Paediatric Intensive Care Unit

Thrombolysis

Staff relevant to:	Medical and Nursing staff caring for children in the PICU
Approval date:	May 2021
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Trust Ref:	C31/2021 **C115/2016 has been archived as incorporated in to this new guideline.**

Related Guidelines and Policies:	
C112/2016	Central Lines UHL Paediatric Intensive Care Guideline
B24/2016	Thrombolysis Therapy in Pulmonary Embolism UHL Guideline
D9/2020	Stroke UHL Childrens Guideline
	PICU Heparin Protocol

1. Introduction and who this guideline applies to:

This guideline applies to all healthcare professionals involved with care of patients (from neonatal age up to 18 years) at paediatric intensive care unit (PICU). This treatment requires close monitoring and is to be used at PICU only under the direction of a PICU consultant in conjunction with cardiologist, cardiac/vascular surgeon and haematology input.
This guideline does not cover neonates and infants being cared for in the special care baby unit (SCBU) or neonatal intensive care unit (NICU). This guideline does not cover stroke treatment.

Contents

2. Guideline standards, considerations and precautions:

The incidence of paediatric venous thromboembolism (VTE) is estimated to be 0.07–0.14/10,000 children [1, 2]; and is increasing. [3] Several risk factors for paediatric thrombosis have been identified, including the presence of a central venous catheter (CVC), cancer, congenital heart disease, and surgery. [4]

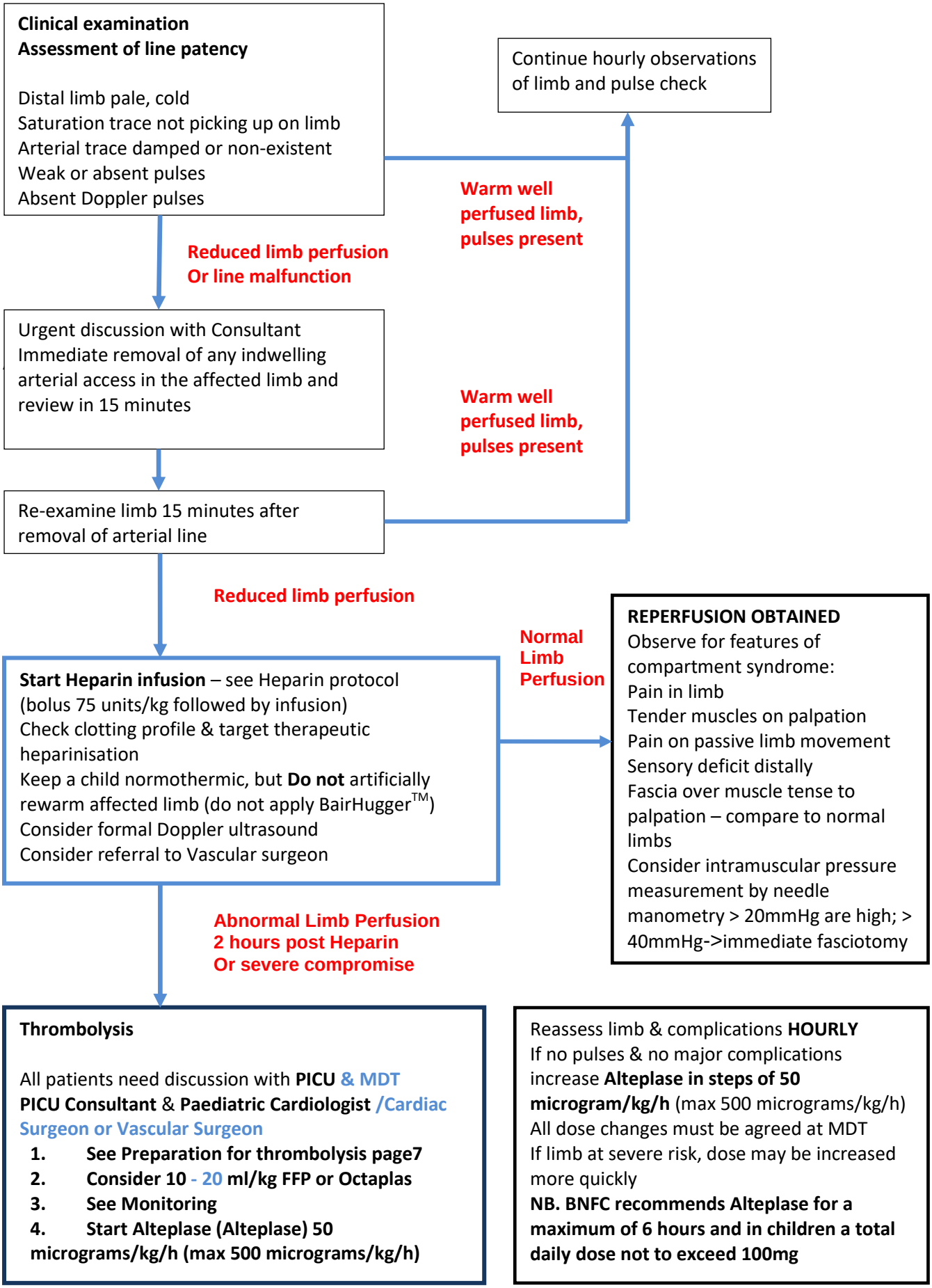
In a systematic review, catheter related arterial thrombosis (CAT) incidence in neonates has been reported as 20% for UAC, 11% for cardiac catheter-related CAT and extremity indwelling catheter-related CAT within a range 3.4-63%. Clinical presentation of CAT included symptoms of limb ischaemia, arterial hypertension and congestive heart failure. Antithrombotic treatment included heparin, thrombolysis and thrombectomy or combination with complete resolution of CAT in 82%. Long term complications included arterial hypertension (26%) or limb amputation (12%). (17)

Alteplase is most commonly used in paediatrics due to its short half-life (3 - 5 min). Dosing for thrombolysis in children is not standardized.

In contrast to anticoagulants that decrease the body's ability to form new thrombus, thrombolytic agents act by converting plasminogen to plasmin and thereby actively reduce clot burden. Recombinant Alteplase has a high affinity for fibrin, and the fibrin-Alteplase complex enhances the binding of plasminogen to fibrin, localising the effects to the site of thrombosis; Alteplase (r-Alteplase) is recommended in paediatrics over other thrombolytics. [5]

Whether systemic or endovascular thrombolysis is used, **concomitant use of anticoagulation** is recommended to prevent new thrombus formation during thrombolysis, as clot lysis releases active thrombin which was bound to thrombi [6]. Reported dosing of concomitant anticoagulation has ranged from therapeutic heparin to heparin at a set dose of 5–10 units/kg/h. [7 - 9] **Anti-Xa levels should be monitored during thrombolysis when possible** as fibrin split products can prolong the activated thromboplastin time (aPTT) - questionable usefulness during thrombolysis.

2.1 Algorithm for Arterial line Associated Reduced limb perfusion



2.2 Algorithm for Systemic Thrombolysis

MDT agreement MDT – (e.g. **PICU Consultant /Paediatric Cardiologist /Cardiac Surgeon /Vascular Surgeon/Haematology Consultant)**

- ✓ Indication confirmed and clearly documented; discussion with parents documented
- ✓ Appropriate investigations to exclude all contraindications prior to starting therapy completed
- ✓ Intracranial imaging (ideally CT) should be considered prior to and after thrombolytic therapy in children < 3 months of age or any child at high risk for ischemic or haemorrhagic stroke
- ✓ **Dosing regimen recorded in the notes– depends on the indication and severity of status**

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Preparation

- ✓ Heparin commenced (ideally 6h or longer prior to Alteplase)
- ✓ FBC, INR/PT, aPTT, Fibrinogen, -> Platelets must be > 100 000/ul & Fibrinogen > 2g/L
- ✓ Valid Xmatch (one adult unit of cross matched packed red cells available);
- ✓ D dimers at the beginning and at the end of treatment
- ✓ Consider administration of FFP 10 - 20ml/kg (+ Furosemide, if needed), might need repeating 8-12hourly as plasminogen source
- ✓ Adequate and reliable iv access to infuse and obtain blood samples

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Decrease Unfractionated heparin to 10units/kg/h

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Precautions

No new arterial punctures or line placements during the treatment

No intramuscular injections

Minimal handling, no chest physiotherapy, no mobilisation

No new urinary catheterization, rectal temperatures, nasogastric tube placement.

Blood samples should be obtained from a superficial vein or indwelling catheter (CVL, arterial line)

Avoid concurrent NSAIDs or anti-platelet therapy or Warfarin

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Observations continuous: HR & sats**; Hourly:** BP, neuro-obs, all puncture sites during infusion and up to 4 h post infusion

If treating peripheral artery occlusion observe hourly: pulse, colour, temperature and CRT

Check Fibrinogen at 3h, at 6h into infusion; continue 6 - 12 hourly and at completion (fibrinogen, FBC, PT, aPTT); antiXa if required

D dimers at the beginning & at the end of treatment

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MONITOR response to treatment:

- Imaging, e.g.ECHO, Doppler daily/pre-post dose
- Watch Fibrinogen – expected to fall by 20-50%;
- Watch DDimers - should rise (if not, consider plasminogen replacement = FFP ; d/c with Haematology)
- Clot lysis failed. Need for further doses?

→

If **Fibrinogen level < 1g/L - STOP Alteplase**, consider cryoprecipitate

If Fibrinogen > 1.2g/L – the dose of Alteplase can be increased if required

The platelet count should be maintained >100.000/µL during thrombolysis

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STOP ALTEPLASE when: Clot resolved

Severe systemic bleeding or suspicion (e.g. deterioration in neurological status)

Fibrinogen level <1g/L

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After thrombolytic therapy increase Unfractionated heparin to 20 units/kg/h - aim aPTT 60-85 or antiXa 0.5 - 1 (no bolus; for further adjustments follow Heparin protocol (see..)

Long term anticoagulant treatment (art catheter associated 3-7 days, vascular device associated venous thrombosis 3-6 months) Bilateral Renal Vein Thrombosis with renal impairment: 6-12 weeks of LMWH

STRONG INDICATIONS for Thrombolysis:

Acute or subacute occlusive venous or arterial thrombosis that is limb - or life-threatening is the primary indication for thrombolysis. Thrombolysis can improve limb or organ perfusion by improving vessel patency and may quickly improve symptoms. Consensus guidelines offer indications for thrombolysis (5), but its use must be carefully considered due to the potential higher risk of major bleeding compared with anticoagulation alone, especially in infants < 6 months of age.

In general, **thrombolysis is used in acute thrombosis of less than 14 days duration** of vessel occlusion:

A. Arterial thrombosis with tissue ischemia/evidence of organ dysfunction

B. Phlegmasia alba/cerulea dolens: extensive venous thrombosis with total occlusion of venous flow, increased compartment pressures and compromise of arterial blood flow.

C. Pulmonary embolism (PE) with hypotension or shock, or PE resulting in right heart strain or myocardial necrosis.

D. Superior vena cava syndrome.

E. Bilateral renal vein thrombosis.

F. Congenital heart disease with shunt thrombosis.

G. Large (>2 cm in infants), mobile right atrial thrombus/right ventricular thrombus; or IVC thrombus with evidence of significant flow obstruction.

H. Kawasaki disease with coronary artery thrombosis (see AHA recommendation)

I. Cerebral sinovenous thrombosis with neurologic impairment and no improvement with anticoagulation or progressive thrombosis

J. Progressive/persistent thrombosis despite adequate anticoagulation therapy for 3 days

POSSIBLE INDICATION: (beyond acute limb- or life-threatening situations)

The goal of therapy in these cases is to improve long-term outcomes or to maintain venous patency in children dependent on central venous access, decrease pain, and potentially decrease the risk of postthrombotic syndrome (occlusive, symptomatic iliofemoral or inferior vena cava DVT). (10,11)

Blocked lines - see CVL guideline

CONTRAINDICATIONS: The decision to use thrombolysis should be made on a case-by-case basis, weighing risks and benefits. There are general contraindications to be considered [12,13]:

- Active bleeding or significant potential serious local bleeding; GI or urinary bleeding in last 3 months
- Major surgery or trauma, organ biopsy, non-compressive vessel puncture within the previous 10 days;
- Neurosurgery or intracranial haemorrhage, infarction or intracranial or spinal surgery within the previous 2 months; active intracranial neoplasm
- Seizures within 48 hours of therapy;
- Prematurity < 32 weeks gestation;
- AV malformations;
- Inability to maintain Platelets > 100.000/ul and Fibrinogen >1g/L using blood products;

- Cardiopulmonary resuscitation or asphyxia within 7 days of therapy (including complicated birth)
- Known right to left intracardiac shunt;
- Uncontrolled hypertension (> 95centile for age and height despite treatment)
- Infective endocarditis
- Any contraindication to the use of unfractionated heparin or radiographic contrast media (if needed for assessment of thrombosis)

DOSING for SYSTEMIC THROMBOLYSIS:

A low-dose Alteplase infusion and a high-dose (previously "standard dose") Alteplase regimen have been described, with low-dose therapy showing equivalent efficacy to a high-dose regimens (10, 14, 15).

1) High-dose Alteplase 100 - 500 micrograms/kg/h can be used for 6 h at a time and may be repeated over a 72-h period if imaging suggests no response.

2) Low-dose Alteplase 10 - 60 micrograms/kg/h can be a continuous infusion over 6–72 h, preferably administered directly into the clot via suitable line; with close laboratory monitoring and imaging at a minimum of daily.

3) Prophylactic Heparin with anti-Xa level of 0.1– 0.3 or Heparin at 10 U/kg/h

4) Labs: Every 6–12 h: fibrinogen, FBC, PT, aPTT; D dimers at the beginning and at the end of treatment; antiXa level (if required for heparin anticoagulation monitoring)

5) Adult recommendation *(see adult protocol (might be useful for 16- 18 years old)* for Acute massive pulmonary embolism where thrombolysis is indicated:

- Acute pulmonary emboli obstructing blood flow to a lobe or multiple lung segments.
- Acute pulmonary emboli accompanied by unstable haemodynamics, e.g., failure to maintain blood pressure without supportive measures.

o Over 65Kg – Alteplase 10mg iv bolus followed by 90mg iv infusion over 2 hours

o Under 65kg – Alteplase 10mg iv bolus then max infusion dose should not exceed 1.5mg/kg

o If cardiac arrest imminent - 50mg bolus

(BNFC recommends max 100mg/day; B24/2016 UHL guideline)

DOSING FOR SITE-DIRECTED THROMBOLYSIS:

6) Alteplase bolus 100 – 300 micrograms/kg (max 10mg), continue 10 – 30 micrograms/kg/h (max 2mg/h) duration up to 72-96h

7) Therapeutic Heparin with anti-Xa level of 0.3 – 0.7 or Heparin at 10 U/kg/h

8) Every 6–12 h: fibrinogen, FBC, PT, aPTT, renal profile, urinalysis, D dimers at the beginning and at the end of treatment, antiXa level (if required for heparin anticoagulation monitoring)

PREPARATION FOR THROMBOLYSIS:

- FBC, INR/PT, aPTT, Fibrinogen, Platelets must be > 100 000/ul & Fibrinogen > 2g/L, valid Xmatch (one adult unit of cross matched packed red cells available); D dimers at the beginning and at the end of treatment
- Consider administration of FFP 10 - 20ml/kg (+ Furosemide, if needed), especially in neonates to supplement plasminogen
- Adequate and reliable iv access to infuse and obtain blood specimen during infusion (ideally arterial line)
- Unfractionated heparin infusion 10U/kg/h to be continued throughout the Alteplase therapy, if possible ideally commenced 6 hours prior to fibrinolysis as this may be advantageous for thrombolytic action
- Alteplase (high or low dose regimen decision based on MDT)
- In catheter - related thrombus, the timing of removal is important:
  - ✓ Peripheral arterial line: remove the catheter at the earliest opportunity
  - ✓ UAC: review ultrasound imaging and, if limb or organ are at high risk, consider thrombolysis via UAC
  - ✓ Central venous line: commence anticoagulation with catheter in situ and continue the treatment for 3-5 days before removal (unless limb perfusion or organ function deteriorating). Long term anticoagulant treatment (arterial catheter associated 3-7 days, vascular device associated venous thrombosis 3-6 months) Bilateral Renal Vein Thrombosis with renal impairment: 6-12 weeks of LMWH.

MONITORING

- Continuous HR& sats; hourly: BP & neuro obs
- All puncture sites hourly during infusion and up to 4 h post infusion
- If treating peripheral artery occlusion observe hourly: pulse, colour, temperature and CRT
- Check Fibrinogen at 3h into infusion, at 6h into infusion, and continue sampling 6 - 12 hourly and at completion (fibrinogen, FBC, PT, aPTT). Fibrinogen is an important marker for systemic fibrinolysis. D dimers at the beginning and at the end of treatment.
  - If Fibrinogen level < 1g/L - STOP Alteplase
  - If Fibrinogen > 1.2g/L - increase the dosage of alteplase (can be doubled to maximum of 500 micrograms/kg/h and total not to exceed 100mg per day
  - If the clot lysis fails, measure D dimers. If level not raised, consider plasminogen replacement (fresh frozen plasma) - discuss with Haematology
- **Cryoprecipitate should be given for hypofibrinogenemia (<1g/L) and the platelet count should be maintained above 100.000/µL during thrombolysis.**
- Daily imaging to monitor clot – e.g. ECHO/ultrasound Doppler

After r-Alteplase cease lytic therapy and increase Unfractionated eparin to 20 units/kg/h aiming for aPTT 60-85 (no bolus; for further adjustments follow Heparin protocol) or antiXa 0.5 - 1. There is lack of data regarding type and duration of anticoagulation treatment required after successful thrombolysis. There is currently insufficient evidence to recommend the use of long term anticoagulant treatment (in general used: art catheter associated 3-7 days, vascular device

associated venous thrombosis 3-6 months) after thrombolysis except in the management of bilateral Renal Vein Thrombosis with renal impairment for which 6-12 weeks treatment with LMWH should be used.

- Arrange for Doppler to determine response or need for further thrombolysis
- If any signs of bleeding/bruising occur - see COMPLICATIONS

DISCONTINUATION:

- Clot resolved
- Severe systemic bleeding or suspicion (e.g. deterioration in neurological status)
- Fibrinogen level <1g/L (consider cryoprecipitate, contact Haematology on call)

COMPLICATIONS:

- 30 - 50% bleeding complications (usually oozing from a wound site)
- 10-15% major bleeding (drop in Hb >20g/L or more within 24h) - cease infusion and contact Haematology; **associated with longer infusions and drop in Fibrinogen levels** immediately after thrombolysis (16).

For major bleeding, such as intracranial or intra-abdominal bleeding:

- stop rAlteplase - it has very short half-life, but there is no reversal agent; and stop heparin
- check FBC, clotting and TEG and seek urgent Haematology consult
- administer cryoprecipitate (each pack contains 0.15 - 0.3g of Fibrinogen; approximately 5 packs provide 1g of Fibrinogen; 50ml/kg of cryoprecipitate ~ 50mg/kg of Fibrinogen concentrate);
- optimise platelets (maintain > 100x10/9/L);
- heparin can be reversed with protamine (1 mg of protamine for 100 U of heparin, maximum protamine dose is 50 mg/dose);
- consider commencing tranexamic acid iv (30mg/kg load over 10 min and 5mg/kg for 10 hours – cumulative doses exceeding this 80mg/kg regimen aare correlated with increased risk of seizures without evidence of better haemostasis);

Minor bleeding, such as bleeding from intravenous lines or catheterization site, can be managed with local control - pressure bandages or topical haemostatic agents, e.g., topical thrombin.

If more extensive bleeding occurs, decrease the rAlteplase infusion or consider stopping the rAlteplase infusion transitorily for at least 1 h. Consider decreasing or holding Heparin if bleeding persists. When bleeding is controlled, the anticoagulation can then be started at lower dose if previously stopped, and the rAlteplase infusion can be restarted at a lower dose.

Menstruating females may receive non-estrogen-containing hormonal suppression with norethisterone before or during thrombolysis. (15)

PRECAUTIONS during THROMBOLYSIS:

- No new arterial punctures or line placements during the treatment
- No intramuscular injections
- Minimal manipulation of the patient (e.g., no chest physiotherapy), no mobilisation
- No new urinary catheterization, rectal temperatures, nasogastric tube placement.
- Blood samples should be obtained from a superficial vein or indwelling catheter (CVL, arterial line)
- Avoid concurrent NSAIDs or anti-platelet therapy or Warfarin
- Intracranial imaging should be considered prior to and after thrombolytic therapy in children less than 3 months of age or any child at high risk for ischemic or haemorrhagic stroke

STANDARD REQUIREMENTS

- All children receiving alteplase should have a clearly documented indication, and discussion with parents including risks of the therapy.
- Appropriate investigations should have been completed to exclude all contraindications prior to starting therapy.
- All infants receiving alteplase should have fibrinogen levels monitored during treatment.
- No infant should continue to receive therapy with alteplase if fulfilling one of the criteria for cessation of therapy.

3. Education and Training

Training and raising awareness are on-going processes. On-going awareness is promoted through the induction and continuous bedside teaching. Training is provided for medical staff during lunchtime teaching (Wednesdays) and other sessions, and at junior doctors' induction training. Nursing education is supported by the Practice Development teams, and nursing educators.

4. Monitoring Compliance

Nil identified at present but will be reviewed once guideline has been put in place and active.

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements

5. Supporting References

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18. **Altepase – detailed guidance (pdf)**

https://www.gene.com/download/pdf/activase_prescribing.pdf

Altepase – Dose & administering guidance:

https://www.activase.com/ais/dosing-and-administration/dosing.html

Refer to Childrens Medusa Monograph and BNFC for detailed information on prescribing, administration and side effects

6. Key Words

Alteplase, thrombolysis, limb ischaemia, thrombembolism

The Trust recognises the diversity of the local community it serves. Our aim therefore is to provide a safe environment free from discrimination and treat all individuals fairly with dignity and appropriately according to their needs.
As part of its development, this policy and its impact on equality have been reviewed and no detriment was identified.

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Julia Vujcikova - Consultant James Whitelaw - Consultant	**Executive Lead** **Chief Medical Officer**
Details of Changes made during review: New document that has incorporated the arterial line associated reduced limb perfusion g/l C115/2016 – now archived	