General Information

These guidelines are for the use of alteplase (tPA; tissue plasminogen activator; Activase®) in the management of patients with significant venous and arterial thrombosis. They do not apply to patients who require catheter clearance.

Though anticoagulation alone is often effective at managing thromboembolism (TE), there are times when more rapid clot resolution is necessary or desirable. In these situations, recombinant tissue plasminogen activator (alteplase, tPA), an agent that activates the fibrinolytic system, is of potential benefit.

A hematology consult is required for the use of alteplase (tPA) infusion in settings other than the cardiac catheterization lab and cardiac surgery.

Indications for Thrombolysis

Indications for thrombolysis in the treatment of pediatric TE are not well established, primarily due to lack of well-designed clinical studies. The benefit of rapid clot resolution must be weighed against the risk of major bleeding, which is greater than with anticoagulation alone. As a result, indications for thrombolytic therapy in children should be restricted to situations in which the benefit of rapid thrombus resolution is thought to outweigh the risk of major hemorrhage.

- Life, limb or organ threatening thrombosis
  - Arterial or venous thrombosis causing tissue ischemia
  - Superior vena cava syndrome due to thrombosis
  - Massive PE with cardiovascular instability or submassive PE
  - Bilateral renal vein thrombosis
  - Cerebral sinovenous thrombosis with progressive neurologic decline
  - Large atrial thrombi
- Extensive obstructive proximal iliofemoral vein or inferior vena cava thrombosis
- Anatomic compressive syndromes
  - May-Thurner Syndrome
  - Paget-Schroetter Syndrome
- Thrombotic events in which the long-term persistence of thrombus would have a significant negative effect
CLINICAL PRACTICE GUIDELINES

Use of Alteplase (TPA) For Thrombolytic Therapy

Disclaimer: These clinical practice guidelines are based upon the opinions of staff members of The Children’s Hospital of Philadelphia. Treatment should be individualized and based upon the clinical conditions of each patient.

Contraindications to thrombolytic therapy

- Major surgery within 7-10 days
- Active bleeding
- Central nervous system surgery/trauma/ischemia*/hemorrhage within 30 days;
- Inability to maintain platelet count > 75,000/mm3
- Inability to maintain fibrinogen >100 mg/dl
- Uncontrolled hypertension
- Severe coagulopathy
- Additional contraindications for use of alteplase for acute ischemic stroke include the following:
  - Stroke or head trauma within 3 months
  - Major surgery within 14 days
  - GI or GU bleeding within previous 21 days
  - Arterial puncture at a noncompressible site within 7 days
  - Lumbar puncture within 7 days
  - Symptoms suggestive of subarachnoid hemorrhage, even if CT is normal
  - CT or MRI with evidence of hemorrhage
  - Clinical presentation consistent with acute MI or post-MI pericarditis requires evaluation by cardiology prior to treatment
  - Prothrombin time (PT) > 15 sec, if on warfarin
  - On heparin therapy within 48 hours and with elevated PTT
  - Pregnant or lactating female
  - Platelet count < 100,000
  - Persistent systolic or diastolic BP > 10 mmHg above the 95%ile for age/height-specific normative values

* With the possible exception of acute ischemic stroke per CHOP stroke team

These contraindications are not absolute or evidence based, and in every individual clinical situation, the relative risks of thrombolytic therapy must be weighed against potential benefits.
Baseline Monitoring (To be completed prior (< 48 hrs) to or upon initiation of alteplase (tPA) infusion)

- CBC
  - Thrombocytopenia is a relative contraindication to thrombolytic therapy and should be corrected to ≥75,000/mL before use.
- PT
- PTT
- Fibrinogen
- D-dimer
- Head ultrasound (all infants < 2 month) or CT for older children whose neurologic status is difficult to assess (to exclude intracranial hemorrhage).

Administration

Thrombolytic drugs may be administered systemically (systemic thrombolysis) or directly into the thrombus via a catheter that has usually been placed specifically for that purpose (catheter-directed thrombolysis). This decision is generally made on a case-by-case basis. In older patients, site-directed thrombolysis may allow lower doses of alteplase (tPA) because the catheter is near the site of occlusion, and allows for easy reimaging of the site. Consider systemic thrombolysis if site-directed is technically difficult or not easily obtainable.

- Patients must have a dedicated line for alteplase (tPA) infusions.
- The infusion must NOT be stopped or interrupted for other medications.

Dosing

Numerous dosing strategies for alteplase (tPA) are used for thrombolytic therapy in pediatrics and there is currently no consensus as to which approach is optimal. Higher doses may restore flow more rapidly, but appear to have a higher risk of bleeding. The regimen used may depend upon the type of thrombotic event, as discussed below.

Systemic Thrombolysis

Low Dose Alteplase (tPA) Regimen

This regimen should be considered for patients with non-life-threatening venous thrombotic events.

Initial Dose: 0.03-0.06 mg/kg/hr for venous thrombosis. Max dose for low dose alteplase (tPA) 2 mg/hr.

Duration: This dose may be continued for a relatively prolonged duration (2-4 days). Ongoing monitoring of hematologic parameters (see below Monitoring) and thrombus assessment are essential.
High Dose Alteplase (tPA) Regimen
This regimen should be considered for patients with arterial or and more critical thrombotic events.

**Initial Dose:** 0.1-0.6 mg/kg/hr (maximum 50 mg/hr)

**Duration:** The duration will depend upon the chosen dose. Patients receiving doses of 0.5-0.6 mg/kg/hr should be assessed at 6 hours. At 6 hours, hematologic parameters and thrombus assessment should be performed (see below Monitoring). If the progress is not adequate, hematologic parameters are within acceptable range (see contraindications for thrombolysis) and the patient is stable, additional 6-hour infusions can be administered, reassessing after each.

Patients at the lower end of this dose range may tolerate longer infusions.

Pulmonary Embolism Protocol
Thrombolysis should be considered for patients who have massive PE and are hemodynamically unstable. This dosing protocol has been used in adult patients and has not been studied in pediatric patients.

**Dose/Duration:**

Massive Pulmonary Embolism
- Patient ≥ 60 kg: 10 mg alteplase over 10 minutes, followed by 90 mg over 2 hours.
- Patient < 60 kg: 0.1 mg/kg alteplase over 10 minutes, followed by 0.9 mg/kg over 2 hours. This dose is extrapolated from adults. Dosing may be higher or lower depending on risk of bleed or thrombosis.

Submassive Pulmonary Embolism
- Patient ≥ 60 kg: 10 mg alteplase over 10 minutes, followed by 40 mg over 2 hours. For patients with submassive PE, an adult study suggested alteplase with a total dose of 50 mg was effective.

SITE DIRECTED THROMBOLYSIS (For use by Interventional Radiology or Cardiology; infusions may continue if patient is admitted to the ICU)

**Delivery options:**
- Bolus delivery in IR - administered via Angiojet or Penumbra Aspiration Catheter located in thrombus
- Catheter directed infusion: administered via a pulse-spray catheter located in thrombus.

**Dose/Duration:** 0.5-2 mg/hr. The duration will vary depending on the dose and indication, but long infusions (96 hours) have been well tolerated. Ongoing monitoring of hematologic parameters (see below Monitoring) and thrombus assessment are essential.
PHARMACOMECHANICAL THROMBOLYSIS: This refers to the use of alteplase in conjunction with one of several devices for mechanical disruption of clot. Specific devices include:

- Angiojet—With this device, saline mixed with alteplase is injected under high-pressure into the thrombus and left to dwell for 20-30 minutes. Simultaneously, the saline/alteplase and thrombus are suctioned back into the catheter. In patients with contraindications to thrombolysis, alteplase may be excluded from the saline infusion but this is an exception. For an adolescent patient (≥ 40 kg), 4 mg of alteplase is a typical dose, maximum of 10 mg if required in larger patients. For young patients (< 40 kg), the dose of alteplase is 0.1 mg/kg. Although some of the alteplase will be suctioned back, much will be systemic.

- Penumbra Aspiration Catheter—This device is placed into the thrombus and advanced through the thrombus with suction engaged to suction out the thrombus into a vacutainer. There is no injection of saline required. There is a separator wire to intermittent declog the aspiration catheter and continue suctioning. If the clot is firm an alternate technique of lacing the clot with alteplase using a regular catheter may be performed prior to using the Penumbra Device. Dwell doses and time will be the same as for Angiojet in that setting.

Use of Concomitant Anticoagulation
The use of unfractionated heparin or low molecular weight heparin during systemic and catheter directed thrombolytic therapy may be helpful in preventing ongoing thrombus formation but will increase the risk of bleeding. This decision should be made on an individual basis. Heparin has a shorter half-life and is reversible, but enoxaparin may be easier to ensure therapeutic levels of anticoagulation.

- Critically ill patients at high risk for bleeding: 0-10 units of heparin/kg/hr
- Otherwise healthy patients (adolescents with proximal DVT): therapeutic doses of heparin (goal PTT 60-85 seconds) or enoxaparin. Refer to Initiation and Maintenance of Heparin Infusion.
- In cases where alteplase is used to treat acute ischemic stroke, other antithrombotic treatments, such as heparin, warfarin, aspirin, and ticlopidine, are held for at least 24 hours.

Monitoring
- Admit patient to the ICU for close monitoring
- Patient must be on strict bedrest
- Place blood drawing IV or arterial line for frequent lab draws prior to initiation of thrombolytic whenever possible. Do not use heparin locks or heparin containing fluid.
- Invasive procedures (blood draws, placement of arterial or venous catheters, NG tubes, rectal temperature probes, placement of urinary catheters) should be avoided for at least 24 hours after high-dose alteplase regimen for acute stroke.
- Check PT, PTT, CBC, Fibrinogen, D-dimer prior to starting, and then every 4-6 hours while the patient is receiving a thrombolytic. An elevated D-dimer and drop in the fibrinogen is indicative of a lytic state.
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- **Dose Adjustment:** If the fibrinogen drops to < 125 mg/dl, decrease the dose of thrombolytic by 50%. If the fibrinogen drops < 100 mg/dl, consider holding thrombolytic or give cryoprecipitate.
- Monitor neurologic status q1 hour for possible ICH. In infants or critically ill patients, whose neurologic status is difficult to assess, consider a head ultrasound or CT to monitor for ICH daily while receiving thrombolytic therapy.

**Safety**

- **Bleeding:** The major adverse event related to thrombolytic therapy is bleeding. The true incidence of bleeding complications is difficult to assess due the lack of prospective studies using uniform protocols. Older studies reported high rates of bleeding complications (40-60%) using high doses of alteplase (tPA) (>0.5 mg/kg/hr). A review of alteplase (tPA) for femoral artery thrombosis in children, reported ICH in 14 of 929 patients (1.5%). The risk was highest in preterm infants (13.5%) compared to older children (0.4%).
  - If a patient has significant bleeding, stop the thrombolytic agent and heparin, administer cryoprecipitate; consider reversing heparin in life threatening situations. Refer to *Initiation and Maintenance of Heparin Infusion*. Antifibrinolytics (aminocaproic acid) can also be considered.
  - Avoid drugs that affect platelet function (e.g., aspirin, NSAIDs, dipyridamole) as they may potentiate the risk of hemorrhage.
  - Avoid IM injections, rectal temps, arterial sticks, NG tube insertion, intubation, lumbar punctures or urinary catheterization during thrombolytic therapy.

**Reversal/ Elective Procedures**

- Alteplase (tPA) can NOT be reversed, but has a relatively short half-life. Hold Alteplase (tPA)/heparin a minimum of 6 hours prior to *surgical* procedure or *lumbar puncture*.

**Complications**

- The attending of record will be responsible for the diagnosis and management of any potential complications (i.e. bleeding, etc) in consultation with the division of hematology as deemed appropriate.
- Reporting of complications, including bleeding requiring transfusion, intracranial hemorrhage, and over-anticoagulation requiring reversal with protamine, into the electronic reporting system, KAPS, is highly recommended.

**Related Document:** Policy: [Heparin Induced Thrombocytopenia (HIT)](https://www.chop.edu/policy/heparin-induced-thrombocytopenia-hit)