Guideline: Thrombolysis for Pulmonary Embolism (PE)

Purpose

This guideline is designed to provide guidance on the use of thrombolysis in the management of patients with pulmonary embolism (PE). Although the benefit of thrombolysis is established in massive PE, the benefits of thrombolysis remain unclear in the sub massive group and the decision to thrombolyse needs to be made on a case by case basis.

Caution:

The decision to thrombolyse a PE is to be made following **discussion with a Consultant** (ICU, ED and/or Respiratory Medicine).

Note:

Tenecteplase is the preferred agent for thrombolysis for PE, however due to current international stock shortage of tenecteplase this guideline has been updated to guide dosing of alteplase as an alternative agent for PE thrombolysis.

Important:

To avoid confusion, Alteplase should always be prescribed by the full generic name – ALTEPLASE. It should NEVER be prescribed using an abbreviated name

This guideline has related protocols in MedChart – Check the protocols tab in MedChart.

Roles and Responsibilities

This guideline is applicable to

All ED and General Medical CMDHB employees (full-time, part-time and casual (temporary)

Indications for thrombolysis

Massive PE

- Haemodynamic instability
  - Systolic BP <90mmHg for >15min
  - BP fall by >40mmHg for > 15min despite resuscitation

- Cardiogenic shock
- Cardiac arrest secondary to PE

Persistent bradycardia: pulse <40 with signs or symptoms of shock

Submassive PE

In normotensive patients with **extensive clot burden** on CT (saddle embolus or involving main pulmonary artery) *consider* thrombolysis on case by case basis if **one or more of the following** are also present:

- Acute RV strain on CTPA (marked enlargement of RV with flattening of the interventricular septum) without evidence of chronic pulmonary hypertension and organised clot
- Severe acute RV dilation (RV:LV >0.9) or dysfunction on echocardiogram (echocardiogram not essential if other indications for thrombolysis already present)
- Elevated troponin
- Elevated NT pro-BNP (>500pg/mL)
- Significant hypoxaemia and large A-a gradient

While not criteria for submassive PE, the following can be considered in the decision whether to thrombolyse a patient:

- Free floating RA or RV thrombus
- Patients with a PFO

Timing and Setting for thrombolysis

Thrombolysis should be initiated as soon as possible within the golden hour (i.e. in ED). In certain cases, thrombolysis may be considered up to 24 hours after positive CTPA or beyond but this warrants a case by case discussion with Respiratory.

Symptoms may have been present for up to 72 hours before presentation.

Patients should be admitted to HDU for monitoring.

Contraindications

These are all relative in a patient who has a life-threatening PE. Each case should be considered on a case by case basis.

- In case of **submassive PE**, there is no proven benefit in patients aged > 75 (above this age risk of bleeding is high, including ICH). For patients with **massive PE**, however, thrombolysis may still be appropriate
- Patient is for palliative care only (irrespective of diagnosis)
- Significant uncontrolled hypertension (SBP> 180 mm Hg or DBP > 110 mmHg)
- History of recent head injury within 4 weeks
- Recent ischaemic stroke e.g. within 3 months
- Previous intracranial haemorrhage or known structural cerebral vascular lesion, or intracranial malignant neoplasm
- Suspected aortic dissection.
- History of recent GI haemorrhage within 4 weeks
- Recent brain or spinal cord surgery
- Other major bleeding risk (e.g. active bleeding, active peptic ulcer disease, bleeding tendency, major surgery within 3 weeks, pregnancy, childbirth within previous 30 days)
- IVC filter or thrombectomy within last 4 days

Cautions

- Therapeutic doses of blood-thinning medications (may require reversal)
- Hypersensitivity to gentamicin and other aminoglycosides (residue from manufacturing process)
- History of severe chronic poorly controlled hypertension;
- Traumatic or prolonged (>10 min) CPR

Treatment Regimen: PE (not in cardiac arrest)

STAT Enoxaparin prior to CTPA/echocardiogram- 1mg/kg subcutaneous, usually capped at 150mg. If there is a strong clinical suspicion for PE and no contraindication, enoxaparin should be administered as early as possible. It should not be delayed until after CTPA.

Once a decision for thrombolysis has been made, follow this pathway:

<table>
<tr><th>STEP</th><th>ACTION</th></tr>
<tr><td>1</td><td>ANTICOGULATION
If stat enoxaparin has been given proceed to step 2
If stat enoxaparin has NOT been given, consider starting intravenous unfractionated heparin (UFH) infusion at 1000 units/hour without a bolus if there will be a delay before thrombolysis.
- Stopping UFH infusion during alteplase infusion is suggested, though practice varies.
If patient is already anticoagulated with an oral agent, discuss reversal of anticoagulation with Haematology.</td></tr>
<tr><td>2</td><td>ALTEPLASE - refer to appendix for administration instructions

<table>
<tr><th>Body weight</th><th>Alteplase dose regimen</th></tr>
<tr><td>Greater or equal to 65 kg</td><td>Total maximum dose of 100 mg administered over 2 hours.
10 mg as an IV bolus over 1 - 2 minutes, immediately followed by
90 mg as an IV infusion over 2 hours</td></tr>
<tr><td>Less than 65 kg</td><td>Total maximum dose of 1.5 mg/kg administered over 2 hours
10 mg as an IV bolus over 1 – 2 minutes, immediately followed by
The remaining dose as an IV infusion over 2 hours</td></tr>
</table>


In patients with increased risk of bleeding complications a 50mg total dose can be considered in place of the 100mg dose (10mg load with the remaining 40mg over 2 hours)</td></tr>
<tr><td>3</td><td>UFH INFUSION AFTER ALTEPLASE

<table>
<tr><td>If subcutaneous enoxaparin has been given:</td><td>- Delay UFH infusion by 12 hours
- Check anti-Xa level 10 hours after giving enoxaparin (specify on lab form that patient has received enoxaparin)
If aPTT is ≤2x ULN and anti-Xa level is ≤0.5 start UFH infusion at 18 units/Kg/hour, without a bolus
Otherwise, consult Haematology; aPTT or anti-Xa may be high for non-coagulation reasons</td></tr>
<tr><td>If subcutaneous enoxaparin has</td><td>- After giving alteplase, take full coag screen including aPTT:
If aPTT ≤2x ULN, start UFH infusion at 18 units/Kg/hour</td></tr>
</table></td></tr>
</table>

	not been given:	without a bolus • Otherwise, consult Haematology; aPTT may be high for non-coagulation reasons
4	**UFH MONITORING** 4-6 hours after starting UFH infusion, check: • Anti-Xa activity (post thrombolysis target 0.3-0.5[5] IU/mL) • aPTT (post thrombolysis target 50-80[1] seconds) Heparin resistance is common post thrombolysis, high doses may be required. It may also resolve abruptly. Anti-Xa monitoring is preferred when heparin resistance is a likely issue. • Monitor and adjust heparin infusion per Commencing IV heparin for treatment of VTE information on Paanui, but with reduced aPTT target as specified above	
5	**SWITCH TO ENOXAPARIN** Continue UFH for 48 hours then change over to subcutaneous enoxaparin. • If anti-Xa level or aPTT are therapeutic, stop heparin, start enoxaparin within 1-2 hours • If patient is over-anticoagulated, consider waiting longer, and if sub-therapeutic, consider not waiting Subcutaneous enoxaparin is 1mg/kg **Q12H** if CrCl > 30ml/min and 1mg/kg Q24H if CrCl < 30ml/min. At CMH, the current practice is to cap the dose at 150mg Q12H.	
6	**ORAL ANTICOAGULATION** Oral anticoagulation can be started after completion of thrombolysis in discussion with the Respiratory, General Medical or Haematology and Thrombosis.	

Treatment Regimen: Suspected PE induced cardiac arrest

<table>
<tr><th>Step</th><th>Action</th></tr>
<tr><td>1</td><td>ALTEPLASE - refer to appendix for administration instructions
<table>
<tr><th>Setting</th><th>Alteplase dose regimen</th></tr>
<tr><td>In Cardiac Arrest due to, or felt to be due to PE:</td><td>0.6 mg/kg over 1-2 min (maximum dose 50 mg)[2,3]</td></tr>
<tr><td>• if ROSC has not occurred 20 minutes after initial bolus</td><td>A further dose of 0.6mg/kg over 1-2 min (maximum dose 50 mg) can be considered</td></tr>
<tr><td>• If ROSC has occurred after initial bolus</td><td>A further dose could be given to complete a total maximum dose of 1.5 mg/kg administered over 2 hours (cap at 100mg)
• I.e. if body weight ≥ 65 kg, a further 50mg may be given over 2 hours
• If a reduced dose of 50mg was planned then a further 50mg infusion is not needed</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td>If a cardiac arrest occurs after alteplase bolus or infusion has started per treatment regimen for PE</td><td>• 0.6 mg/kg over 1-2 min (maximum dose 50 mg) can be given at SMO discretion
• If ROSC is achieved after bolus, the remaining dose can be administered over 2 hours if appropriate (total maximum dose 1.5 mg/kg, cap at 100mg).</td></tr>
</table></td></tr>
<tr><td>2</td><td>UNFRACTIONATED HEPARIN OR ENOXAPARIN
Heparin or Enoxaparin are not part of the resuscitation of a patient that has arrested from a PE. They can be considered per the PE treatment pathway if ROSC is achieved.</td></tr>
</table>

References

1. NZ Medsafe Datasheet: Alteplase accessed online 16.2.21. Produced by Boehringer Ingelheim NZ Ltd. Last updated 14.2.19.
2. Konstantinides et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). EHJ 41(4); 2020,543 -603.
3. Tapson V, Weinberg A (2021). Upto date. Approach to thrombolysis therapy in acute pulmonary embolism: patient selection and administration.
4. Life in the Fast Lane: https://litfl.com/thrombolysis-for-massive-pulmonary-embolus/

5. https://depts.washington.edu/anticoag/home/content/heparin-infusion-guidelines

Definitions/Description

Terms and abbreviations used in this document are described below:

Term/Abbreviation	Description
CTPA	Computed tomography pulmonary angiogram
ED	Emergency Department
HDU	High Dependency Unit
ICU	Intensive Care Unit
IVC	Internal vena cava
PE	Pulmonary embolism
PFO	Patent foramen ovale
RA	Right atrium
ROSC	Return Of Spontaneous Circulation
RV	Right ventricle
SC	Subcutaneous
UFH	Unfractionated heparin

Appendix: Alteplase Administration

Presentation	Alteplase 50mg vial (powder), solvent (water for injection 50mL).
Reconstitution	• The full volume of solvent provided should be transferred to the vial containing the alteplase powder using the provided transfer cannula. • Final concentration 1mg alteplase/1mL. • Refer to Alteplase (Actilyse) Medsafe datasheet for detailed reconstitution instructions
Administration	After reconstitution, alteplase does not require further dilution prior to administration: • Draw up bolus dose required and administer as prescribed - usually given over 2 – 3 minutes • Remaining dose is given as an infusion, over 2 hours via a burette.
Stability	The reconstituted solution is stable for 24 hours at 2 - 8 °C and for 8 hours at 25 °C.