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Trust Guideline for the Management of: Trust Guideline for the use of Thromboprophylaxis and Thrombolytic therapy in Neonatal Intensive Care Unit (NICU)

A Clinical Guideline

For Use in:	Neonatal Intensive Care Unit
By:	Neonatal Medical and Nursing staff
For:	Infants in NICU
Division responsible for document:	Women / Children
Key words:	Thrombosis, Thromboprophylaxis, Thrombolysis, Alteplase
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Assessed and approved by the:	Thromboprophylaxis and Thrombolytic Committee 19/05/2022 Clinical Guidelines Assessment Panel (CGAP) If approved by committee or Governance Lead Chair's Action; tick here √
Date of approval:	09/06/2022
Ratified by or reported as approved to (if applicable)**:**	Clinical Safety Effectiveness Sub-Board
To be reviewed before: This document remains current after this date but will be under review	09/06/2025
To be reviewed by:	Dr Dyke, Consultant Neonatologist
Reference and / or Trust Docs ID No:	1274
Version No:	5
Compliance links: *(is there any NICE related to guidance)*	No
If Yes - does the strategy/policy deviate from the recommendations of NICE? If so, why?	N/A

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

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Version and Document Control:

Version Number	Date of Update	Change Description	Author
5	09/06/2022	Reviewed no significant changes	Dr Mark Dyke

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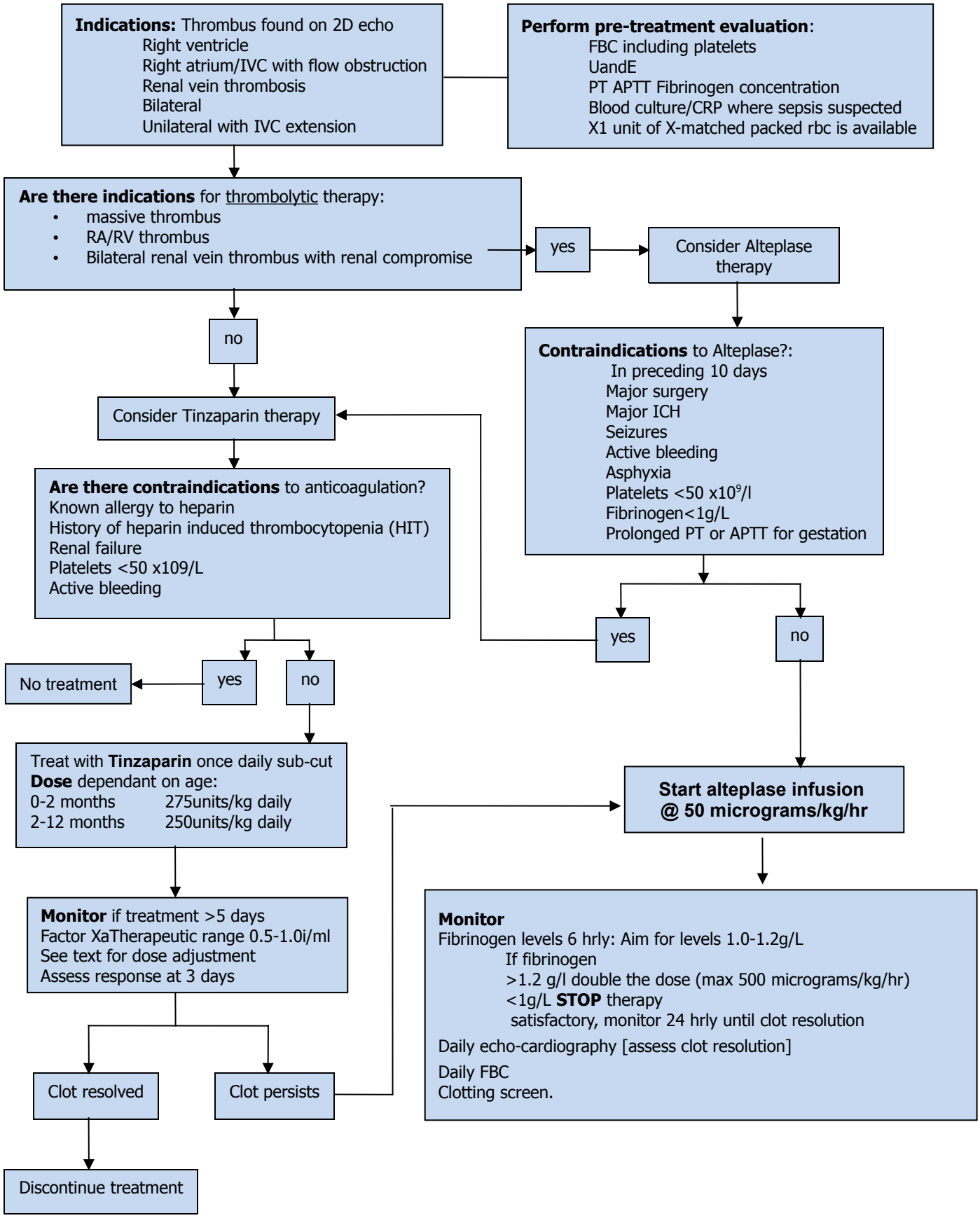
Key

EoE	East of England
ODN	Neonatal Operational Delivery Network
PT	Prothrombin time
aPTT	Activated partial thromboplastin time
LMW	Low molecular weight
tPA	Thrombolytic therapy with Tissue Plasminogen Activator
UAC	Umbilical artery catheter
UVC	Umbilical venous catheter

1. Quick reference guideline/s for treatment of established thrombosis



2. Objective of Guideline

To aid decision-making in the use of thromboprophylaxis, anti-coagulation and thrombolytic therapy in the prevention and management of neonatal thrombosis.

3. Rationale for the recommendations

The incidence of thrombosis is around 2.4-6.8/1000 in new-borns admitted to NICU. There are many factors which may increase the risk of thrombosis, but most thromboses are related to the presence of an intravascular catheter. Complications of thrombosis may occasionally be severe or even life-threatening e.g., intracardiac thrombosis but there is little published data on the frequency of such complications in treated or untreated infants. Nevertheless, it is reasonable to offer strategies to reduce the risk of thrombosis and to consider treatment of established thrombosis with anti-coagulation or thrombolysis when the risk of complications from vascular obstruction or the potential for important propagation or embolization of clot are considered to outweigh the risk associated with systemic treatment.

4. Broad recommendations

4.1 Prevention

In relation to arterial and central venous catheters, the key issues to consider are:

- Catheter placement
- Prophylaxis with unfractionated heparin
- Duration of catheter placement

4.1.1 Catheter placement

- Umbilical Venous Catheter: BAPM guidance [Jan 2016] states that *"a UVC tip should ideally be sited at T8-T9 (assuming this lies outside the cardiac silhouette). A UVC tip sited at T10 or below carries a significantly higher risk of extravasation. It may be necessary to use these catheters in the short term, but they should be replaced at the earliest opportunity"* [for full details, refer to Trust Guideline for the Management of: Insertion of an Umbilical Venous Catheter Trustdocs Id: 1241
- Peripherally inserted central venous catheters: the ideal position is just proximal to the junction of the superior vena cava and right atrium or in the inferior vena cava above L4-5 ie towards the level of the diaphragm but outside the right atrium [for full details, refer to the East of England Neonatal (EoE) Network Guideline on Insertion of a Percutaneous Venous Long Line]
- Umbilical Arterial Catheter [UAC]: the catheter tip should be in the aorta. High placement is regarded as between T6 – T10; Low placement below L3 (ideally between L4 and L5). High placement is associated with a lower risk of thrombosis and is therefore preferred. For full details, refer to EoE Neonatal Operational Delivery Network (ODN) Guideline for the Management of: Insertion of Umbilical Artery Catheter [UAC] see Intranet]

4.1.2 Use of unfractionated heparin prophylaxis in infusion

The routine use of heparin in infusions through arterial catheters is associated with prolonged catheter patency. Recommendations are:

- Peripheral arterial catheters: unfractionated heparin 1unit/ml solution at 0.5 mL/hr
- Umbilical arterial catheter: unfractionated heparin at 1unit/ml solution at 0.5-1.0 mL/hr

Data in support of the use of heparin for venous catheters is mixed and at present is not considered sufficient to justify its routine use.

4.1.3 Duration of catheter placement

The risk of thrombosis increases with duration of catheter placement [eg aortic thrombosis rates reach around 80% with UACs in situ for 21 days] but the absolute risk for an individual infant/catheter cannot be quantified. The American Centre for Disease Control and Prevention has recommended that UVCs should not be left in situ more than 14 days.

In general, both UACs and UVCs should be removed at the earliest safe opportunity and almost always by 10 days of age unless there are over-riding clinical reasons for keeping them. Peripherally placed central venous catheters can usually be used for several weeks providing that there are no signs of catheter-related sepsis or obstruction.

4.2 Indications for treatment of established thrombus [anti-coagulation and/or thrombolysis]: see quick reference algorithm above

Not all thromboembolic events require treatment. Treatment is usually indicated where the thrombus is in a high-risk area [see list below] or is causing clinical and/or ultrasonographic evidence of obstruction of flow with actual or potential clinical compromise, such as:

- Right ventricle
- Right atrium [or inferior vena cava with evidence of significant flow obstruction]
- Renal vein thrombosis
    - Unilateral – consider anticoagulation with low molecular weight [LMW] heparin if there is extension into the IVC
    - Bilateral – start treatment:
        - No renal impairment: use anti-coagulation with LMW heparin
        - With renal impairment: use thrombolysis with tPA followed by anti-coagulation with LMW heparin
- Arterial thrombosis with evidence of organ dysfunction: use anti-coagulation

The earlier the treatment is commenced; the greater is the chance of achieving clot lysis

4.3 Pre-treatment evaluation before starting treatment, check:

- FBC including platelets

- UandE
- PT
- APTT
- Fibrinogen concentration
- Blood culture and CRP [where sepsis is suspected]
- One unit of cross matched packed red cells is available

4.4 Removal of catheters

In catheter-related thrombus, removal of the line is an important part of management, but timing of removal may differ:

- Peripheral arterial line: remove the catheter at the earliest opportunity
- UAC: first, review the ultrasound imaging and, if limb or organ is thought to be at high risk, then consider thrombolysis via UAC
- Central venous line: commence anti-coagulation with catheter in situ and continue treatment for 3-5 days before removal

4.5 Choice of treatment

4.5.1 <u>Anticoagulation with LMW heparin</u>:

Anticoagulation with low-molecular weight heparin [usually tinzaparin or, alternatively dalteparin] is the usual first-line treatment [see also section 4.2] for:

- Catheter-related venous thrombosis [unless indications for Thrombolysis are met: see section 4.5.2]
- Renal Vein thrombosis
- Arterial thrombosis with organ/limb compromise

4.5.1.1 Contraindications to LMW heparin:

- Known allergy to heparin or history of heparin induced thrombocytopenia (HIT)
- Renal failure (glomerular filtration rate <20ml/min)
- Known bleeding disorder or severe thrombocytopenia [Platelets <50 $x10^9$/L]

4.5.1.2 LMW [Tinzaparin] Regimen

Tinzaparin is given by once daily subcutaneous injection

Dose is dependant on age:

- 0-2 months 275units/kg every 24hours
- 2-12 months 250units/kg every 24hours

Dalteparin is given by twice daily subcutaneous injection

Dose is dependant on age:

- 0-2 months 150units/kg every 12hours
- ≥2 months 100units/kg every 12hours

4.5.1.3 Monitoring

- Assessment for bleeding should be performed daily using the Bleeding Assessment Tool
- If treatment is to continue for >5 days an anti-Xa level should be measured 5 days after commencement of treatment.
- The haematology laboratory should be contacted prior to sample collection. Please state whether the result is required that day. Anti Xa levels can be requested using web ICE
- Samples should be taken 4-6 hours post injection of tinzaparin and handed to a member of staff in pathology specimen reception

Anti XaTherapeutic range 0.5-1.0 Units/ml

Dose adjustment:

Anti Xa level	Action
<0.35	Increase dose by 25%
0.35-0.49	Increase dose by 10%
0.5-1.0	No change in dose required
1.1-1.5	reduce dose by 20%
1.6-2.0	delay next dose by 3hours and reduce dose by 30%
>2.0	Omit

If dose adjustment is made, repeat levels should be checked after next 1-2 doses. If no change required and patient clinically stable further levels can be checked after 1 week

4.5.1.4 Possible side effects and suggested management

If bleeding occurs omit next dose. If bleeding is severe and Tinzaparin was administered <12hours previously, Protamine Sulphate may be given. 1mg of protamine will correct 100 units of tinzaparin (maximum dose 50 mg)

4.5.1.5 Duration of therapy

If anti-coagulation is required, the recommendation is for 6-12 weeks of therapy

4.5.2 <u>Thrombolytic therapy with Tissue Plasminogen Activator [tPA]</u> should be reserved for infants with:

- thrombosis causing major threat to life, limb or organ such as:
  - massive thrombosis
  - right atrial/ventricular thrombus
  - bilateral renal vein thrombosis with compromised renal function
- progressive/persistent thrombosis despite adequate anti-coagulation therapy for 3 days

4.5.2.1 Contraindications to thrombolytic therapy.

- Major surgery in previous 10 days.
- Major intracranial haemorrhage in previous 10 days.
- Major surgical procedure in previous 3 days.
- Active bleeding.
- A history of seizures in previous 10 days.
- A history of asphyxia.
- Inability to maintain haemostatic levels of coagulation factors [using transfusion support if necessary]
- Platelets <50 $x10^9$/L
- Fibrinogen<1g/L.
- Prolonged PT or aPTT for gestational age (see Appendix 1).

4.5.2.2 Choice of agent

In recent years, recombinant tissue plasminogen activator (tPA = alteplase) has been increasingly favoured over streptokinase and urokinase in the management of thromboembolic disease. Alteplase has a clot selective mechanism owing to increased fibrin specificity and converts plasminogen-fibrin to plasmin. Furthermore, alteplase shows a low affinity for circulating plasminogen and has a short half-life.

4.5.2.3 Dose regimen Two dosage regimen for alteplase are described:

Low-dose: alteplase should **usually be started at low doses**, preferably administered directly into the clot via a suitably placed percutaneous long-line

Dosage range 50-100 microgrammes/kg/hour

High dose: alteplase can be used at higher dose, but this may cause a systemic proteolytic state, as indicated by a decrease in fibrinogen concentration (less than 1g/L).

Dosage range 100-500 microgrammes/kg/hour

Evidence on clinical risk using high doses is mixed:

- in a review of alteplase use in neonates by Hartmann, neither severe bleeding complications such as IVH nor side effects such as allergic reaction were observed.[5]
- in a study by Nowak–Gottl[6] of 182 neonates and infants treated with streptokinase, urokinase or alteplase:
  - 2 deaths (1.1%) were directly related to a major bleeding complication
  - other major complications [such as pulmonary bleeding (0.6%), gastro-intestinal bleeding (0.6%), intraventricular haemorrhage (2.7%) and pulmonary embolism (1.1%)] were relatively rare.
  - local bleeding complications occurred relatively frequently eg at recent puncture and catheterisation sites (10.4%).

4.5.2.4 Indications for discontinuation of alteplase

- Resolution of clot.
- Severe systemic bleeding.
- Fibrinogen level<1g/L (where ongoing therapy is imperative discuss with consultant haematologist regarding cryoprecipitate to support continued treatment)

4.5.2.5 Management of bleeding while receiving alteplase

Symptomatic intracranial bleeding

- Discuss with consultant on call.
- Stop alteplase it has a very short half-life but there is **NO** reversal agent for alteplase.
- Check Fbc and clotting screen: prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen level.
- Ensure transfusion lab have sample for group and save.
- If fibrinogen level is <1g/L, discuss with haematologist regarding cryoprecipitate.
- Consider giving 15-20 mls/kg of platelet transfusion if platelet count <$50x10^9$/L

4.5.2.6 Monitoring

Fibrinogen: is an important haemostatic protein and a marker for systemic fibrinolysis. Fibrinogen levels should be measured regularly, initially every 6 hrs:

- If fibrinogen levels < 1g/L - STOP alteplase.
- If fibrinogen levels > 1.2g/L - dosage of alteplase can be doubled (to maximum of 500 microgrammes/kg/hour).

D dimers: In the infant who fails to demonstrate clot lysis with thrombolytic therapy within 4 days, measure D dimers. If levels are not raised, discuss with a Consultant Haematologist the role of replacement of plasminogen in the form of fresh frozen plasma.

Echocardiography: Regular assessment (preferably daily) by echocardiography is mandatory for intracardiac and IVC thrombi, allowing minimisation of duration of fibrinolytic therapy and monitoring cardiac function, especially when partial obstruction of the inflow or outflow tract may lead to major haemodynamic complications.

Fbc and clotting studies: daily

4.5.2.7 Anticoagulation following thrombolysis.

The literature lacks 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 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.

4.6 Long term follow up

Thrombophilia screen is not routinely required but should be reserved for:

- Unprovoked extensive thrombosis [Protein S or C deficiency]
- Arterial ischaemic stroke [factor V Leiden mutation]
- Renal vein thrombosis [variable]

Out-patient follow-up should be arranged for all infants receiving anti-coagulation or thrombolytic therapy.

5. Clinical Audit Standards derived from guideline

- All infants with indwelling central lines should have heparin thromboprophylaxis as per this guideline
- All infants receiving heparin anti-coagulation should meet one of the described indication criteria
- All infants receiving alteplase should have a clearly documented indication.
- 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.

6. Summary of development and consultation process undertaken before registration and dissemination

The original guideline on the Management of Thrombolytic Therapy was drafted on behalf of NICU and discussed in a guideline meeting on 18/07/2007, attended by consultant haematologists and neonatologists and other medical and nursing staff on NICU. Further modifications were made based on suggestions received both at the meeting and from the unit pharmacist before submission to the guideline assessment panel**.** The 2012 update including new guidance on the use of anti-coagulation was written after a further literature review and submitted to Consultants in Neonatology and Haematology for feedback.

Further amendments were made, presented at a guideline meeting May 2012 and, with minor modifications, the guideline was approved. The 2016 version has been modified to include guidance on thrombo-prophylaxis as well as thrombolytic and anti-coagulation therapy for established thrombosis. It was based predominantly on a major review of published evidence and a set of published national guidelines from the USA. It was circulated for comment, presented at a guideline meeting 03/02/16 and further minor modifications made based on comments received.

Further review in 2019 yielded no new evidence requiring any changes. In 2022 it was reviewed and again no significant changes

7. Distribution list/ dissemination method

a. Hospital intranet
b. Neonatal Unit.

8. References/ source documents

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Source documents

Insertion of an Umbilical Venous Catheter Trustdocs Id: 1241

Appendix: 1

Table 1 Coagulation status in each gestational age group

	Term		**Preterm**	
	Day 1	**Day 5**	**Day 1**	**Day 5**
Platelets	150-450 x10^9/L			
PT	13 (11.6-14.4)	12. 4 (11.9-13.9)	13 (10.6-16.2)	12.5 (10-15.3)
aPTT	43 (37-49)	43 (35-51)	53.6 (27.5-79.4)	50.5 (27-74)
Fibrinogen	2.8 (2.2-3.4)	3.12 (2.37-3.87)	2.43 (1.5-3.7)	2.8 (1.6-4.2)