SYSTEMIC THROMOBOLYSIS WITH ALTEPLASE IN PICU - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- There are limited paediatric data on the use of systemic thromobolysis with alteplase, therefore any decision to treat should be carefully balanced against the risk of bleeding. This may involve discussions with the Intensivist, Haematologist and other relevant consultants for the patient, including general and transplant surgeons, cardiologists and cardiac surgeons, or the interventional radiologist.
- Indications include life, organ or limb threatening arterial or venous thromboses.
- Contraindications (some relative) include previous allergic reacition to alteplase recent general, cardiac or neurosurgery; conditions where there may be active bleeding and recent trauma, or significant potential for serious local bleeding.
- Prior to commencement of alteplase, any concurrent haemostatic defect should be appropriately corrected (FFP, cryoprecipitate, vitamin K). Notably the effect of alteplase is diminished if plasminogen levels are low, suggested by a fibrinogen level of < 1 g/L.
- A heparin infusion should be administered concurrently.
- The patient must be carefully monitored for signs of bleeding during the infusion, including local bleeding at the sites of venepunctures, cannulas and wounds, or intracranial bleeding by monitoring level of consciousness.
- If any signs of bleeding and/or bruising occur – consider cessation of alteplase and heparin infusions. Alteplase is cleared rapidly from the circulation after cessation of an infusion.

Approved by:	Director, Clinical Governance	
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CHANGE SUMMARY

(This section is to be completed only for revised documents – Not applicable for new documents.)

Outline a summary of changes to the revised document. The summary should include:

- Information on reasons for the update, eg. response to an incident/s.
- A description of the changes made.
- List the sections/items that have changed from the previous version.

READ ACKNOWLEDGEMENT

Outline who needs to read or know about the document (roles only – do not use names).

Outline using ONE of the following requirements:

- Training/Assessment Required – nil
- Read Acknowledge Only – PICU Medical and Nursing Staff; Pharmacist, Haematologist
- Discretionary – [local manager to determine which staff, if any, are to read and acknowledge the document or acknowledge the document only.]

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Background

There are limited data on the efficacy, dose, and safety of systemic or local thrombolysis in the paediatric population, with the exception of intracatheter instillation for CVAD blockage [1]

Therefore any decision to treat with lytic therapy should be balanced against the risk of bleeding, and must be individualised for each patient. Decision making must involve the Intensivist, Haematologist and other relevant consultants (cardiac surgeon, interventional cardiologist, neurosurgeon, general surgeon, interventional radiologist) prior to administration.

Catheter directed therapy (mechanical thrombectomy, stent deployment and local thrombolysis)[2] may be considered under some circumstances, but these treatment strategies are also poorly supported in the paediatric literature by good clinical evidence. Surgical clot removal may have a higher risk of clot recurrence than either systemic or catheter-directed therapy, but should nevertheless be considered. Locally delivered alteplase may be appropriate if there is a catheter-related clot and the catheter is still in-situ.

Finally anticoagulation with heparin alone may be the treatment of choice, or potentially no therapy if the risk of bleeding is considered excessive.

Indications

- Massive pulmonary embolism;
- Pulmonary embolism (further embolism) despite heparin;
- Arterial occlusions threatening organ or limb viability;
- Acute, extensive venous thromboembolism threatening organ or limb viability.
- Prosthetic valve thrombosis.

Contraindications

- Previous allergic reaction to ateplase or gentamicin (the latter a trace residue from the manufacturing process)
- Active bleeding;
- Significant potential for serious local bleeding (e.g. CNS tumour; uncontrolled hypertension) ;
- General or cardiac surgery within the previous 10 - 14 days;
- Neurosurgery, including spinal surgery, within the previous 3 weeks;
- AV malformations;
- Recent significant trauma

Note that under certain circumstances, some of the contraindications may be relative and the decision to treat with alteplase must be carefully considered.

Relative contraindications

- Known bleeding diathesis

Notes

1. Thrombolytic therapy is generally ***not*** recommended in children with right-to-left cardiac shunts because of the risk of arterial emboli to the central nervous system.
2. Numerous case reports have described successful use of alteplase for purpura fulminans,[3, 4] however an international, multi-centre, retrospective, observational study found intracerebral haemorrhage in 5 of 62 consecutively treated children with fulminant meningococcal sepsis.[5] It is uncertain if this rate is excessive (as there are no randomised controlled trials), however caution is recommended if alteplase is used. Importantly, another agent with fibrinolytic activity (recombinant human activated protein C) [6] has been found to increase significant bleeding complications (including intracerebral haemorrhage) when used to treat severe sepsis and septic shock.
3. The American College of Chest Physicians evidence based clinical guideline (2012) does not generally recommend thrombolytic therapy for ischaemic arterial stroke in children.[1] Note: The Thrombolysis in Pediatric Stroke (TIPS) trial (NIH #R01 NS065818) was closed in 2013 due to low enrolment.[7]
4. Based predominantly on adult data, current evidence favours the use of thrombolytic therapy for prosthetic valve thrombosis.[8] Paediatric literature is sparse, and limited to case studies.[9]

Baseline Investigations

- FBC, PT, APTT, fibrinogen and platelet count;
- Group & Hold;
- Other imaging to rule out active bleeding may be required and should be individualised (e.g. neurological imaging)

Human recombinant tissue plasminogen activator (tPA, alteplase)

- Tissue plasminogen activator (t-PA) is a naturally occurring protein synthesised mainly by the endothelial cell. [10] Alteplase is a purified fibrinolytic glycoprotein of 527 amino acids, synthesised using the cDNA for natural human tissue-type plasminogen activator. Alteplase binds to fibrin in a thrombus and catalyses the conversion of the inactive proenzyme plasminogen into the active serine protease plasmin. This initiates local fibrinolysis. Alteplase exhibits greater fibrin specificity, lower immunogenicity, and

more effective clot lysis in vitro compared with either streptokinase or urokinase and is the preferred agent for systemic thrombolysis. The efficacy of alteplase is diminished if the plasminogen levels are low (suggested by a fibrinogen level of < 1 g/L).

Pharmacokinetics

- Alteplase is cleared rapidly from the circulation after cessation of an infusion, principally by the liver. In normal adults, more than 50% present in the plasma is cleared within 5 minutes and 80% is cleared within 10 minutes.

Treatment Regimen (Standard Dose)

Systemic thrombolysis with should be performed in the Intensive Care Unit

1. Before alteplase administration correct any concurrent hemostatic defect:
   a. Correct platelet count if < 100, maintain platelets >100
   b. Correct fibrinogen with FFP (or cryoprecipitate) if < 1.5 g/L
   c. Correct other coagulopathy with FFP 20 ml/kg; and/or IV vitamin K (not IM Vit K)
2. Commence heparin infusion at 10 - 20 units/kg/hour (ideally several hours prior to alteplase). Consult Haematology; dosage determined by age of patient and duration of heparin prior to starting alteplase. In massive PE or limb/organ threatening arterial occlusions, start heparin and alteplase concurrently if not already on heparin
3. Administer alteplase intravenously 0.5 mg/kg/hour for 6 hours.[1]
4. At the end of the alteplase infusion, increase the heparin infusion to a therapeutic dose for age, targeting an antiXa level of 0.3-0.7 units/mL. Do not give a loading dose of heparin.

Observations and Investigations during the Alteplase Infusion

1. Minimal handling of patient, no intramuscular injections, and avoid concurrent warfarin or anti-platelet agents if possible.
2. Monitor fibrinogen at 3 -4 hours and at the completion of the alteplase infusion. Expect a fibrinogen decrease of 30 – 50% from baseline if dosage was adequate. If the fibrinogen level is < 1 g/L at either time frame, consider further supplementation with either cryoprecipitate or FFP and review alteplase (after discussion with Haematology).
3. Observe all puncture sites and other wounds for signs of bleeding
4. Monitor level of consciousness with regular (hourly) neurological observations. Alterations in the neurological observations should raise the possibility of central nervous system bleeding.
5. If any signs of bleeding and/or bruising occur – consider cessation of alteplase and heparin infusions. Mild bleeding can be controlled with local pressure or topical

thrombin preparations. Consider reversal of heparin with protamine. If life threatening haemorrhage occurs, stop alteplase and give cryoprecipitate and/or FFP; use antifibrinolytic agent such as tranexamic acid with caution.

6. Monitor peripheral circulation hourly if treating a limb threatening thrombosis (pulse and or Doppler pulse, colour, capillary return and limb temperature)
7. Re-image to assess benefits of thrombolysis
8. A second 6-hour course of alteplase may be considered after discussion with the intensivist and haematologist.

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