Decrease by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>0.81 – 1.0</td>
<td>0</td>
<td>30</td>
<td>Decrease by 10%</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>0</td>
<td>60</td>
<td>Decrease by 15%</td>
<td>4-6 hours</td>
</tr>
</tbody>
</table>

Children 1 – 16 years of age: 20 units/kg/hour
Children older than 16 years and adults: 18 units/kg/hour

Obtain blood for an UFH level 4 hours after administration of the heparin loading dose (NOT earlier) and adjust to maintain the UFH level at 0.3 to 0.7 units/mL (refer to nomogram below (Table 1). Blood samples for the UFH levels should NOT be drawn through heparinized lines. During the alteplase infusion the aPTT may be markedly prolonged. This prolongation of the aPTT may not be related to the heparin level. The UFH anti-Xa level is the preferred method for following unfractionated heparin levels during alteplase infusions. If half-dose heparin is used, monitoring of UFH levels is not necessary.

When enoxaparin is restarted at the conclusion of thrombolysis, continue unfractionated heparin for 4 hours after the first enoxaparin dose.

At the conclusion of site-directed thrombolysis for that day obtain a CBC and an aPTT, UFH level and fibrinogen level.

**Safety Monitoring**
The most common complication of thrombolytic therapy is adverse bleeding. Variables associated with adverse bleeding risks include increased alteplase dose, duration of infusion, adjunctive antithrombotic therapy (e.g., heparin, aspirin, or other antiplatelet agents), and hypertension. Physicians should be aware of these risk factors and use appropriate caution during treatment.

Developed by the CCHMC Anticoagulation and Thrombolytic Therapy Subcommittee.
Please contact the CCHMC Anticoagulation and Thrombolytic Therapy Subcommittee with questions.
Minor bleeding from puncture sites is common during thrombolytic therapy. If major bleeding occurs during infusion therapy, heparinization should be decreased to half the usual therapeutic infusion rate, and a CBC, aPTT and fibrinogen level should be obtained. Consider termination of alteplase after consultation with IR (NS should be infused through the alteplase catheter sheath to prevent clotting the sheath.) Fresh frozen plasma and/or cryoprecipitate should be administered to reverse hypocoagulability. Packed red cells should be given to correct severe anemia.

If severe life-threatening bleeding occurs, stop the infusion of the thrombolytic agent (i.e., alteplase) and heparin. Consider administration of cryoprecipitate (usual dose of cryoprecipitate is 0.25 Units/kg body weight will raise the fibrinogen level by 75 mg%) with a goal of increasing the fibrinogen level to greater than 100 mg%). If life-threatening bleeding continues consider reversing the fibrinolytic process by infusing epsilon aminocaproic acid (Amicar®). If heparin has been given, protamine sulfate may be required to reverse its effect. Consult CCHMC formulary for Amicar® and protamine sulfate dosing.

References


7. Enden T, Haig Y, Klow N-E, Slagsvold C-E, et al. on behalf of the CaVenT Study Group. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment


