NCCU CLINICAL GUIDELINES

SECTION: 9

HAEMATOLOGY

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Thromboembolic Disorders
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Neonatology Clinical Guidelines
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THROMBOEMBOLIC DISORDERS

Thrombosis in the neonate occurs most often in premature and other high-risk infants and 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. Clinically apparent thromboses are precipitated by low flow, severe acidosis and vascular occlusion. Other risk factors include infection, hypotension, hypoxia, maternal diabetes mellitus, polycythaemia, dehydration, NEC, pulmonary hypertension and other causes of DIC.

Diagnosis of thrombosis is suspected on clinical observations (white pulseless limb, or black, necrotic areas, enlarged kidneys) and imaging studies (doppler ultrasound, CT, MRI). Renal vein thrombosis may present with haematuria, hypertension and a flank mass +/-DIC. Aortic thrombosis may present with pale lower limbs and weak or absent femoral pulses, upper extremity or pulmonary hypertension and DIC.

LABORATORY TESTS

Subtle evidence of coagulation and fibrinolytic abnormalities are so common in sick neonates that sensitive markers of activation are rarely useful. D-dimer assay may be helpful in diagnosing DIC and coagulation parameters frequently improve when heparin therapy is begun.

The probability of genetic thrombophilia in a neonate with a thrombotic event is unknown although the occurrence of homozygous, compound heterozygous or multiple heterozygous abnormalities has been noted. Rarely maternal lupus anticoagulant can cause severe perinatal thrombosis and maternal testing should be performed.

All neonates with extensive or large vessel thrombosis should be evaluated with a panel including antithrombin, protein C and S, factor V Leiden, homocysteine and prothrombin 20210 mutation. However since neonatal levels are lower than adult levels and frequently overlap with adult heterozygous levels, it is difficult to make a causal association. Family studies and follow-up studies are necessary to confirm the diagnosis.

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 (eg neonatal seizures) should be performed under the auspices of a clinical research protocol.

The classical clinical presentation of homozygous protein C or S deficiency is of 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.

TREATMENT OF MAJOR THROMBI

1. HEPARIN ANTICOAGULATION

There are no controlled trials of therapy but the use of unfractionated heparin has resulted in resolution of 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 low molecular weight heparins in the newborn may be more predictable as there is less heparin resistance. In addition LMWH can also be given subcutaneously and requires less monitoring.

2. THROMBOLYTIC THERAPY

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 0.06mg/kg/hr however optimal dosing is yet to be established. Because rtPA does not inhibit clot propagation or directly affect hypercoagulability, simultaneous insfusion of UFH is recommended. FFP given at 10ml/kg is a good source of plasminogen and can be given as adjuvant therapy.

3. LONG TERM ANTICOAGULATION

Rarely required except for those with homozygous or multiple thrombophilic traits who may need life-long anticoagulation.

ANTICOAGULANT THERAPY OF NEONATAL AND PAEDIATRIC THROMBOSIS USING UNFRACTIONATED AND LOW MOLECULAR WEIGHT HEPARINS.

DOSING OF UNFRACTIONATED HEPARIN

Developmental age	Initial bolus dose: U/kg	Initial infusion U/kg/hr
• Preterm <28wks	25	15
• Preterm 28-36wks	50	15
• Full term ≥37wks	100	28
• Infants >4wks	50	20

DOSE ADJUSTMENT UNFRACTIONATED HEPARIN		
Heparin assay U/ml	**APTT / baseline**	**APTT Dose adjustment U/kg/hr**
0.0 - 0.14	1.00 - 1.24	Rebolus, increase by 10
0.15 - 0.29	1.25 - 1.49	Increase by 5
0.30 - 0.70	1.5 - 2.49	Continue dose
0.71 - 0.85	2.5 - 2.99	Decrease by 5
> 0.85	≥ 3.0	Hold 1hr, recheck, decrease by 10

DOSING OF LOW MOLECULAR WEIGHT HEPARIN (LMWH) (Enoxaparin)	
MG/KG OR U/KG GIVEN SUBCUTANEOUSLY EVERY 12 HRS	
Preterm neonates	Initial dose 2.0 mg/kg
Full Term ≥ 37 weeks	Initial dose 1.7 mg/kg
ANTI-XA HEPARIN ASSAY	**LMWH DOSE ADJUSTMENT**
0.00 – 0.24	Increase by 50%
0.25 – 0.49	Increase by 25%
0.50 – 1.20	Continue dose
1.21 – 1.5	Decrease by 25%, recheck after 2 doses
>1.05	Hold dose, decrease by 50%, recheck after 2 doses

Anti-Xa assay should be obtained after second dose then after each dose until therapeutic; then every 2-4 doses for first week, then once a week for a month then monthly.

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