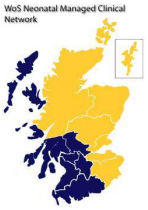
MCN for Neonatology
West of Scotland
Neonatal Guideline



Haematology Guideline

A guide to the management of unexplained bleeding, anaemia (including haemolysis), thrombosis and neutropenia in the neonate, and the immediate management of inherited haematological disorders.

This document is applicable to all medical, nursing and midwifery staff caring for the newborn in hospital or community. It is intended as a guide to common haematological problems in the newborn, and the immediate postnatal investigation and management of babies who are at risk of an inherited haematological disorder

The guideline should be used with reference to the relevant pharmacy monographs.

Contents

1. UNEXPLAINED BLEEDING IN THE NEONATE

1.1 Overview

The majority of haemorrhagic problems in the neonatal period are due to acquired haemostatic defects, either thrombocytopenia or coagulation disorders. These are most often observed in the context of underlying illness or in sick preterm neonates, although neonatal alloimmune thrombocytopenia (NAIT) may present in otherwise clinically well babies at any gestation.

Inherited coagulopathies may present as abnormal bleeding in an apparently healthy baby; in the presence of a positive family history the diagnosis is usually straightforward, but there will often be no such family history and so a high index of clinical suspicion is required.

Whom to investigate

- any haemorrhagic neonate
- positive family history of bleeding disorder (remember to take a family history, including consanguinity)
- sick low birth weight or preterm neonates
- severe metabolic disease, respiratory distress, sepsis or other factors predisposing to DIC
- neonates undergoing surgical intervention who have had previous bleeding problems
- maternal anticonvulsant / anti-tuberculosis / warfarin therapy at time of delivery
- babies born to mothers with ITP (FBC only; no need for a full coagulation screen). NB this does not apply to pregnancy-associated thrombocytopenia; if mother's platelet count was normal in early pregnancy there is no need to test the baby.

Presentation

- excessive oozing from venepuncture / heel prick is the commonest presenting feature
- intracranial / extracranial haemorrhage - accounts for a third of bleeding reported in haemophilia (FVIII, FIX deficiency) during the first month of life and is common in severe FVII, X and XIII deficiencies
- umbilical bleeding / delayed cord separation - classically associated with homozygous FI or FXIII deficiency and relatively uncommon in haemophilia
- GI bleeding is uncommon
- NAIT may present as an isolated purpuric rash in an otherwise well neonate

Investigation

- coagulation screen, FBC and film - requires 1ml citrated blood for coagulation plus 0.5 mls EDTA sample for FBC and film (if specific factor assays are required discuss with haematology laboratory staff ***before*** bleeding the baby).
- sample bottles must be accurately filled and care should be taken to avoid contamination from IV fluids or heparin. If sampling is slow, the sample may become "activated", resulting in shortening of the PT and APTT.
- Heel pricks should not be used for coagulation tests.

	Acquired				Congenital	
	DIC	vitamin K deficiency	liver disease	heparin contamination	haemophilia A/B	Von Willebrand's
PT	↑	↑↑	↑	N	N	N
APTT	↑	↑ or N	↑	↑	↑	↑ or N
TCT	↑↑	N	↑ or N	↑↑	N	N
Fibrinogen	↓	N	↓	N	N	N
d-dimers	↑	N	↑	N	N	N
Platelets	↓ or N	N	↓ or N	N	N	N
Manage-ment	treat cause FFP Cryo-precipitate platelets as required for bleeding	not bleeding – vitamin K bleeding – vitamin K + 4 factor concentrate (Beriplex) or FFP	vitamin K (FFP cryo - precipitate, platelets as required - if bleeding)	repeat sample	appropriate factor replacement *discuss with haematology*	Voncento *discuss with haematology*

N.B. Reference ranges are dependent on the gestational and postnatal age of the infant and may vary between laboratories.

Be aware that severe FXIII deficiency can result in major haemorrhage and **normal** baseline coagulation.

Treatment options

For DIC, treatment of the underlying cause (including management of sepsis, correction of acidosis etc.) is paramount. Correction of coagulation using appropriate blood products should occur if the patient is bleeding or at very high risk of significant bleeding (e.g. ICH) and/or prior to surgical interventions. There is limited evidence to support the use of FFP to correct abnormalities of the coagulation screen alone, and FFP should not be used for simple volume replacement.

Fresh Frozen Plasma (FFP)

- should be group AB or compatible with recipient's ABO red cell antigens
- volume – see transfusion guideline

Platelets

- volume - see transfusion guideline
- if there is co-existent thrombocytopenia and coagulopathy give 20ml/kg platelets and recheck coagulation screen prior to ordering FFP

Cryoprecipitate (virally inactivated)

- consider if fibrinogen <1g/l on repeated samples (*i.e.* after FFP has been given) (see transfusion guideline)

Vitamin K

- for the treatment of vitamin K deficiency (includes liver disease)
- ideally given IV, but subcutaneous administration can be used if IV access problematic
- dose 1mg – may need repeated

Specific factor concentrates

- recombinant or plasma derived

- discuss with haematology

1.2 Inherited bleeding disorders

Note: At risk infants born to mothers who are known carriers of an inherited bleeding disorder will have a neonatal delivery plan in the obstetric notes which should be consulted and followed.

Haemophilia A and B

Usually presents in male infants of known haemophilia carriers but up to one-third of cases may arise due to a new mutation and therefore a high-index of suspicion is needed. Coagulation testing and consideration of factor assays should be undertaken in the context of a neonate presenting with:

- iatrogenic bleeding, eg post IM injection, circumcision
- intra / extra cranial haemorrhage, esp. significant cephalohaematoma
- unexplained bleeding in an otherwise well infant, especially if associated with an isolated elevated APTT

Von Willebrand's disease

This is a condition which results from a quantitative or qualitative defect of von Willebrand factor (vWF) resulting in an increased tendency to bleed. Up to 1% of the population have vWD as defined by reduced levels of vWF activity (VWF GP1b) but not all have a clinically significant bleeding disorder. There are a number of subtypes, of which type 1 is the most common.

	inheritance	Description	Severity	neonatal diagnosis
Type 1	AD	quantitative partial deficiency of vWF	mild to moderate, usually asymptomatic in neonatal period	delay until 10-12 months
Type 2A	AD	qualitative functional deficiency of vWF	bleeding may occur and can be severe	sometimes possible - d/w haematology (and consult delivery plan)
Type 2B	AD			
Type 2M	AD			
Type 2N	AR			
Type 3	AR	quantitative complete deficiency of vWF	Severe	Yes

Management of neonates with suspected inherited bleeding disorder

Cord sampling

A cord blood sample should be sent for relevant factor assays where the neonate:

- is male and may have haemophilia
- has a parent with moderate/severe VWD (*i.e.* Type II VWD, Type III VWD or Type I VWD with baseline VWF RiCof <20%)
- may have inherited a bleeding disorder that has been defined as moderate or severe
- has excessive bleeding or bruising at time of delivery

These samples should be discussed with haematology; it is important that the cord sample is not contaminated with maternal blood.

Note: female neonates who are or may be carriers of haemophilia do not require cord blood sampling as they rarely have low factor levels.

Interpretation of results

Factor VIII and VWF are increased in the healthy neonate at delivery and therefore most boys with haemophilia A can be diagnosed at birth. Very mild forms of haemophilia A/VWD may however not be able to be confirmed or excluded without a further blood sample at 6 months of age.

Factor IX levels are decreased in the healthy neonate at delivery and therefore mild forms of haemophilia B may not be able to be confirmed or excluded without a further blood sample at 6 months of age.

Neonatal Vitamin K

As a rule, if cord blood has been taken a standard dose of oral vitamin K should be given as soon as possible after delivery. If cord blood excludes the diagnosis of a bleeding disorder either one dose of IM vitamin K can then be given or the full course of oral regimen completed.

In all cases, neonatal blood spot samples can and should still be taken (normal technique; ensure pressure applied to the heel for 5 minutes post sampling).

Neonatal Factor testing

Abnormal or suspicious factor results from a cord specimen should be repeated on a neonatal blood sample

Cranial Ultrasound

Cranial ultrasound should be undertaken prior to discharge in all male neonates suspected of having a moderate or severe bleeding disorder e.g. moderate/severe VIII or IX deficiency, severe Type I (baseline RiCof <20%), Type II or Type III VWD.

Cranial ultrasound should also be considered in those with:

- signs of bleeding
- traumatic delivery e.g. forceps or prolonged 2nd stage (>3 hours for primiparous, >2 hours for multiparous women)
- preterm delivery (<34 weeks gestation)

If a neonate has neurological signs suggestive of an intracranial bleed, cranial ultrasound +/- subsequent MRI should be performed.

Factor therapy for neonates

Prophylactic factor therapy is indicated for neonates with low factor levels and:

- signs of bleeding
- traumatic delivery or prolonged 2nd stage of labour (see above)
- preterm delivery (<34 weeks)
- unexplained neurological signs

Two or three treatment doses (aiming for target level of 100%) should be given over the first 3 days of life. DDAVP is contraindicated under the age of 2 years. Prior to administration, the need for treatment should ***always*** be discussed with Haemophilia Unit, RHC (or GRI adult haemophilia unit).

Note: primary prophylaxis is not at present recommended for all severe haemophiliacs but is appropriate in some of the rare coagulation disorders (e.g. severe deficiencies of FVII, X and XIII due to the high risk of ICH). Children with Type III vWD require intermediate purity factor VIII (Voncento) rather than recombinant products. Discuss with Haemophilia Unit, RHC.

Referral to Paediatric Haematology

The following neonates should be referred to Dr Pinto, Haemophilia Unit at RHC:

- all male neonates with reduced or suspicious factor VIII or IX (these neonates will usually be reviewed within 2-3 days if severe/moderate deficiency, or within a few weeks if mild deficiency). They should be referred by telephone to Dr Pinto's secretary (ext 86505)
- all possible or obligate haemophilia carriers (these infants will usually be reviewed at 6-12 months, or earlier if bleeding symptoms or other concerns)
- all other neonates who were tested at birth and found to have reduced factor levels (these infants will usually be reviewed at 1-2 months, or earlier if bleeding symptoms)
- all other neonates with possible mild bleeding disorder (e.g. Type 1 VWD), but levels not yet measured (they will usually be reviewed at 6-12 months)

Neonates whose levels have been assessed and are clearly normal do not need referral to RHC, unless from families with borderline deficiencies (e.g. mild Type 1 VWD) where there may be overlap with what is physiologically normal at birth.

Childhood vaccinations

All children in whom a bleeding disorder is diagnosed at or shortly after birth should have their routine vaccinations by ***subcutaneous*** injection (many of the severe patients come to the haemophilia centre, at least for the first dose).

Infants with possible mild vWD or possible carriers (i.e. those who are due to be assessed at RHC at 6-12 months of age) usually have their vaccinations as normal, although this should be reviewed in symptomatic neonates or carriers with particularly low levels.

1.3 Rarer coagulation disorders

Factor XIII deficiency

This is an autosomal recessive condition. Homozygous deficiency (activity <10%) classically causes umbilical stump bleeding with a high rate of ICH, haematomas and impaired wound healing. Heterozygous deficiency (activity 50-60) is not associated with bleeding. Neonatal diagnosis of severe deficiency is possible. Note that the coagulation screen is normal – diagnosis is made by measuring Factor XIII (assay performed at Glasgow Royal Infirmary). Due to the very significant risk of ICH, prophylactic administration of high purity Factor XIII concentrate is recommended for homozygous deficiency. Dose - 30 units/kg/month intravenously to maintain Factor XIII levels >3%. ***Always*** discuss with Haemophilia Unit, RHC (or GRI adult haemophilia unit) prior to administration.

Others e.g. Dysfibrinogenaemia, Factor V/VII/X deficiencies.

For babies with a known family history there should be a neonatal bleeding disorders delivery plan in the maternal notes – this should be consulted and followed. All other babies should be discussed with a consultant haematologist on a case by case basis

1.4 Platelet Disorders

Thrombocytopenia is frequently encountered in neonatal intensive care units, particularly among very low birth weight or sick neonates.

Early-onset thrombocytopenia (<72 hours old)

This is the commonest time to present with thrombocytopenia and most cases are seen in preterm neonates born to pregnancies complicated by placental insufficiency (e.g. maternal pre-eclampsia, hypertension or diabetes) and/or chronic fetal hypoxia / idiopathic intrauterine growth restriction. Affected neonates often have a low normal or modestly reduced platelet

count at birth (120-200x10^9/L), which falls to a nadir of 80-100 at day 4 -5 of life before recovering to >150x10^9/L by 7 -10 days of age.
In contrast to the mild-moderate thrombocytopenia seen in most cases of placental insufficiency, severe early onset severe thrombocytopenia (<50x10^9/L) requires urgent investigation. The two most important causes are neonatal alloimmune thrombocytopenia (NAIT), which is discussed in detail below, and hypoxic ischaemic encephalopathy (HIE) due to acute perinatal asphyxia. Up to 30% of all neonates with HIE develop thrombocytopenia which is often severe and prolonged and principally appears to be precipitated by disseminated intravascular coagulation. Treatment is supportive.

Late-onset thrombocytopenia (>72 hours old)

This is often severe, develops acutely and may be prolonged. Most cases are secondary to sepsis or necrotising enterocolitis (NEC), often associated with DIC (check coagulation screen). Thrombocytopenia may be prolonged for several weeks beyond the onset of sepsis/NEC.

Neonatal alloimmune thrombocytopenia (NAIT)

NAIT is the commonest cause of severe thrombocytopenia in well, term infants and is caused by maternal sensitisation to paternally derived fetal platelet antigens. It has a prevalence of 0.7 per 1000 pregnancies. In Caucasian populations, human platelet antigen HPA1a is implicated in 80% cases of NAIT, and HPA5b in 10-15%. The laboratory diagnosis of NAIT involves assays to detect maternal anti-HPA antibodies; both parents as well as the infant should be genotyped for the most common HPA alloantigens (HPA-1a, -2, -3, -5b, and -15). This testing is performed by the National Blood Service Platelet Immunology Laboratory Bristol; samples will be sent via the local blood bank (discuss with the Blood Transfusion service [telephone 0141 451 9104] regarding which samples are required), and ask the obstetric team to arrange for a sample of blood from mum).
Most neonates with NAIT present with severe thrombocytopenia, often <20x10^9/L. The most feared complication is intracranial haemorrhage (ICH) which occurs in ~20% of neonates with HPA1a- associated NAIT and is associated with a very high risk of severe neurodevelopmental problems, including cerebral palsy. A high proportion of ICH (~80%) occurs *in utero* and NAIT has been reported as early as 20 weeks gestation. Since NAIT can affect first pregnancies, the diagnosis at birth is often unsuspected; the clinical presentation varies from asymptomatic thrombocytopenia or petechiae to seizures secondary to ICH.

Management of NAIT

All cases of suspected NAIT should undergo cranial ultrasound scans to exclude ICH. Most cases of NAIT resolve within a week without long-term sequelae. Since the platelet count usually falls over the first 4-7 days of life, all thrombocytopenic neonates with NAIT should be monitored until there is a sustained rise in their platelet count into the normal range. In well neonates with documented or suspected NAIT who have no evidence of haemorrhage, transfusion of HPA-compatible platelets is recommended only when the platelet count is <20-30x10^9/L. Consult the MCN neonatal transfusion guideline for further information on management of NAIT
(http://www.knowledge.scot.nhs.uk/media/CLT/ResourceUploads/4078849/5ad90226-aef2-4236-babc-715bb0f60b8f.pdf).
Usually HPA-1a, 5b-negative platelets are given pending an accurate diagnosis. In the event of major haemorrhage, including ICH, the platelet count should be maintained >50x10^9/L using appropriate HPA-negative platelets. If appropriate HPA-negative platelets are unobtainable, random donor platelet transfusions and/or intravenous immunoglobulin (IVIG) can be used in an emergency. In all cases, such platelets should be CMV antigen-negative and single-donor apheresis units; neonates who have received intrauterine platelet transfusions should be given irradiated platelets. In some cases, thrombocytopenia may persist for up to 8 -12 weeks; in these babies IVIG is usually a better option than repeated platelet transfusions.
Parents should be counselled about the potential risk of NAIT in future pregnancies, which should be managed in conjunction with a fetal medicine unit.

Neonatal Thrombocytopenia secondary to maternal ITP

Transplacental passage of maternal platelet autoantibodies due to maternal immune thrombocytopenia (ITP) or systemic lupus erythematosus (SLE) can cause neonatal thrombocytopenia. Severe thrombocytopenia ($<50x10^9$/L) occurs in about 10% neonates with maternal platelet autoantibodies of whom about half have platelet counts of $<20x10^9$/L. However, studies have shown that risk of severe haemorrhage, including ICH, is low in these babies.
All neonates with a history of maternal thrombocytopenia should have their platelet count checked at birth; if found to be $>150x10^9$/L, no further action is necessary. Thrombocytopenic neonates should have their platelet count rechecked after 2-3 days, as the platelet count often drops to its lowest levels at this age, after which it tends to resolve spontaneously by 7 days of age in the majority. More rarely, thrombocytopenia may persist up to the age of 12 weeks. When the thrombocytopenia is severe (platelet count $<30 \times 10^9$/L in the first week of life and $<20x10^9$/L thereafter), treatment with IVIG (1 gram/kg) may be useful.

Other causes of thrombocytopenia

In the case of unexplained thrombocytopenia always consider rarer causes such as:

Congenital infections: most commonly CMV and rubella but enteroviruses (Coxsackie A and B and echovirus), HIV and parvovirus B19 can also cause severe, acute neonatal thrombocytopenia. In most cases, thrombocytopenia will be present in combination with other clinical features suggestive of congenital infections, e.g., intracranial calcification, hepatosplenomegaly, jaundice, or "viral" lymphocytes on the blood film. Severe thrombocytopenia (platelet count $<50x10^9$/L) that is present in the first days of life and persists for more than the first week is a common feature in congenital infections and may suggest the diagnosis even in the absence of other more common clinical features.

Perinatal bacterial infection: especially Group B strep and E. coli, are often associated with DIC.

Chromosomal abnormalities: fetal thrombocytopenia is seen in up to 86% of cases of trisomy 18, 31% of trisomy 13, 75% of triploidy and 31% of Turner syndrome babies at the time of fetal diagnosis.
Thrombocytopenia is also common in trisomy 21. The latter may be part of a transient abnormal myelopoiesis (Transient Leukaemia of Down Syndrome (TL-DS)) seen in 10-20% of neonates with Down syndrome and characterised by increased peripheral blood myeloblasts, abnormal megakaryocytes and variable thrombocytopenia. Screening for TL-DS should occur in all infants with trisomy 21 as per the MCN trisomy 21 pathway (http://www.knowledge.scot.nhs.uk/media/CLT/ResourceUploads/4095474/9105c350-b9ef-46c9-b501-55b4ae004cea.pdf). FBC and film (0.5ml in EDTA bottle) should be sent and can be carried out via cord bloods (same sample type and volume) if antenatal diagnosis has been carried out.
In most cases TL-DS resolves spontaneously, but ~30% of neonates with TL-DS develop acute megakaryocytic leukaemia within the first 5 years of life. Clinically, TL-DS has a variable neonatal presentation from asymptomatic mild thrombocytopenia to fulminant hepatic fibrosis due to hepatic infiltration with abnormal megakaryocytes and blasts. TL-DS is due to acquired somatic mutations in the key megakaryocytic transcription factor GATA-1. GATA-1 mutations can be tested for at birth – liaise with the Paediatric Haematology unit to arrange testing.

Inherited thrombocytopenia: thrombocytopenia generally presents at birth and persists in the absence of any other symptoms such as sepsis or NEC. Examples include Bernard Soulier syndrome, congenital amegakaryocytic thrombocytopenia (CAMT) or thrombocytopenia with absent radii (TAR) syndrome. If any of these is suspected the baby should be discussed with the paediatric haematology department.

Indications for platelet transfusion

Thrombocytopenia usually occurs as a response to a systemic disorder, and in most cases, resolves spontaneously or following resolution of the underlying pathology. However, the risk of significant or serious haemorrhage in thrombocytopenic neonates is high, particularly in those who are very preterm or of low birth weight. The treatment of thrombocytopenia, particularly in the context of platelet transfusion thresholds, remains controversial and lacks consensus among neonatologists. Consult the MCN neonatal transfusion guideline for local policy and platelet thresholds.

2. ANAEMIA IN THE NEONATE

2.1 Overview

Presentation

- hydrops fetalis
- signs of acute haemorrhage: pallor, bleeding, cardiovascular instability (MCV and MCH usually normal)
- signs of chronic blood loss: pallor, poor feeding, cardiac failure (low MCV and MCH)
- jaundice / unconjugated hyperbilirubinaemia (very suggestive of a haemolytic process)
- may be asymptomatic

History and clinical assessment

- maternal and birth history (consider Kleihauer to investigate feto-maternal transfusion)
- consanguinity, ethnicity
- family history of anaemia or neonatal jaundice
- clinical examination – signs of cardiovascular compromise, jaundice

  think about possible mechanisms of anaemia :

  - loss of red cells
  - increased red cell destruction
  - underproduction of red cells

Investigation

- ***REMEMBER TO TAKE A PRE-TRANSFUSION SAMPLE FOR NEWBORN SCREENING***
- FBC blood film and reticulocyte count (normal reticulocyte count in the newborn is 110-450 $x10^9$/l on day 1 of life falling to 10-80 $x10^9$/l by 1 week of age)
- blood group and direct Coomb's test (DCT [named 'direct AHG test' on Trakcare])
- serum bilirubin

2.2 Haemolysis in the neonate

Diagnosing non-immune haemolysis and identifying the cause can be very difficult in the neonatal period. Treatment may have to be with supportive care (phototherapy +/- exchange transfusion) pending further investigations in later childhood.

Identifying haemolysis

- high unconjugated bilirubin
- falling haemoglobin
- elevated reticulocyte response in absence of overt bleeding

Immune-mediated haemolysis

- DCT is positive because of antibody coating the baby's red blood cells
- the commonest cause is ABO incompatibility
- maternal alloantibodies (eg Rh, Kell) can cross the placenta and cause haemolytic disease of the newborn (HDN) and so all infants born to women who have clinically significant antibodies should be closely observed for evidence of HDN. A DCT should be performed and if positive, haemoglobin and bilirubin levels should be measured

- IF DCT is positive, it is important to establish both the maternal and infant blood group and maternal antibody screen (if maternal anti-A and anti-B titres are not available discuss with haematology)

ABO incompatibility

- occurs when there is ABO incompatibility between mother and baby
- is commonest with blood group A or B babies born to group O mothers;
    - although this situation is present in 12-15% of pregnancies, only 3% will have a positive DCT
- blood film characteristically shows microspherocytes
- birth order is not a risk factor; can affect 1st born infants
- onset of jaundice is usually within 24 hours of birth
- the mild haemolysis is compensated by an effective reticulocyte response therefore haemoglobin should be within the normal range

Effect of routine antenatal anti-D prophylaxis (RAADP)

Anti-D prophylaxis is being increasingly used antenatally. This can cross the placenta and bind to fetal cells; consequently, up to 3-6% of D positive cord or infant samples will have a positive DCT in the absence of significant haemolysis.

Isolating a cause for haemolysis

- DCT
- blood film
- maternal antibody screen (to include anti-A and Anti-B titres)
- family history
- red cell enzyme analysis
- haemoglobinopathy screen
- red cell membrane analysis

Samples required (pre-transfusion!)

(don't forget blood spot screening card if baby < 5days old)

- 0.5ml EDTA for FBC, reticulocytes and blood film
- 0.5ml EDTA for DCT, blood grouping and rhesus/Kell phenotyping
- 0.5ml EDTA for EMA dye binding if hereditary spherocytosis is suspected
- consider maternal sample to check alloantibody screen (including Anti A and Anti-B if relevant ABO mismatch exists)

***If** haemolysis has been confirmed and the cause is uncertain*

- enzymopathy screen (G6PD and pyruvate kinase)
- haemoglobinopathy screen - haematology

2.3 Inherited conditions; Enzyme Disorders

Hereditary spherocytosis

Inheritance	• autosomal dominant - predominantly autosomal recessive – rare, but tends to be more severe • 30% have no family history (new mutation or recessive)
Ethnicity	northern European
Clinical features	• jaundice persisting beyond the first week of life • infections may precipitate haemolysis.
Is neonatal diagnosis possible?	• yes - although often difficult in neonatal period especially if no family history. Discuss with haematology.
Investigations	Investigations are generally deferred until 3-6 months of age: • family history, FBC & film (from baby and parents) • eosin 5-maleimide (EMA) binding by flow cytometry • red cell membrane studies (Bristol - discuss with haematology) ***babies considered to require investigation in the neonatal period should be discussed with the neonatal consultant on call, and with haematology.***
Treatment	• folic acid – start if diagnosis is probable or confirmed • phototherapy as required – jaundice may worsen over first few days of life so there should be a low threshold for readmission if the baby is discharged early • top up transfusion (rarely required) • exchange transfusion (very rarely required)
Referral	• Paediatric Haematology unit • refer at discharge from the maternity unit (where jaundice has been particularly severe [and particularly if complex neonatal investigations are being considered] these babies should have been discussed with haematology prior to discharge)

Glucose-6-phosphate dehydrogenase deficiency

Inheritance	• X-Linked recessive • female carriers have 50% enzyme activity
Ethnicity	• Central Africa / Middle East/ S.E Asia up to 25% prevalence Mediterranean 3-10% prevalence (Greece/Sardinia 20%) Northern European < 0.5% prevalence
Clinical features	• neonatal jaundice (classically late onset 2-40 days) • may be precipitated by drugs given to mother perinatally • reduced G6PD in hepatocytes may worsen jaundice by contributing to subnormal handling of unconjugated bilirubin • baby at risk for kernicterus
Is neonatal diagnosis possible?	• yes – lithium heparin sample to biochemistry for G6PD activity
Investigations	• see above (PK assessment possible on the same sample) • test all boys of appropriate ethnic background with significant neonatal jaundice • may require repeat investigations when acute haemolysis has settled.
Treatment	• avoid precipitants e.g. oxidant drugs, sepsis, dehydration • phototherapy • top up transfusion / exchange transfusion rarely required • information leaflet for families • consider folic acid if severe haemolysis

Miscellaneous information	• screening tests are unreliable when reticulocyte count is high (e.g. during an acute haemolytic episode) or when the baby has already been transfused. • activity testing is usually accurate
Referral	• if well and no significant haemolysis then no haematology follow-up is required but ensure parents and GP have patient information leaflets and know to check before taking any new medications • if significant haemolysis start folic acid and refer to Paediatric Haematology Unit

2.4 Haemoglobinopathies

These comprise a large group of inherited blood disorders which result in abnormalities of the haemoglobin molecule. There are two main groups: the haemoglobin variants (*e.g.* sickle cell disease (SCD)), which are associated with the production of abnormal forms of haemoglobin, and the thalassaemias in which there is an imbalance between alpha and beta globin chain production.

Antenatal Haemoglobinopathy Screening

- Haemoglobinopathy screening is offered at booking to mothers from high risk areas (who should have been identified by a Family Origins Questionnaire). Partners of those women found to carry a haemoglobin variant or thalassaemia trait should also have been screened and antenatal counselling/prenatal diagnosis offered as appropriate.

Newborn Haemoglobinopathy Testing

- Because of the difficulties in interpreting samples processed by different laboratories, newborn haemoglobinopathy testing, outside of the universal screening programme, is no longer recommended, **even if both parents are known carriers.** Diagnosis before day 5 will not influence management, but if parents are extremely anxious early diagnostic testing may be undertaken ***after discussion with the neonatal consultant.*** Diagnostic testing is via a blood spot card sent to the screening laboratory – note that routine screening will still need to be performed on day 5 for the other conditions included in the newborn screening programme *(vide infra)*.
- **All newborns, regardless of risk, should be offered routine neonatal bloodspot screening at day 5.

Neonatal Screening

- Universal newborn haemoglobinopathy screening for SCD was introduced in Scotland in October, 2010 as part of the neonatal bloodspot screening.
- Note that only SCD (not thalassaemia) is screened for, although the majority of babies with thalassaemia major will be detected.

Sickle cell disease

Conditions	homozygote	- HbSS (Sickle cell disease)
	heterozygote	- HbAS (Sickle cell trait)
	compound heterozygotes	- HbSC, HbS/ßthalassaemia (will sickle) - HbSD (unlikely to sickle)
Ethnicity	• African, Afro-Caribbean	
Clinical features	• SCD is rarely symptomatic in the neonatal period as high levels of fetal haemoglobin prevent sickling, but neonatal fatalities have been reported. Symptoms usually appear after 3-6 months as the switch is made from fetal to adult haemoglobin. • early diagnosis reduces mortality/morbidity during early infancy • symptoms include anaemia, jaundice, acute crises • sickle cell trait is rarely symptomatic, and only in situations of extreme hypoxia or dehydration, e.g. sepsis	

Neonatal diagnosis possible?	• Yes
Investigations	• haemoglobin electrophoresis after routine neonatal blood spot screening • sickle cell solubility tests are not reliable in neonatal period
Treatment	• treatment if required is supportive • parental education is vital to pick up and react to infections early • all HbSS neonates should receive hyposplenic prophylaxis - penicillin V - pneumococcal vaccine • folic acid if signs of haemolysis • exchange transfusion - rarely required • discuss all neonates with a positive haemoglobinopathy screen for sickle cell haemoglobin by telephone with the Paediatric Haematology Unit

β thalassaemia

Conditions	• there are many β thalassaemia syndromes caused by mutation or deletion of one or both β-globin genes • homozygotes and compound heterozygotes develop transfusion dependent haemolytic anaemia (thalassaemia major) • heterozygotes usually have low MCV and MCH with no anaemia
Ethnicity	• Mediterranean, Middle East, SE Asia, North Africa. Sporadic cases in Northern Europeans
Clinical features	• very few in the neonatal period - (high fetal haemoglobin level protects)
Is neonatal diagnosis possible?	• yes - but most cases will require genotyping studies
Whom to test?	• both parents known carriers. Diagnostic testing is not indicated unless both parents are *known* carriers as β thalassaemia major is likely to be detected on routine screening. When father's status is unknown, refer baby to haematology for consideration of further testing at 3-6 months
Investigations	• haemoglobin electrophoresis/HPLC with follow up testing at 6-8 weeks (refer to RHC haematology) • molecular analysis if defect known
Treatment	• treatment very rarely required in the neonatal period • if required, treatment is supportive with blood transfusion • refer urgently to RHC by telephone if no HbA is seen
Miscellaneous information	symptoms generally appear at 3-6 months as the switch is made from fetal to adult haemoglobin, but may be apparent from 6-8 weeks

α thalassaemia

Conditions	• Normally there are four α–globin genes, two on each chromosome 16. • loss of 4 alleles results in hydrops fetalis and loss of 3 alleles results in HbH disease (ß4) (thalassaemia intermedia) which causes moderate haemolytic anaemia. • loss of 1 or 2 alleles results in an asymptomatic trait
Ethnicity	• Mediterranean, Middle East, North Africa - α^+ common α^+ can also be found in native Northern Europeans * • SE Asia, Greece or Cyprus - α^o deletion common

Clinical features	• HbH disease can present in the neonatal period, otherwise asymptomatic
Is neonatal diagnosis possible?	• yes - but may require genetic testing • note that newborn screening will detect most cases of HbH disease
Investigations	• haemoglobinopathy screen • antenatal diagnosis preferable if high risk of hydrops fetalis
Treatment	• very rarely required in the neonatal period • if required, treatment is supportive
Referral	• if HbH is detected in an anaemic baby then refer to Paediatric Haematology unit

3. NEONATAL THROMBOSIS

3.1 Overview

Neonatal thrombosis may be either arterial or venous and is usually associated with indwelling catheters. Spontaneous thrombosis is very rare and mostly involves the renal vein (although it can extend to the SVC).

Predisposing Factors

Inherited	**Acquired**
protein S deficiency	asphyxia
antithrombin deficiency	septicaemia
protein C deficiency	cardiac disease
factor V leiden mutation	dehydration
prothrombin gene mutation	maternal diabetes
maternal inherited antiphospholipid syndrome	

Investigations

Thrombophilia screening is not generally indicated in neonates presenting with thrombosis in the setting of known risk factors (indwelling lines, sepsis, dehydration etc). Consider measuring protein C, protein S and antithrombin levels if there are spontaneous or unusual thrombotic events, including purpura fulminans.

Family history of thrombophilia:

Protein C, protein S and antithrombin. Babies born to mothers who are heterozygous for a thrombophilia, do not need to be tested for that thrombophilia at birth, unless they have severe symptoms to suggest they are homozygotes, when expert input from haematology should be sought regarding testing and management.

In the case of a family history of **factor V leiden mutation or prothrombin gene mutation** the risk of thrombosis low and no investigation is necessary in the neonatal period.

Treatment of thrombosis

- ensure thrombosis is confirmed
- remove central lines associated with thrombosis, ideally after 3-5 days of anticoagulation therapy
- ***discuss with haematology***
- anticoagulate with low molecular weight heparin (enoxaparin; http://www.knowledge.scot.nhs.uk/media/CLT/ResourceUploads/4097849/9f3ec487-ba67-46e3-8819-01074a295ad6.pdf)
- Warfarin is NOT recommended
- monitor platelets whilst on heparin
- recommended duration of anticoagulant treatment is between six weeks and three months
- consider thrombolysis if clot is extending or critical limb or organ hypoperfusion occurs

NEUTROPENIA IN THE NEONATE

- neutropenia is a common problem within the NICU setting; infection risk is directly related to the severity and duration of neutropenia
- in general, a neutrophil count of $<1.5 \times 10^9$/L is used to define neutropenia
- neutrophil counts tend to be high at birth, rise within the first 12 hours, then gradually fall to normal adult levels around 1 month of age
- VLBW infants tend to have lower neutrophil counts at birth

Acquired	**Congenital**
infection bacterial, viral, fungal	severe congenital neutropenia (Kostmann syndrome) cyclic neutropenia chronic benign neutropenia familial non familial (chronic granulocytopenia of childhood) idiopathic chronic severe neutropenia neutropenias associated with congenital immune defects neutropenia with immunoglobulin abnormality neutropenia with defective cell-mediated immunity reticular dysgenesis neutropenias associated with phenotypic abnormalities Shwachman syndrome cartilage-hair hypoplasia Dyskeratosis congenita Barth syndrome Chédiak-Higashi syndrome myelokathexis metabolic disease
drugs	
immune (see below)	
nutritional deficiency eg. B12/folate/copper	
complement activation with ECMO	

Neonatal alloimmune neutropenia

Clinical features	• severe neutropenia, resulting in fever, bacterial infection and sometimes death from overwhelming sepsis • incidence < 1:1000 births • duration of neutropenia around 7 weeks (range 2-17 weeks)
Mechanism	• neutrophil equivalent of NAIT/Rh haemolytic disease • mother becomes sensitised to fetal neutrophil antigens (HNA) and produces an antibody which crosses the placenta
Investigations	• demonstrate anti-HNA antibodies in maternal blood against baby's HNA antigens
Treatment	• appropriate broad spectrum antibiotics • there is no evidence that GCSF reduces the incidence of infection
Referral	• Paediatric Haematology unit

Useful Resources

British Committee for Standards in Haematology (BCSH) – Website

UK Haemophilia Centre Doctors' Organisation (UKHCDO) - Website

Chakravorty et al, Br J Haematol. 2012 Jan;156(2):155-62

Literature review & References

See national guidelines on BCSH and UKHCDO Websites (*above)*

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