Neonatal Coagulation Guidelines

Where to find help

Samples are sent to the haematology laboratory, RIE.

Haematology advice: RIE lab	26840
Haematology registrar, RHSC	Bleep 9290
Out-of-hours haematology cover (RIE and RHSC)	via switchboard
Dr Matthew Howard-Jones, Consultant Paediatric Haematologist	60772 or via switchboard
Dr Susan Baird, Consultant Paediatric Haematologist	20428 or via switchboard
Dr Rosina Shujaat	51744
Email	loth.rhcyphaematology@nhslothian.scot.nhs.uk

Samples

You need one pink tube and two green tubes:

Full blood count

- Hb, WCC, platelets, blood film
- EDTA sample (**1 pink tube**). Minimum volume 100 microlitres

Coagulation

- PT, APTT, fibrinogen.
- Citrate sample (**green tube**). Must be 1.3ml - i.e. up to line on tube. One correctly filled tube is better than two partially filled tubes.

Normal ranges

Platelets

- Platelet count >150x10^9/l regardless of gestational age
- Platelets often increase to 300 - 400x10^9/l in the first month of life

Fibrinogen

- Fibrinogen should be within the normal adult range if the gestational age is >25 weeks: 1.5 - 4 g/l

Clotting times

- The normal ranges for APTT & PT vary with gestational age

Healthy full term infants in first 6 months of life (approximate values)

Tests	day 1	day 5	day 30	day 90	day 180	adult
PT	8.7 - 12	8 - 11.5	8 - 10.5	8 - 10.5	8 - 10.5	8 - 10.5
APTT	35 - 45	35 - 48	32 - 42	32 - 40	32 - 37	32 - 37

Preterm infants

- It is difficult to define clotting times on which we should act in the preterm baby as the risk of bleeding, such as IVH, varies with both gestational age and postnatal age.
- **Discuss with the consultant if the PT is >20s and/or the APTT is >100s or treatment is thought necessary**.

Indications for a coagulation screen

- Significant birth asphyxia
- Falling platelet count
- Unexplained bleeding or bruising
- Family history of haemophilia or inherited factor deficiency (see Guideline on the care of the fetus and neonate with a potential bleeding disorder)
- Post exchange transfusion

Further Investigations

Mixing Studies

- These should be performed when there is a prolonged APTT & PT
- The sample is mixed 50:50 with normal plasma in the lab
    - If the abnormal clotting is due to a factor deficiency then mixing the specimen with normal plasma should correct the prolongation by >50% of the difference between the result and the control.
    - In the presence of an inhibitor (e.g. heparin) there will not be a correction

Examples:

- APTT >200, control 32, mix 140 - heparin contamination
- APTT 85, control 32, mix 39 - factor deficiency

Factor Assays

Indicated

- in the presence of prolonged APTT/PT which completely corrects on mixing
- where there is a history of inherited factor deficiency e.g. haemophilia

These are arranged after discussion with a haematologist. Samples must be fresh.

How to interpret a coagulation screen

- Always look at the coagulation screen in conjunction with the platelet count
- Sudden changes in the absence of clinical deterioration should be viewed with caution and repeated
- Sampling errors are the commonest cause of problems eg partially clotted samples, small sample size, sample contamination

- Use normal ranges appropriate for gestational age (note laboratory quoted ranges in the RIE are for adults)

Common causes of Abnormal coagulation screens

In vitro

- Contamination with heparin - isolated prolongation of APTT which fails to correct with mixing studies. Sample should be repeated using a peripheral stab.
- Activation of sample - difficult venepunctures can result in activation of the sample causing shortened APTT. Fibirn clots may form resulting in low fibrinogen & thrombocytopenia.
- Incorrect plasma to citrate ratio in the sample - this may occur in the presence of a high Hct or a short sample

In vivo

- Check vitamin K has been given
- Isolated prolongation of APTT which fails to correct on mix - heparin
- Isolated prolongation of APTT which corrects completely on mix - factor deficiency
- Isolated prolongation of PT - liver disease, vitamin K deficiency, rarely factor deficiency
- Prolonged APTT & PT associated with low fibrinogen & thrombocytopenia - DIC

When to treat

Treatment needs to be based on individual case

- presence or absence of bleeding
- perceived risk of IVH in infant. Discuss with consultant.

For guidelines on treatment please refer to clinical guidelines on blood products

Referral to Haematology

If after discussion with haematology consultant he/she confirms referral is warranted, use the haematology referral letter.

Disorders of coagulation: Acquired

Disseminated Intravascular Coagulation

- Always has an underlying cause
- Clinical features vary from asymptomatic to bleeding (usually around venepuncture sites) & thrombosis
- Diagnosis
    - prolonged APTT (may initially be shortened)
    - prolonged PT
    - thrombocytopenia
    - falling fibrinogen levels
    - raised D-dimers (NB d-dimers do not have to be raised to make the diagnosis & raised d-dimers in isolation should be viewed with caution as they are often seen in the neonatal period due to activation of coagulation system)

Causes

Neonatal

- Hypoxia - acidosis, birth asphyxia, respiratory distress syndrome, infection
- Necrotising enterocolitis
- Meconium aspiration
- Aspiration of amniotic fluid
- Brain Injury
- Hypothermia
- Haemolysis
- Giant haemangioma
- malignancy
- Homozygous protein C deficiency

Maternal/obstetric

- dead twin
- placental abruption
- severe pre eclampsia

Management

- treat the underlying cause
- blood replacement therapy - see clinical guidelines on blood products
- aim to maintain platelet count > 50 x 10^9/l
- FFP to correct coagulopathy
- cryoprecipitate to correct hypofibrinogenaemia (<1g/l)

Liver disease

- Reduced synthesis of procoagulant proteins & reduced clearance of activated clotting factors
- Prolonged APTT & PT which may be associated with reduced fibrinogen
- Treatment is supportive

Thrombocytopenia

Background:

The platelet count of all healthy newborn infants, regardless of gestational age, should be ≥150x10^9/L and counts below this represent thrombocytopenia.

Thrombocytopenia occurs in 1-5% of newborns at birth. However, in the NNU population the incidence can be as high as 22-35%.

There are many fetomaternal and neonatal conditions associated with thrombocytopenia which are listed and explained in the appendix of this guideline. The most common conditions have been highlighted.

Assessment:

The important first step is to confirm the result. Spurious results can occur due to platelet clumping which is more common in heel prick samples and in polycythaemic babies. Ideally only free flowing blood for FBC's should ever be sent. A repeat free flowing venous sample should be performed.

In the meantime, assessment of the thrombocytopenic neonate is important to help identify the likely cause, including:

- Obstetric history: maternal platelet count, medication in pregnancy, pregnancy-induced hypertension (PIH) or pre-eclampsic toxaemia (PET), diabetes
- Family history of bleeding disorders
- Look for active bleeding, visible petechiae
- Plot the infant on growth chart ?IUGR
- Examine for features of trisomies
- Examine for features of congenital infections

The most likely cause depends on the timing of the thrombocytopenia and the gestation and clinical status of the neonate.

<u>If after 72 hours of life</u>, the most likely cause is sepsis or NEC.

<u>If <72 hours of life</u>, assess the clinical status of the infant in combination with the level of thrombocytopenia:

➢ If platelets 50 -150 $x10^9$/L and baby well

- If >100, in general just repeat leaving a period for recovery

- If preterm infant, particularly if history of maternal PIH or placental insufficiency: observe, repeat platelet count at 10 days

  -If repeat count is normal, no further action is required

  -If repeat count remains <150 $x10^9$/L consider immune causes and congenital infection.

- If term infant: consider immune thrombocytopenia (e.g. NAIT, ITP, SLE) but only investigate following discussion with NICU Consultant and Haematology.

➢ If platelets 50 - 150 $x10^9$/L and baby unwell

- Think sepsis, consider septic screen and appropriate antibiotic therapy

- Check a coagulation profile

- Only consider immune causes if septic screen negative and platelets fail to normalise and no other cause identified

➢ If platelets < 50 $x10^9$/L or there is active bleeding with platelets 50-100 $x10^9$/L

- Check a coagulation profile

- Exclude sepsis +/- DIC

- Exclude immune thrombocytopenia (e.g. NAIT, ITP, SLE) following discussion with NICU Consultant and Haematology

- Exclude congenital infection (i.e. TORCH screen)

Management

- Treat underlying disease
- Indications for platelet transfusion

Neonatal Alloimmune Thrombocytopenia:

- This is analogous to Rhesus haemolytic disease and is caused by transplacental passage of maternal alloantibodies directed against fetal platelet antigens, inherited from father but absent in mothers.
- Majority caused by antibodies against platelet antigens, HPA-1a (80%) and HPA-5b (10-15%)
- Can present in a first pregnancy.
- Thrombocytopenia can develop in utero as early as 20 weeks.
- Common presentation is unexplained thrombocytopenia in a well neonate with no history of maternal thrombocytopenia.
- 20% associated with intracranial haemorrhage (intraventricular, periventricular or parenchymal haemorrhages), of which 75% occur in utero, so important to carry out cranial USS on all newborns with suspected NAIT irrespective of symptoms as intracranial haemorrhage would lead to a higher target platelet count of 100 $x10^9$/L.
- Platelet count generally returns to normal by 2-4 weeks (although can rarely remain low for up to 12 weeks)

Who to test:

- If platelets < $50x10^9$/L on two free flowing venous samples
- Always consider in term neonates that are otherwise well

Diagnosis:

- Identification of maternal platelet alloantibodies to paternally inherited antigens in the newborn
- In suspected cases discuss with Neonatal Consultant and BTS duty doctor, RIE to arrange testing prior to sending bloods.
- Bloods needed:
    - 5ml EDTA (adult pink or blue top) and 10ml clotted blood (adult white top) from Mother.
    - One EDTA bottle (paediatric pink or blue top, as full as possible) from Baby, ideally sent at the same time as the maternal sample.
    - 5ml EDTA (adult pink top) from Father **ONLY** if not bleeding the baby.
- Use “Histocompatibility and Platelet Immunohaematology form” shown below which can be found under the usual BTS forms in duty room filing cabinet.
- The additional requested FNAIT form is available on the intranet on the following link: http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/AdminDocs/Documents/FNAIT%20Request%20Form.pdf
- Send to tissue typing lab via BTS within working hours (before 1pm).
- Depending on initial results, further samples may be requested from both parents.
- NB – Father is bled as a surrogate for baby therefore need to be confident re paternity and this should be confirmed by confidential discussion with Mother.

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE
HISTOCOMPATIBILITY AND PLATELET IMMUNOHAEMATOLOGY
ROYAL INFIRMARY, LITTLE FRANCE CRESCENT, EDINBURGH, EH16 4SA
Tel: 0131 242 7528 Fax: 0131 242 7530
http://www.scotblood.co.uk/about-us/publications

NHS National Services Scotland

Lab hours: Monday to Friday 0830-1700hrs

Request forms and samples not labelled in accordance with SNBTS sample acceptance policy may not be tested (see reverse of form)

Patient / donor information
Hospital / CHI no:
Surname:
Forename (in full):
DOB: M/F
Hospital / ward:
Clinical condition:

Requesting clinician:
Contact details (bleep no./ ext):
Sample taken by:
Date and time:
Routine / urgent*
Risk of infection: Yes/No
Please contact lab directly if result is required urgently

Solid organ transplant (including islets)
Initial / confirmatory HLA type:
6ml EDTA ☐
HLA antibody screen (inc. DSA investigation):
10ml clotted ☐
Initial (Virtual) crossmatch:
10ml EDTA (donor) ☐
10ml EDTA and 10ml clotted (recipient) ☐
Final "wet" crossmatch*:
(by prior arrangement only)
40ml EDTA (donor) ☐
40ml EDTA and 10ml clotted (recipient) ☐
*Please complete one request form for donor and one for recipient

Haematology
6ml EDTA + 10ml clotted ☐
(HLA A,B,C type and antibody investigation)

Platelet refractoriness / HIT / FNAIT
ALL SAMPLES MUST BE HANDWRITTEN
All tests must be arranged via BTS duty haematologist (Daytime #2218 / OOH - switchboard)

Platelet refractoriness:
6ml EDTA + 10ml clotted (HLA/HPA type and antibody investigation) ☐

HIT screen:
4T score:_____
10ml clotted + vial of patient's heparin ☐

FNAIT investigations:
(also complete FNAIT form available on NHS Lothian intranet)
Mother: 6ml EDTA + 10ml clotted ☐
Child*: 6ml EDTA ☐
*Smaller sample volume for paediatric patients by arrangement
Father (if required): 6ml EDTA ☐

Disease association testing
All 5ml EDTA
HLA B27 ☐
Narcolepsy ☐
Coeliac ☐
HLA B*57:01 ☐
Other – please specify ☐
.....

Lab use only
Date / time received:
Accepted by:
Registered by:
Archive location(s):
Serum - S
DNA - D

Management:

- Whilst thrombocytopenic neonate is at high risk of bleeding, particularly ICH.
- Discuss management with BTS doctor - options include
    - Empirical transfusion of HPA 1a/5b negative platelets before the results of HPA antibodies are available – such platelets may be available "on the shelf", however, access may be difficult out of hours, so important to request these early if there is probable NAIT.
    - Transfusion of antigen negative platelets according to anti-HPA results.
    - If above not available, transfusion of random donor platelets +/- intravenous immunoglobulin (if have had >2 platelet transfusions)
    - Transfusion of washed maternal platelets (very rarely indicated)
- Diagnosis is important for the management of future pregnancies and future transfusions of the mother. Further counselling will be undertaken by a BTS and Obstetric Consultant. A formal referral should be made to the BTS Consultant, with a copy to the Mother's Obstetrician, that includes:

    1. Baby's history including gestation
    2. Copy of the badger discharge summary if on NNU or a discharge letter if on PNW
    3. Results of the CrUSS
    4. Other possible causes
    5. Documentation that the parents have been told of the reason for the BTS referral (i.e. this discussion must have taken place)
    6. Name of Neonatal Consultant

Neonatal Autoimmune Thrombocytopenia:

- Transplacental passage of maternal platelet autoantibodies in mothers with idiopathic thrombocytopenic purpura or systemic lupus erythematosus may cause neonatal autoimmune thrombocytopenia in about 10% of cases.
- Newborn thrombocytopenia is difficult to predict because newborn platelet counts do not always correlate with maternal platelet counts or antiplatelet antibody titres, but the clinical manifestations are less severe than in NAIT, and the risk of intracranial haemorrhage is ≤1%.
- If available, there is better a correlation to the platelet count of previous siblings at birth.
- However, all neonates of mothers with autoimmune disease should have a cord blood platelet count determined at birth and neonatal sample at 24 hours.
- In thrombocytopenic neonates, the platelet count should be repeated daily for the next three to four days, as platelet counts are commonly at their lowest during this time before rising spontaneously by day 7.
- IVIg may be considered to increase platelet count if $<50 \times 10^9/l$

Indication for platelet transfusion:

See indications for platelet transfusion in use of blood products guidance for when to consider platelet transfusion.

Appendix 1: Fetal and neonatal causes of thrombocytopenia

Fetal and neonatal causes of thrombocytopenia	
Fetal	**Alloimmune** **Congenital infection** (e.g. CMV,toxoplasma, rubella, HIV) **Aneuploidy** (e.g. trisomies 18, 13, 21, or triploidy) **Autoimmune** (e.g. ITP, SLE) Severe Rh haemolytic disease Congenital/inherited (e.g. Wiskott-Aldrich syndrome)
Early onset neonatal **(<72 hours)**	**Placental insufficiency** (e.g. PET, IUGR, diabetes) **Perinatal asphyxia** **Perinatal infection** (e.g. E coli, GBS, Haemophilus influenzae) **DIC** **Alloimmune**, i.e. neonatal alloimmune thrombocytopenia (NAIT) **Autoimmune** (e.g. ITP, SLE) Congenital infection (e.g. CMV, toxoplasma, rubella, HIV) Thrombosis (e.g. aortic, renal vein) Bone marrow replacement (e.g. congenital leukaemia) Kasabach-Merritt syndrome Metabolic disease (e.g. proprionic and methylmalonic acidaemia) Congenital/inherited (e.g. thrombocytopaenia absent radii syndrome (TAR) or congenital amegakaryocytic thrombocytopenia (CAMT))
Late onset neonatal **(>72 hours)**	**Late onset sepsis** **NEC** Congenital infection (e.g. CMV, toxoplasma, rubella, HIV) Autoimmune Kasabach-Merritt syndrome Metabolic disease (e.g. proprionic and methylmalonic acidaemia) Congenital inherited (e.g. thrombocytopenia absent radii syndrome (TAR) or congenital amegakaryocytic thrombocytopenia (CAMT))

Most cases of thrombocytopenia in babies admitted to NNU are discovered “incidentally”. The majority are preterm neonates and most (75–90%) will develop early onset thrombocytopenia because of placental insufficiency/fetal hypoxia and subsequent impaired platelet production. This thrombocytopenia has a remarkably consistent pattern with a platelet nadir around day 4 and resolution by 7–10 days of life. In these cases precipitous falls in platelet count are uncommon, and the platelet nadir rarely falls below 50x $x10^9$/L.

By contrast, severe early thrombocytopenia (platelets < $50x10^9$/L) at < 72 hours of life is much less common and occurs in term as well as preterm infants. The mechanism behind this process is normally increased platelet consumption and sequestration and the usual causes are severe perinatal infections (i.e. GBS, E.coli), perinatal asphyxia, or in the well term baby the diagnosis of neonatal alloimmune thrombocytopenia (NAIT) must always be considered.

It is important to remember that many neonates may develop thrombocytopenia as a result of multiple mechanisms, for example a preterm neonate who develops NEC may initially be thrombocytopenic as a result of underlying impaired platelet production (secondary to intrauterine growth restriction) and then become rapidly increasingly thrombocytopenic due to platelet consumption during sepsis. Subsequently these infants will have a slow recovery phase again due to their underlying impaired platelet production. Therefore it is important to always reconsider the cause of thrombocytopenia if a baby with slowly evolving thrombocytopenia thought to be secondary to IUGR or placental insufficiency counts drop suddenly.