Yorkshire and Humber Neonatal ODN (South) Clinical Guideline

Title: Thrombosis-management of line associated
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This clinical guideline has been developed to ensure appropriate evidence based standards of care throughout the Yorkshire and Humber Neonatal ODN (South). The appropriate use and interpretation of this guideline in providing clinical care remains the responsibility of the individual clinician. If there is any doubt discuss with a senior colleague.

Best practice recommendations represent widely used evidence-based practice and high quality standards that all Neonatal Units across the Network should implement. Subsequent suggested recommendations may be put into practice in local units. However, alternative appropriate local guidelines may also exist.

A. Summary page and best practice points

For all line associated thrombosis, line removal is recommended.

For arterial thrombosis;

Asymptomatic	Radiographic monitoring. Consider anticoagulation if extension occurs
Symptomatic	Anticoagulation is recommended for at least 5-7 days
Limb or organ threatening	Consider thrombolysis (i.e. including renal failure secondary to obstructed renal artery flow)

For venous thrombosis;
Anticoagulation for 3-5 days prior to line removal

Asymptomatic	Radiographic monitoring Consider anticoagulation if extension occurs 6-12 weeks
Symptomatic	Anticoagulation for 2-12 weeks, guided by radiographic monitoring
Life/limb/organ threatening	Consider thrombolysis

B. Full guideline

1) Background
Insertion of any venous or arterial line may result in a line associated arterial or venous thrombosis

2) Aim
The aim of this guideline is to provide an evidence based approach to management of these situations.

3) Areas outside remit
Management of other causes of thrombosis.

4) Evidence
Where there is minimal evidence, best practice guidance has been sought from national and local sources.

5) Core guideline

5.1 Umbilical arterial lines

5.2 Management of central line associated thrombosis
There is limited evidence to support any recommendations and much of the advice is based on extrapolation of adult studies, however the following is based on the American College of Chest Physicians, Evidence-based clinical practice guidelines[1]. Discussion with a paediatric haematologist is recommended prior to therapy.

5.3.1 Arterial thrombosis
For all infants, line removal is recommended. If the line is felt to be essential, consider anticoagulation.
Mortality associated with arterial thrombosis is said to be up to 20% with significant morbidity also occurring.

Asymptomatic	Radiographic monitoring. Consider anticoagulation if extension occurs
Symptomatic	Anticoagulation is recommended for at least 5-7 days
Limb or organ threatening	Consider thrombolysis (i.e. including renal failure secondary to obstructed renal artery flow) (see below)

5.3.2 Venous thrombosis
Line removal is recommended. However, 3-5 days of anticoagulation is often recommended prior to line removal to reduce the risk of paradoxical emboli.

Asymptomatic
Following line removal, radiological monitoring is recommended with use of anticoagulation for 6-12 weeks if extension of thrombosis occurs. If line removal is not possible, anticoagulation is recommended for up to 3 months or until the line is removed. Radiological monitoring may be a suitable alternative with treatment only if clot extension occurs or the neonate becomes symptomatic

Symptomatic
Following line removal, anticoagulation for 2-12 weeks with the treatment period guided by radiological monitoring. If line removal is not possible, anticoagulation is recommended at least until the line is removed.

Life/organ/limb threatening
Consider thrombolysis (see below)

5.3.3 Anticoagulation/Thrombolysis

Risk factors for bleeding must be carefully considered before starting anticoagulation or thrombolysis.

Platelets must be >50 for heparin to be used. If there is a clear indication for anticoagulation platelet support may be used to maintain platelets >50 to allow anticoagulation to be given
There is minimal evidence to support dosage regimes. Neonates, especially preterm infants have different levels of all elements of the haemostatic pathway leading to challenges in monitoring and dosages.

Low molecular weight heparin
Due to the reduced monitoring requirement and lack of interference by drugs, LMWH is often used provided it is unlikely that an urgent invasive procedure is required and bleeding risk is low since the half life of LMWH is several hours. LMWH should be avoided in renal impairment.

The usual recommended starting dose of Enoxaparin for a neonate is 1.5mg/kg/dose twice daily subcutaneously with subsequent dose adjustment based on anti-Xa levels (aim for 0.5-1.0 units/ml 4 hours post dose). Often higher doses are required to achieve this therapeutic range, especially in premature infants.
A suggested dose adjustment regime is as below[2]

Anti-factor Xa level (U/mL)	Dosage adjustment	Next anti-factor Xa level
< 0.35	Increase next dose by 25%	Following day, 4 hr following adjusted dose
0.35-0.49	Increase next dose by 10%	In 1-2days 4 hr following adjusted dose
0.50-1	No change	Weekly levels whilst an inpatient, 4 hr following a dose. If change in renal function, addition of antibiotics, signs of bleeding, check level 4 hr after next dose
1.1-1.5	Reduce next dose by 20%	4 hr following next adjusted dose
1.6-2	Delay next dose by 3hrs and reduce dose by 30%	Consider trough level before next dose (see below). Check level 4 hr following dosage adjustment
>2	Withhold dose until anti-factor Xa level <0.5, then reduce next dose by 40%	Every 12 hr until anti-factor Xa level <0.5, then 4 hr following reinstitution of therapy

In the event of overdose or need for reversal, discuss with a haematologist. Protamine can be used but does not achieve complete reversal of LMWH.

Unfractionated heparin (UFH)
This may be considered if invasive procedures are felt to be likely or there is a significant concern regarding haemorrhage, as it has a short half life and can be more easily reversed. UFH is also recommended over LMWH if there is renal impairment. Otherwise LMW heparin is the drug of choice for anticoagulation.

Again, there is limited evidence of dosages but BNFc suggests[3]:

- **Loading dose of 75units/kg with a lower dose of 50units/kg for infants <35 weeks** corrected gestational age. The loading dose should be omitted if there are significant haemorrhagic concerns
- Maintenance infusion of 25units/kg/hour, adjusted to anti-Xa levels

Due to limitations in APTT monitoring and confusion regarding "normal ranges" in neonates, heparin therapy should also be monitored by anti-Xa levels with a target of **0.35-0.7U/ml** (note different to LMW range). See table below for suggested adjustments[4]

aPTT ratio	*Anti-Xa*	Bolus (units/kg)	*Hold (mins)*	*Rate change*	*Repeat aPTT*
≤1.2	*≤0.1*	*50*	*0*	*Increase 10-20%*	*4 hours*
1.2-1.4	*0.2*	*0*	*0*	*Increase 10%*	*4 hours*
1.5-2.5	*0.3-0.7*	*0*	*0*	*0*	*4 hours until 2 in range, then daily*
2.6-3.2	*0.8-0.9*	*0*	*0*	*Decrease 10%*	*6 hours*
3.3-4.0	*1.0-1.1*	*0*	*30-60mins*	*Decrease 10-20%*	*6 hours*
≥4.1	*≥1.2*	*0*	*60-120 mins until aPTT ratio <3.5*	*Decrease 15-30%*	*6 hours after restart of infusion*

In the event of overdose or need for reversal stop the heparin infusion and discuss with a haematologist,

Thrombolysis
The primary use of systemic thrombolytic agents for neonates with venous or arterial thromboses is not recommended outside of clinical trials. If considered, the risk of major bleeding MUST be taken into account.

Thrombolysis is not recommended as an option for treatment of thromboses in neonates unless major vessel occlusion is causing critical compromise of organs or limbs. In these, surgical intervention should also be considered as an alternative to thrombolysis however this option may be limited by site of thrombosis, infant size and associated comorbidities. Consultation between the neonatal consultant and paediatric general or plastic surgical consultant and/or cardiologist is recommended to decide between surgical intervention and thrombolysis. A paediatric haematologist should be consulted for advice on the practicalities of thrombolysis.

If thrombolysis is undertaken tPA (alteplase) is the thrombolytic agent of choice due to in-vitro evidence of improved clot lysis and reduced antigenicity. Due to the low levels of plasminogen which is required for the formation of plasmin and therefore the function of tPA, FFP can be given prior to tPA to increase its efficacy.

There are a number of case series' now reporting use of tPA in neonates with life/limb threatening thrombosis and also a number of reviews of the literature. [5-11]

The case series' report of 14 infants demonstrated clot resolution in 11 infants and partial resolution in 3 after an average of 3 days of treatment. 2 infants suffered minor bleeding requiring interruption of therapy. In this series bolus doses of 700micrograms/kg followed by infusions of 200micrograms/kg/hour until clot resolution were used. Many of these infants also had heparin infusions (to prevent clot propagation) and the majority were >30 weeks corrected gestational age.

The major concern for thrombolysis is intracranial haemorrhage. Zenz reported ICH in 1.2% of term infants and 13.8% of preterm infants, however another controlled trial demonstrated no difference in haemorrhage rates between the treatment and control

arms, demonstrating the increased rates of ICH in all preterm infants with or without thrombolytic therapy.

Suggested **contraindications** are as follows[12] however there is increasing usage in preterm infants such that these are no longer absolute.

- Major surgery or significant bleeding within 10 days
- Severe asphyxia within 7 days
- Invasive procedures within 3 days
- Seizure within 2 days
- Gestational age of <32 weeks
- Severe septicaemia
- Active bleeding at the time of therapy
- Inability to maintain a platelet count above 100-10^9/l or fibrinogen >1.0g/l

If it has been decided to use thrombolysis, the following methodology has been used successfully at the Jessop wing based on all the available literature.[5-13]

Preparation before therapy:

- Request packed red cells to be made available in blood bank in case transfusion is urgently needed
- Check clotting (including d-dimers) and ensure fibrinogen >1.0 g/l
- Check platelets >100. Give platelets if necessary
- Pre-treat with FFP 20ml/kg to provide plasminogen for the tPA to act
- Simultaneously infuse heparin at 10units/kg/hour (to prevent propagation). Ideally this low dose intravenous heparin infusion should be commenced, **without** a loading bolus dose, a few hours prior to t-PA to ensure there are no bleeding complications. In severe ischaemia the low dose heparin infusion (10units/kg/hr) should be commenced thirty minutes before the alteplase infusion is started. If the patient is already receiving a therapeutic intravenous heparin infusion, reduce the infusion dose to 10 units/kg/hr for 30 mins prior to starting t-PA.

Therapy;
Dosages vary, however BNFc recommends a dose of 100 - 500 microgram/kg/hr of t-PA for 3-6hrs .
Administer this by starting a t-PA infusion at a dose of 100 microgram/kg/hr. If there is an inadequate clinical and/or radiological response increase the administered dose by 100 micrograms/kg/hr hourly up to a maximum dose of 500 microgram/kg/hr.

- Commence tPA at 100microgram/kg/hour
- Keep platelet count above 100 (check at baseline, 2 hours, 2 hours after changing dose and 6 hours)
- Keep fibrinogen above 1.0g/l (using cryoprecipitate as needed)
- Recheck clotting and d dimers at 2 hours, 2 hours after changing dose and 6 hours. If increasing this is evidence of clot breakdown and therefore stop infusion after 4 hours at that dose.
- If d dimers are not increasing, increase tPA infusion in 100microgram/kg increments to maximum of 500micrograms/kg/hour for 6 hours, rechecking platelet count, fibrinogen and d-dimers 2 hours after any dose change.
- Stop tPA if any major haemorrhage occurs and treat with FFP/other products as clinically indicated
- Minor haemorrhage (oozing from puncture sites) can be treated with local pressure

Precautions during thrombolysis

No surgical procedures, arterial punctures or central line insertions or insertions of urinary catheters during thrombolysis
No intramuscular injections during thrombolysis
Minimal manipulation of patient e.g. avoid physiotherapy
Avoid concurrent use of antiplatelet agents when possible (e.g. NSAIDs, aspirin)
Avoid venepuncture, if possible. Try to take blood samples from indwelling lines.

After therapy

- Titrate heparin infusion to therapeutic anticoagulation (aim APTT ratio 1.8-2.6 or anti Xa level 0.35-0.7). Unfractionated heparin is chosen due to ease of reversal.
- Reassess clot and repeat thrombolysis regime daily if necessary.

7) References

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3. British national formulary for Children https://www.evidence.nhs.uk/formulary/bnfc/current/2-cardiovascular-system/28-anticoagulants-and-protamine/281-parenteral-anticoagulants/heparin/heparin
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5. Diagnosis and management of central line associated thrombosis in newborns and infants. Revel-Vilk. Seminars in fetal and neonatal medicine 2001; *16;* 340-344
6. Guideline on the investigation, management and prevention of venous thrombosis in children. Chalmers. British Journal of Haematology 2011; *154;* 296-207
7. Thrombolysis in children. Williams. British Journal of Haematology 2009*; 148*;26-36
8. The preterm infant with thrombosis. Bhat. Arch Dis Child Fetal Neonatal Ed. 2012 *97*; F423-F428
9. Neonatal haemostasis and the management of neonatal thrombosis. Will. British journal of haematology. 2015 *169 324-332*
10. Guideline for the management of catheter associated arterial thrombosis. Sheffield Children's hospital 2011. Nigel Humphries, Jeanette Payne
11. Guideline for the use of anti-thrombotic treatment in children. Leeds General Infirmary. Dr Mike Richards
12. Recommendations for tPA thrombosis in children/ On behalf of the Scientific Subcommittee on Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. Manco-Johnson Thrombosis and Haemostasis 2002 *88* 157-158
13. Treatment of neonatal thrombus formation with recombinant tissue plasminogen activator: six year's experience and review of the literature. Hartman. Arch Dis Child Fetal Neonatal Ed. 2001; *85*; F16-22

C. Appendices

Appendix 1 Grades of recommendation

Grade	
A	Requires at least one meta analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, and demonstrating overall consistency of results
B	Requires a body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	Requires a body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+