Thrombosis in the neonate occurs most often in premature (incidence of 6.8/1000 admissions <32 weeks) and other high-risk infants. It frequently involves arterial, larger vessels or may be related to indwelling venous or arterial catheters.

The fetus and newborn are more susceptible to thrombosis because of a deficiency of thrombin inhibition and relatively deficient thrombolysis. The infant is protected from thrombosis by physiologic depression of factors II, VII, IX and X but the balance favours thrombin formation over inhibition especially in the sick neonate (plasminogen, anti-thrombin and protein C may be extremely low).

The majority of thromboses in the neonatal period are related to intravenous or intra-arterial catheters.

**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, dehydration, polycythaemia (Hct>55%), fluctuations in blood pressure, hypoxia.

- **Maternal**: pre-eclampsia, diabetes mellitus, autoimmune disorders, chorioamnionitis. 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.
<table>
<thead>
<tr>
<th>Site/ Type</th>
<th>Clinical features</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>UVC thrombosis</td>
<td>Persistent +ve blood cultures from catheter, thrombocytopenia, line dysfunction</td>
<td>Doppler USG (DUSG - safest and widely used)</td>
<td>Removal of UVC after 3-5 days of therapeutic anticoagulation (American college of chest physicians); LMWH/UFH for 6 weeks -3 months</td>
</tr>
<tr>
<td></td>
<td>Bilateral lower limb edema with IVC thrombus</td>
<td>Venogram (gold standard), MR venogram (pelvic and intra-abdominal venous thrombus)</td>
<td></td>
</tr>
<tr>
<td>UAC thrombosis</td>
<td>Aortic and renal arterial involvement Lower limb ischemia, impaired renal function, hypertension, congestive heart failure and NEC</td>
<td>DUSG (preferred)</td>
<td>Remove catheter, anticoagulation with UFH/LMWH, fibrinolytic therapy, surgery (if life/ limb threatening)</td>
</tr>
<tr>
<td>PICC lines/ long lines</td>
<td>Depends on device location and size Upper venous system thrombosis-SVC syndrome (swelling, pain, discolouration of upper limbs, chylothorax, chylopericardium) Right atrial placement- intracardiac thrombus (new onset murmur, unresolving sepsis, thrombocytopenia, heart failure) and embolic complications</td>
<td>CXR, AXR and echocardiography</td>
<td>Remove PICC line after 3-5 days of therapeutic anticoagulation</td>
</tr>
<tr>
<td>Peripheral arterial line (PAL)</td>
<td>Limb oedema, pallor or cold extremities distal to cannulation site, weak/ absent pulse, reduced or immeasurable BP</td>
<td>DUSG</td>
<td>Remove catheter, topical nitro-glycerine, anticoagulation with UFH, rarely surgical thrombectomy and microvascular repair</td>
</tr>
<tr>
<td>Arterial ischemic stroke</td>
<td>Additional risk with fetal heart abnormalities, twin to twin transfusion syndrome, hypoglycaemia and maternal antiphospholipid antibody syndrome and placental abnormalities Presents as- apnoea, seizures, poor feeding, abnormal tone</td>
<td>Bedside cranial USG (sensitive 16-70%), first week of life MR angiogram</td>
<td>Antithrombotic therapy - controversial Supportive treatment in acute phase (fluid balance, anti-seizure medications, ventilation) Initiate UFH/LMWH (with cardio-embolic source) Recurrent stroke- aspirin and anticoagulation therapy.</td>
</tr>
</tbody>
</table>

Portal venous thrombosis, cerebral sino-venous thrombosis and spontaneous aortic thrombosis are rare events in neonates
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. Treatment should continue until all the manifestations resolve. 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, baseline laboratory tests in the neonate before initiation of any therapy should include: platelet count, prothrombin time, activated partial thromboplastin time (aPTT) and fibrinogen concentration.
- Maternal blood should be tested 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) should be conducted in newborns with thrombosis which is clinically significant, recurrent or spontaneous following the guidelines set by the Subcommittee for Perinatal and Pediatric Thrombosis of the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis (*Manco-Johnson, 2002*), but the timing of this evaluation may better be left until the acute clinical event has resolved. The results must always be interpreted in the light of age-appropriate normal ranges and laboratory-specific reference ranges. Whether newborns with catheter-related thrombosis require these studies is uncertain.
- 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.
- Tests that are abnormal in the newborn should be repeated within 6–8 weeks.
- Both parents should be tested for the prothrombotic state if the results of the newborn’s tests are abnormal, as this will help to distinguish acquired from congenital deficiencies.
- There is no data to support screening for thrombophilias 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.

**Treatment of Major Thrombi**

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

There are no controlled trials of therapy but the use of UFH has resolved vascular occlusion in most instances. Newborns show relative resistance to heparin compared with adults and it has a shorter half-life. Heparin Anti-Xa level is better than APTT for monitoring as the APTT is frequently prolonged in sick neonates. The dose response of LMWH in the newborn may be more predictable as there is less heparin resistance. In addition LMWH can also be given subcutaneously and
Thromboembolic Disorders

requires less monitoring. Low levels of AT-III and increased clearance of UFH doses are different between term and preterm neonates to achieve a **target anti-Xa level between 0.3-0.7 U/ml**.

Refer to Neonatal Medication Protocol – **Heparin Sodium**

**Long Term Anticoagulation (Warfarin, Aspirin, Clopidogrel)**

Rarely required except for those with homozygous or multiple thrombophilia traits or congenital cyanotic heart disease who may need life-long anticoagulation.

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

This is reserved for recent arterial thromboses that compromise perfusion. The most critical complication is intracranial haemorrhage and a cranial ultrasound should be performed prior to therapy. Neurologic signs suggestive of stroke, recent history of severe hypoxia and recent surgery are contraindications to thrombolytic therapy. Recombinant tissue plasminogen activator (rt-PA) is available and is given at 0.01-0.5 mg/kg/hr. Because rtPA does not inhibit clot propagation or directly affect hypercoagulability, simultaneous infusion of UFH is recommended. Transfusion of 10 ml/kg of FFP prior to r-TPA increases incidence of clot resolution by providing adequate plasminogen levels.

Streptokinase and Urokinase- not evaluated in neonates.

**Nitro-glycerine patch**

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

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**References**

1. 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
10. Marilyn Manco-Johnson and Rachelle Nuss Neonatal thrombotic disorders Neoreviews 2000;1;e201

Related WNHS policies, procedures and guidelines

Neonatal Medication Protocol – Heparin Sodium

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