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 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 (including renal failure secondary to obstructed renal artery flow).

For venous thrombosis:
Depends on site of thrombus- see guideline below

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 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 (including renal failure secondary to obstructed renal artery flow) (see below).

5.2 Venous thrombosis

There is limited evidence to support any recommendations and much of the advice is based on extrapolation of adult studies. Consideration of discussion with a paediatric haematologist is recommended prior to therapy, particularly when thrombolysis is being considered.

Following review of the American Society of Haematology 2018 guidelines[14], The American College of Chest Physicians 2012 guidelines[1], and discussions with local sources; the following is advised:

Consideration of line removal
Non-functioning or unneeded lines should be removed. Guidelines suggest giving anticoagulation for 3-5 days before removal of non-functioning or unneeded lines in patients with symptomatic central venous line-related thrombosis, to reduce the risk of emboli.

Functioning lines should not be automatically removed in patients with symptomatic line-related thrombosis who continue to require access. If symptoms worsen despite anticoagulation, and the baby still requires venous access, then removal of the line should be considered, depending on the availability of alternative venous access.

Superficial vein thrombosis
Consider anticoagulation or giving no treatment. Consider anticoagulation especially for babies with a line that is still functioning who continue to need central access, and in those whose symptoms progress.

DVT/PE
If asymptomatic, consider anticoagulation or giving no treatment, on an individual basis. If symptomatic, guidelines recommend anticoagulation.

Right atrial thrombosis
Guidelines suggest anticoagulation. Occasionally the haemodynamic status, size or mobility of the thrombus may warrant thrombolysis or surgical thrombectomy. Discuss these cases with cardiology and haematology.

Renal vein thrombosis
Consider anticoagulation. The indication for anticoagulation is stronger if there is bilateral involvement or progression to the inferior vena cava. Severity of disease, age, gestational age and thrombocytopenia will impact bleeding risk. Consider thrombolysis if life-threatening (ie bilateral renal vein thrombosis with renal impairment).

Portal vein thrombosis
Guidelines suggest anticoagulation if thrombus is occlusive. If thrombus is not occlusive or if portal hypertension is present (suggesting an old thrombus), guidelines suggest not to give anticoagulation. In those who are not anticoagulated, follow up monitoring is important as treatment may be required if the thrombus extends or if liver function becomes impaired.

Cerebral sinus vein thrombosis
Guidelines recommend anticoagulation in cases of cerebral sinus vein thrombosis (CSVT) without haemorrhage. Presence of haemorrhage is not a contraindication to anticoagulation in patients with CSVT, but the risk of further bleeding needs to be considered.

5.3 Anticoagulation/Thrombolysis

Risk factors for bleeding must be carefully considered before starting anticoagulation or thrombolysis. Guidelines from the American College of Chest Physicians suggest a duration of anticoagulation of 6 weeks to 3 months for line associated thrombosis where the line has been removed[1]. The Kids-DOTT study, which is looking at duration of anticoagulation, is ongoing[15].

Platelets must be >50 for therapeutic dose 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 (enoxaparin) 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. In patients with renal impairment, the risk of bleeding is increased and unfractionated heparin may be preferable. The dose should be reduced in severe hepatic impairment.

For preterm infants (corrected gestational age 36+6 weeks and below) start enoxaparin 2mg/kg/dose twice daily subcutaneously.

For term infants (corrected gestational age 37+0 weeks and above), start enoxaparin 1.5mg/kg/dose twice daily subcutaneously.

Check anti-factor Xa level four hours after the second dose of enoxaparin. Consider checking anti-factor Xa level sooner (four hours after the first dose) in cases of severe hepatic or renal impairment.

Subsequently doses should be adjusted based on anti-factor Xa (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 preterm infants[16].

A suggested dose adjustment regime is as below:

Anti-factor Xa level (units/mL)	Hold next dose?	Dose change	Next anti-factor Xa level
<0.35	No	↑25%	Next day 4 hours after morning dose
0.35-0.49	No	↑10%	1-2 days 4 hours after morning dose
0.5-1	No	No change	Weekly 4 hours following a dose. If change in renal function/ addition of antibiotics/ signs of bleeding, check level 4 hours after next dose
1.1-1.5	No	↓20%	Next day 4 hours after morning dose
1.6-2.0	Delay by 3 hours	↓30%	Consider trough level before next dose and check peak level 4 hours after adjusted dose
>2.0	Until anti-Xa <0.5 U/ml	↓40%	Before next dose until anti-Xa <0.5 units/ml, then 4 hours after adjusted dose

Adapted from table in Reference 2 following consultations with local sources

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 if there is a significant concern regarding haemorrhage, as it has a short half-life and can be more easily reversed. UFH may also be preferable to 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 starting at 25units/kg/hour.

BNFc suggests adjusting to APTT levels[3]. However due to limitations in APTT monitoring and confusion regarding "normal ranges" in neonates, heparin therapy should be monitored by anti-factor Xa levels with a target of **0.35-0.7units/ml** (note different to LMW range[1]). See table below for suggested adjustments[17,18].

Anti-Xa level (units/ml)	***Bolus (units/kg)***	***Time to hold UFH infusion***	***UFH infusion rate change***	***Repeat Anti-Xa level***
<0.1	*50*	*-*	*Increase 10%*	*4 hours*
0.1-0.34	*-*	*-*	*Increase 10%*	*4 hours*
0.35-0.7	*-*	*-*	*0*	*4 hours until 2 in range, then daily*
0.71-0.89	*-*	*-*	*Decrease 10%*	*4 hours*
0.9-1.2	*-*	*30 minutes*	*Decrease 10%*	*4 hours after restart of infusion*
>1.2	*-*	*60 minutes*	*Decrease 15%*	*4 hours after restart of infusion*

Adapted from tables in Reference 17 and Reference 18 following consultations with local sources

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

Thrombolysis
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 cases, 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].

American Society of Haematology 2018 guidelines advise there are insufficient data to recommend local thrombolysis via interventional radiology over systemic thrombolysis or vice versa[14]. The Jessop Wing is not an interventional radiology centre so thrombolysis is done systemically. However if a baby has a line in situ which is functioning and the clot is at the end of it, then thrombolysis can be directed at the clot.

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 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 tPA 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 thirty mins prior to starting tPA.

Therapy:
Dosages vary, however BNFc recommends a dose of 100-500 microgram/kg/hr of alteplase (tPA) for 3-6 hours[3].

Administer this by starting a tPA 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, therefore stop infusion after 4 hours at that dose.
- If D-dimers are not increasing, increase tPA infusion in 100microgram/kg increments to a maximum of 500micrograms/kg/hour for 6 hours. Recheck 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.

6) References

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