GUIDELINE

Thromboembolic Disorders

Scope (Staff):	Nursing and Medical Staff
Scope (Area):	NICU KEMH, NICU PCH, NETS WA

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this disclaimer

Contents

Aim

To provide a guide for the diagnosis, management, and treatment of thrombosis in the neonate.

Risk

Inadequate diagnosis, management and treatment of thrombosis in the neonate.

Background

Thrombosis in the neonate is an uncommon complication and occurs most often in premature and other high-risk infants (incidence of 5.1/100,000 live births and 2.4/1000

NICU with 45-55% affecting preterm infants). It frequently involves arterial, larger vessels or is usually related to indwelling venous or arterial catheters.

The majority of thromboses in the neonatal period are related to *indwelling vascular access device.* Common sites: upper/lower venous system, portal veins, renal veins, cerebral venous sinuses, peripheral and CNS arterial thrombosis.

Risk factors

Catheter-related factors that increase the risk of thrombosis include:

- **UVC**: large catheter size, blood vessel occlusion, infusion of hyperosmolar solutions especially parenteral nutrition, low flow of infusion fluid, polyurethane (PU)/polyvinyl chloride (PVC) catheter, degree of endothelial damage on catheter placement and prolonged duration of UVC placement.
- **UAC**: longer duration of UAC placement, presence of calcium in the UAC infusate, hypertonic solution, smaller umbilical artery calibre, manipulation and replacement of UAC, low UAC position at L3 to L4 vertebral bodies, and PVC catheter material.

Other direct **risk factors** include:

- **Neonatal:** infection, foetal growth restriction, dehydration, polycythaemia (Hct>55%), fluctuations in blood pressure, hypoxia, abnormal umbilical cord insertion.
- **Maternal:** pre-eclampsia, diabetes mellitus, autoimmune disorders, chorioamnionitis, high preconception BMI. Certain genetic polymorphism haemostasis genes (factor XIII-Val34Leu polymorphism, PAI-1 mutation gene 4G/5G polymorphism) are associated with higher incidence of sepsis and longer hospital stay and thus contribute indirectly to thrombogenesis in sick preterm infants.

Clinical presentation and management (refer to Table 1)

For asymptomatic catheter-thrombosis: supportive care and close monitoring of thrombus size. Remove central catheter and arrange follow-up imaging in 3-5 days, if stable repeat 1-2 weeks later. If thrombus extends or if not feasible to remove catheter or if becomes symptomatic, treatment with anticoagulation or fibrinolytic therapy is recommended after discussion with PCH haematology.

For symptomatic thrombosis: treatment recommended. Involve PCH haematologist for management plan.

Table 1: Thrombosis Presentation and Management

Site/ Type **Clinical features**	**Diagnosis**	**Management** *Individualised (risk vs benefit)*
UVC thrombosis Persistent +ve blood cultures from catheter, thrombocytopenia, line dysfunction. Bilateral lower limb oedema with IVC thrombus	Doppler USG (DUSG- safest and widely used) Venogram (gold standard), MR venogram (pelvic and intra-abdominal venous thrombus)	Removal of UVC after 3-5 days of therapeutic anticoagulation (American college of chest physicians); LMWH/UFH for 6-12 weeks.
UAC thrombosis Aortic and renal arterial involvement Lower limb ischemia, impaired renal function, irritability, mesenteric ischemia, hypertension, congestive heart failure and NEC	DUSG (preferred) Contrast angiography (gold standard),	Remove catheter, anticoagulation with UFH/LMWH for 5-7 days, fibrinolytic therapy, surgery e.g.: thrombectomy (if life/ limb threatening)
PICC lines/ long lines Depends on device location and size ***Upper venous system thrombosis-*** *SVC syndrome* (limb or face swelling, pain, discolouration of upper limbs, distension of superficial veins, chylothorax, chylopericardium) ***Right atrial placement-*** intracardiac thrombus (new onset murmur, unresolving sepsis, thrombocytopenia, heart failure) and embolic complications	CXR, AXR and echocardiography Venography (MR, CT or conventional) can be considered	Remove PICC line after 3-5 days of therapeutic anticoagulation Acute and symptomatic: LMWH for 6-12 weeks
Renal vein thrombosis Most common non catheter associated thrombosis (present in-utero, by 72 hrs of life or around four weeks of life); maybe associated with adrenal hemorrhage. h/o perinatal asphyxia, GDM, prematurity, dehydration, infection and congenital heart disease. Males>females Flank mass, hematuria, thrombocytopenia, rare (AKI, embolization and hypertension)	DUSG	***Unilateral without renal insufficiency and no IVC extension***: LMWH for 6-12 weeks/ supportive management ***Unilateral with IVC extension***: LMWH for 6-12 weeks ***Bilateral RVT, associated renal insufficiency OR IVC extension***: LMWH (no/mild renal insufficiency) for 6-12 weeks, UFH (severe renal impairment), **consider** concomitant thrombolysis
Peripheral arterial line (PAL) Limb oedema, pallor or cold extremities distal to cannulation site, weak/ absent pulse, reduced or immeasurable BP	DUSG	Remove catheter, topical nitro-glycerine, anticoagulation with UFH, rarely surgical thrombectomy and microvascular repair
Arterial ischemic stroke Additional risk with foetal heart abnormalities, twin to twin transfusion	Bedside cranial USG (sensitive 16-70%), first week of life	Antithrombotic therapy - controversial

syndrome, hypoglycaemia and maternal antiphospholipid antibody syndrome and placental abnormalities Presents as- apnoea, seizures, poor feeding, abnormal tone	MR angiogram	Supportive treatment in acute phase (fluid balance, anti-seizure medications, ventilation) Discuss with PCH hematology regarding UFH/LMWH (indicated ONLY if confirmed embolic source present) Recurrent stroke- aspirin ± anticoagulation therapy in consultation with haematology and neurology.
Portal venous thrombosis Associated with UVC placement, incidence (1.3-43%), may present as unexplained thrombocytopenia, may cause portal hypertension and hepatic lobar atrophy.	Doppler US	Close observation (asymptomatic), discussion with haematology (if symptomatic) and treatment

- The classical clinical presentation of homozygous protein C or S deficiency is with cerebral or ophthalmic damage occurring **in utero**, purpura fulminans within hours of birth (acute lethal form of DIC with skin necrosis from dermal vasculature thrombosis) and rarely large vessel thrombosis. The diagnosis requires the clinical picture and undetectable levels of protein C/S as well as heterozygous levels in the parents.
- Treatment for these disorders is with FFP 10-20 mL/kg every 6-12 hours. Protein C concentrate is also available. Higher protein C levels desirable with concomitant sepsis/ perioperative period. Treatment should continue until all the manifestations resolve. Protein C replacements may be needed long-term in consultation with haematologist. Long term therapy with warfarin aims to keep the INR 2.5-4.5 but the effect on bones of long-term warfarin beginning in infancy is not known.

Laboratory Tests

- In addition to diagnostic imaging (***including cranial ultrasound***), baseline laboratory tests in the neonate before initiation of any therapy should include: FBP (including platelet count), prothrombin time and INR, activated partial thromboplastin time (aPTT), plasma fibrinogen, renal and liver function test.
- Test maternal blood for lupus anticoagulant and anticardiolipin antibody.
- Evaluation for prothrombotic disorders (panel including antithrombin/AT-III, protein C and S, Factor V Leiden, homocysteine and prothrombin 20210 mutation) is rarely indicated. To discuss with PCH haematology prior to ordering.
- Testing can be deferred if blood sampling is difficult because the results will not affect therapy, although they may affect the risk of recurrent thrombosis. Alternatively, these conditions can be excluded by testing the parents.

- Both parents should be tested for the prothrombotic state if the results of the newborn's tests are abnormal, this will help to distinguish acquired from congenital deficiencies.
- No data to support screening for thrombophilia in neonates without clinical evidence of thrombi. Use of these screening tests for non-specific symptoms (e.g. neonatal seizures) should be performed under the auspices of a clinical research protocol.
- During anticoagulant treatment, maintain platelet count >50,000/microL and fibrinogen >100mg/dL. Duration of anticoagulant therapy depends on clinical course; if thrombus resolves (10-14 days); if thrombus persists (up to 3 months).
- Echocardiography not effective in excluding thrombi of cardiac origin for infants with normal foetal scans. Routine postnatal echo is unnecessary except in those with genetic abnormalities.

Treatment of Major Thrombi

1. Heparin Anticoagulation (UFH: unfractionated heparin, LMWH: low molecular weight heparin)

LMWH preferred (to UFH) as can be administered subcutaneously and require minimal monitoring and dose adjustment. LMWH also has reduced risk of immune-mediated thrombocytopenia and osteoporosis.

Anti-Xa level (target between 0.3-0.7 U/ml) is better than APTT for monitoring as the APTT is frequently prolonged in sick neonates and does not correlate well with anti-Xa effect. Refer to Neonatal Medication Protocol – Heparin Sodium

Reversal: If serious bleeding occurs, discontinue LMWH and give protamine sulphate

2. Long Term Anticoagulation (Warfarin, Aspirin, Clopidogrel)

Not used as high risk of bleeding, availability in tablet form and need for frequent INR monitoring.

3. Thrombolytic Therapy (r-TPA/ recombinant tissue plasminogen activator)

This is reserved for significant thromboses that compromise perfusion of organs or limb. Refer to **algorithm 1**.

Thrombocytopenia (<100,000/microL), low fibrinogen (<100mg/dL) and severe coagulopathy to be corrected before treatment

Contraindications to treatment: major surgery or haemorrhage in previous 10 days, neurosurgery within three weeks, severe asphyxia event within seven days, invasive procedure within previous three days, seizures within 48 hrs, prematurity<32 weeks, systemic sepsis, active bleeding or inability to maintain platelets >100,000/microL or fibrinogen >1g/L.

Recombinant tissue plasminogen activator (rt-PA) is available and is given at 0.1-0.6 mg/kg/hr (without a loading dose) over 6 hrs. Transfusion of 10 ml/kg of FFP prior to r-TPA increases incidence of clot resolution by providing adequate plasminogen levels.

Streptokinase and Urokinase- very rarely used in neonates.

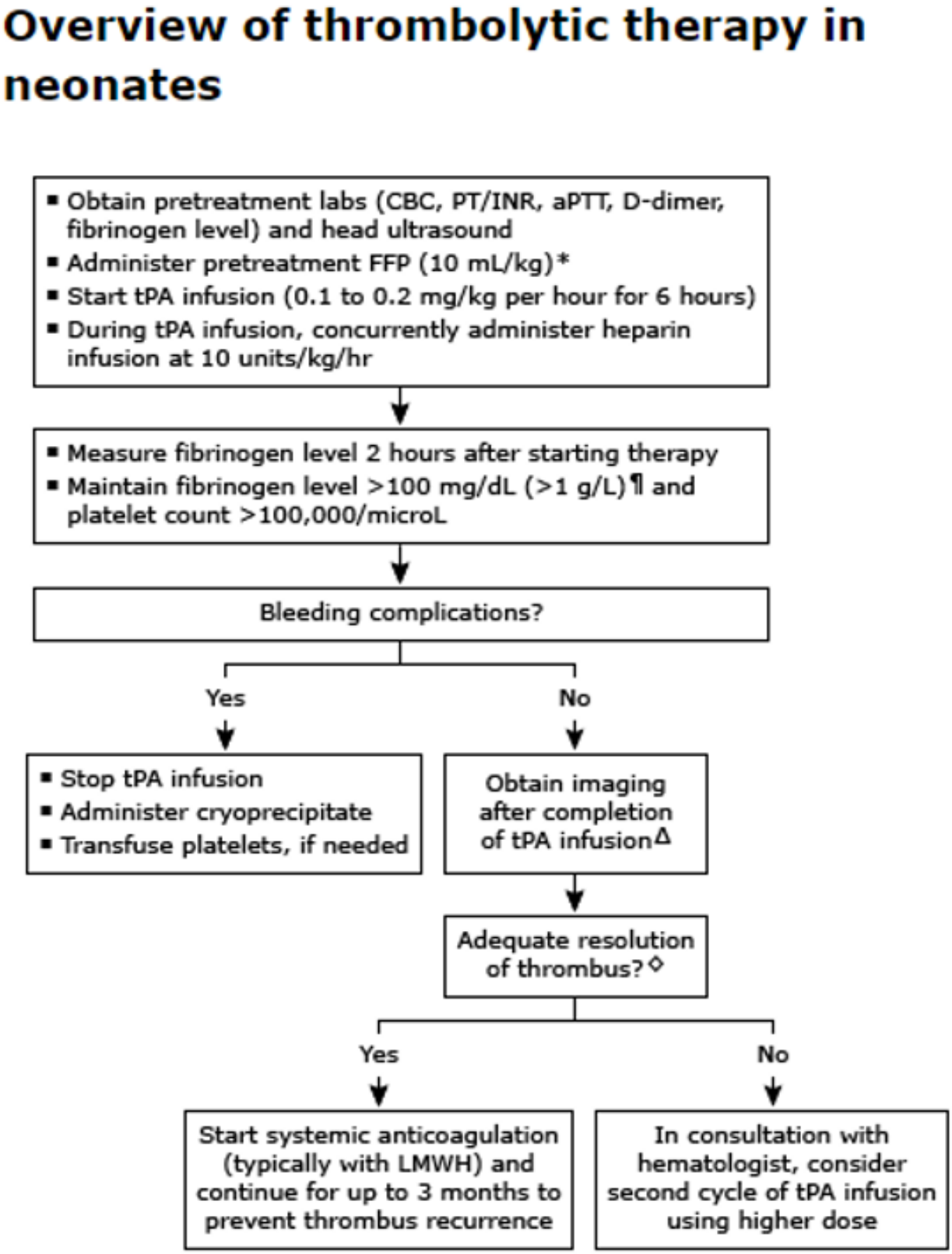
4. Nitro-glycerine patch

Apply to contralateral limb in peripheral vasospasm post insertion of UAC or PAL.

Outcome

Long term complications depend on location and type of thrombus. Most asymptomatic have no sequelae. PTS (post thrombotic syndrome) is uncommon but includes hepatic lobar atrophy and portal hypertension. RVT is associated with chronic kidney disease and hypertension.

Algorithm 1



Chan A, Bhatt M. ed: O'Brien S, Garcia-Prats J, Armsby C. Neonatal thrombosis: management and outcome. UpToDate 2024

Related CAHS internal policies, procedures and guidelines

Neonatal Medication Protocols

Heparin Sodium

Protamine sulphate

Aspirin

References and related external legislation, policies, and guidelines

1. Pan S, Xu A, Lu X, Chen B, Chen X, Hua Y. Umbilical artery thrombosis risk factors and perinatal outcomes. BMC Pregnancy Childbirth. 2024 Feb 14;24(1):137.
2. Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. Blood Adv 2018; 2:3292.
3. Rajagopal R, Cheah F-C, Monagle P. Thromboembolism and anticoagulation management in the preterm infant Seminars in Fetal and Neonatal Medicine, Volume 21, Issue 1, February 2016, Pages 50-56
4. Resontoc LP, Yap HK.. Renal vascular thrombosis in the newborn. Pediatr Nephrol. 2016 Jun; 31(6):907-15
5. Barrington KJ. Umbilical artery catheters in the newborn: effects of heparin. Cochrane Database Syst Rev 2000;2:CD000507
6. Bhat, R. Monagle, P. The preterm infant with thrombosis. Arch Dis Child Fetal Neonatal Ed 2012: 97(6): F423-8
7. Bose J, Clarke P. Use of tissue plasminogen activator to treat intracardiac thrombosis in extremely low-birth-weight infants. Pediatr Crit Care Med 2011;12(6): e407–9.
8. Chalmers EA. Perinatal stroke—risk factors and management. Br J Haematol 2005;130:333–43.
9. Thornburg C, Pipe S. Neonatal thromboembolic emergencies. Semin Fetal Neonatal Med 2006;11:198–206.
10. Greenway, A. Massicotte, M. P. Monagle, P Neonatal thrombosis and its treatment Blood Rev. 2004; 18:75-84
11. Malowany JI, Monagle P, Knoppert DC, et al. Enoxaparin for neonatal thrombosis: a call for higher dose for neonates. Thromb Res 2008;122(6):826–30.
12. Saliba E, Debillon T; et al. Neonatal arterial ischemic stroke: Review of the current guidelines]. Arch Pediatr. 2017 Feb;24(2):180-188. French.
13. Michaels LA, Gurian M, Hegyi T, et al. Low molecular weight heparin in the treatment of venous and arterial thromboses in the premature infant. Pediatrics 2004; 114(3):703–7.
14. Nowak-Gottl U, Duering C, Kempf-Bielack B, et al. Thromboembolic diseases in neonates and children. Pathophysiol Haemost Thromb 2004;33(5-6):269–74.
15. Raju TN, Nelson KB, Ferriero D, et al. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007;120:609–16.
16. Saxonhouse, M. A. Management of neonatal thrombosis Clin Perinatol 2012 Mar, 39(1):191-208
17. Bhagat I, Sarkar R, Bapuraj JR, Sarkar S. Routine Echocardiography is not Required in Neonates with Arterial Ischemic Stroke. Am J Perinatol. 2024 Jan 12. doi: 10.1055/a-2237-8711.
18. Chan A, Bhatt M. ed: O'Brien S, Garcia-Prats J, Armsby C. Neonatal thrombosis: management and outcome. UpToDate 2024

This document can be made available in alternative formats on request.

Document Owner:	Neonatology		
Reviewer / Team:	Neonatal Coordinating Group in conjunction with Pharmacy and Haematology		
Date First Issued:	August 2006	Last Reviewed:	June 2024
Amendment Dates:		Next Review Date:	June 2027
Approved by:	Neonatology Coordinating Group	Date:	25/06/2024
Endorsed by:	Neonatology Coordinating Group		
Standards Applicable:	NSQHS Standards:  Child Safe Standards: 1,10		

Printed or personally saved electronic copies of this document are considered uncontrolled

Healthy kids, healthy communities

Compassion | Excellence | Collaboration | Accountability | Equity | Respect

Neonatology | Community Health | Mental Health | Perth Children's Hospital