HAEMATOLOGY

Guidelines on Transfusion and Anaemia of Prematurity

Samples required for cross-match

Mother: ABO & Rh (D) group antibody screen
10 ml clotted sample

Baby: ABO & Rh (D) group direct antiglobulin test
1 ml clotted sample (minimum)

Please note that all samples and request forms must contain handwritten surname, forename and hospital number. If maternal sample not available, send 1 ml clotted sample from the baby.

If these tests are negative, cross-match prior to transfusion is a not required in infant less 4 months of age. A sticker will be placed on the baby's notes.

If either of these tests are positive, cross-match is required for each blood transfusion. Send blood sample from mother or baby.

If it is anticipated that the baby will need multiple transfusions, mark this clearly on the initial request form - "baby for multiple transfusions". In these cases, blood from a single donor will be divided into mini packs for that baby to reduce exposure to multiple donors as much as possible.

Red Blood Cell transfusion

The usual blood group for blood transfusion will be **0 Rh negative.**

Blood for top up transfusion may be up to 35 days old.

From October 1999 the blood supplied is leuco-depleted and therefore CMV negative, and plasma reduced to give a PCV less than 70 %.

Calculation of volume to be transfused: **15 - 20ml/kg** (body weight) transfused over **3-4 hours under close monitoring.**

The volume of blood infused should be considered as extra to the baby's normal fluid requirements. If babies are hypotensive then blood can be transfused more rapidly (see chapter on circulation and hypotension).

Indications for transfusion

Anaemia

There is a physiological decline of haemoglobin after birth, even in term babies. The decline continues for at least 6-8 weeks until the bone marrow is able to replace the fetal haemoglobin with adult type haemoglobin.
A major course of anaemia is due to the relatively large blood volumes taken from the premature infant in intensive care. This is most significant in infants with birth weights of < 750 g in the first week of life.

Guidelines for Red Blood Cell transfusion threshold for preterm neonates:

Before deciding on the need of a blood transfusion for a baby, the following points should taken into consideration. The decision should not be made on haemoglobin threshold levels alone.

Clinical signs of anaemia

Tachycardia
Tachypnoea
Increased number of apnoeas
Increased number of desaturations
Poor microcirculation
Failure to thrive when fed on sufficient amount of calories (e.g. > 90 – 100 kcal/kgBW/day)

Level of ventilatory support

Level/type of ventilatory requirement
Level of supplemental oxygen may influence the decision to transfuse.

Low haemoglobin level

See table

Reticulocyte count

The reticulocyte count may help in determining the level of bone marrow response and activity. It may be possible to hold off a transfusion if there is a good response (e.g. reticulocyte counts > 10% or else ask for absolute reticulocyte count number e.g. > 100 would indicate an active bone marrow)

Haemoglobin Transfusion Algorithm		
	Resp Support	**No Resp Support**
Age	Haemoglobin g/dl	
Week 1	**11.5**	**10.0**
Week 2	**10.0**	**8.5**
Week 3+	**8.5**	**7.5**

Other haemoglobin thresholds for individual babies will be defined by the attending consultant, if the condition of the baby warrants this. Reasons for transfusions outside the guidelines should be documented in the babies clinical notes.

Other preventative measurements for Anaemia of Prematurity

(for all preterm infants less than 37 weeks gestation)

Possible steps to minimise blood volumes taken:

Rationalisation of blood taking. Decide on the necessary tests on the afternoon handover ward round.
Use of gas machine for haemoglobin and electrolytes and lactate measurement
More regular communication with the laboratory staff with regard to any problems with processing of samples

Protein and Nutrition

When treatment of a preterm infant is initiated, make sure that special attention is paid to nutrition. Protein supplement of 2.5-3.5 g/kg/day should be achieved as soon as possible. This protein is needed for the creation of new red blood cells.

Iron requirements

Iron supplementation is an important nutritional requirement for building up new red blood cells, as it is going to take time to work. Iron supplementation should be started at 7 - 10 days of age if oral feeds of 5 ml/kg/feed are tolerated.
Starting dose is 6 mg/kg/day (= 1.1 ml/kg of Sytron) if oral feeds are tolerated. Iron should not be stopped if a blood transfusion is given. The iron supplementation should be given irrespective of the kind of milk feeds.

Once a baby reaches **36 weeks** corrected age, sytron will be changed to 1 ml OD daily inorder to prepare the baby for discharge. It is recommended in the discharge letter to the GP that the baby should continue on this medication until one year of age.

Studies show that a higher supplementation of protein and iron together can increase endogenous production of new red blood cell without using rh-EPO.

rh-EPO (recombinant Epoetin beta)

Large number of studies have been performed to evaluate the use of rh-EPO (neo-recormon) in preterm infants. It takes about two weeks to act efficiently. rh-EPO (neo-recormon) is very costly and therefore is currently not routinely used on our unit. The decision for use will be made by the Consultant in specific cases. (eg. certain haemolytic diseases and babies of parents who are Jehovah's Witnesses)

Dose of rh-EPO

250 I.U./kg/dose alternate days, subcutaneously.

Please note that the rh-EPO can only work if the baby has got sufficient supplementation with protein and especially iron. The iron supplementation should be 6 mg/kg/day and may need to be increased.

Monitoring should be with measurement of transferrin receptor every 1-2 weeks. If the transferrin receptor is > 2.8 mg/l, then the iron intake should be increased up to 12 mg/kg/day.

Special cases

If there is a risk of congenital immune deficiency, ensure that blood is irradiated before use to prevent graft versus host disease. This will involve a delay of several hours, especially at weekends.

Emergency Blood
IS AVAILABLE IN THE THEATRE FRIDGE ON LEVEL 5

There is an 0 negative, CMV negative, paediatric unit (approx 50 ml).
There is also an 0 negative, CMV negative adult unit of packed cells (approx 200 ml).
The units will be changed regularly by the haematology department.

Emergency blood should only be used if there is no alternative.

Procedure for use

If it is suspected that a baby who is about to be born has lost significant blood volume, contact Transfusion immediately to make a unit of blood for a neonate available.
Send a porter with specific instructions to get blood for the baby from Transfusion.

In most instances, blood can be on Level 13 with 20 minutes.

If there is going to be a delay in Transfusion supplying the blood, or if 20 minutes is considered too long to wait, send the porter with specific instructions to get blood for the baby from the blood fridge on level 5.

Very occasionally, a baby will need a large volume transfusion without any warning, e.g. snapped umbilical cord, arterial line disconnection. In this case, an adult emergency unit of packed cells (0 neg, Kell neg, CMV neg) is also available in the fridge on level 5. The porter should be asked to get either the paediatric unit (50 ml) **OR** the adult unit **OR** both.

On most occasions the blood will not be used, so ensure that the blood is returned to the blood fridge with minimum delay, recording that the blood has been out of the fridge. 30 mins is the maximum time blood may be out of the fridge before it must be discarded. If used, the accompanying form must be completed with the baby's name, hospital number and blood unit number, and then returned to the Transfusion Department.

Exchange transfusion

The blood for exchange transfusion should be plasma reduced, irradiated and less than 5 days old.

NOTE: This is not kept at RSCH and must be ordered from South Thames Blood Transfusion Service, Tooting. Give as much notice as possible, in particular, when

expecting babies with severe rhesus haemolytic disease. Blood should be used within 24 hours.

References

Bechensteen AG et al.: Erythropoietin, protein and iron supplementation and the prevention of anaemia of prematurity. Arch Dis Child 1993; 69:19-23
Feelders RA et al.: Structure, function and clinical significance of transferrin receptors. Clin Chem Lab Med 1997; 3:1052-1057
Kivivuori SM et al.: Oral iron is sufficient for erythropoietin treatment of very low birth weight infants. Eur J Pediatr 1999; 158:147-151

(Up-dated Feb 2005 HR, review Feb 2007)

Neonatal Polycythaemia

Polycythaemia is a relatively common finding in the neonatal period. Only a fraction of these infants however go on to develop overt clinical signs attributable to hyperviscosity. It is therefore necessary to identify an at risk group to ensure that these infants are monitored in order to anticipate the possible problems, in particular the late neurological sequelae.

Infants AT RISK
The following infants are at risk and should always have their haematocrit checked:

Increased erythropoesis	Erythrocyte transfusion
IUGR	Maternal - fetal
Maternal diabetes	Twin - twin
Neonatal thyrotoxicosis	Delayed cord clamping
Cong adrenal hyperplasia	Home delivery
Chromosomal abnormalities	

The Clinical Picture of Polycythaemia
The signs of polycythaemia usually evolve over the first 24 hours as the haematocrit rises with the physiological decrease in plasma volume. At rest these infants may not appear plethoric, but when disturbed they seem flushed or even cyanotic.

Other clinical features include:
lethargy, hypotonia, poor suck, vomiting, irritability when aroused, tremulousness, easily startled, tachypnoea, tachycardia, heart failure, jaundice and hypoglycaemia.

The following may all result from the sludging and formation of microthrombi that occur with the hyperviscosity associated with polycythaemia:

Cerebral vascular occlusion	-	Convulsions and permanent neurological sequelae
Renal vein thrombosis	-	Haematuria, Oliguria
Intestinal vascular occlusion	-	Necrotising enterocolitis
Platelet consumption	-	Thrombocytopenia

Late neurological sequelae described include fits, fine motor and speech abnormalities, spastic diplegia and significant neurodevelopmental abnormalities.

Late manifestations are however very rare in untreated polycythaemic neonates with no or only minor symptoms.

MANAGEMENT OF POLYCYTHAEMIA

All infants in the 'at risk' group should have their haematocrit checked as should any infant felt on clinical grounds to be polycythaemic.

This should be done at about 8 hours of age, unless clinically polycythaemic when it should be done without delay (samples with a high Hct done on admission will act as a guide for those at risk). A capillary haematocrit of > 65% indicates the need for a free flowing venous sample (or a central sample from UAC or UVC). A haematocrit of 65% from any of these sources reflects underlying hyperviscosity. These infants should be carefully examined and these additional tests should be considered:

Ca, SBR and Random Blood Sugar

Those with only mild symptoms can be managed by keeping the infants warm and well hydrated. This is best achieved with intravenous hydration as polycythaemic infants tolerate feeds badly and 'pushing oral feeds' can provoke further problems!

Infants with a venous haematocrit of 65% - 70% should be considered for partial exchange depending on symptoms. An haematocrit of 70% is usually a definite indication - **discuss with Consultant!**

Management continued
Those with significant symptoms should undergo partial exchange with saline 0.9% (or occasionally FFP) to bring the haematocrit down to a safe level of about 55%.

THIS SHOULD ONLY BE DONE AFTER DISCUSSION WITH THE CONSULTANT!

This formula is used:

$$\text{Volume to be exchanged} = \text{Total blood volume} \times \frac{\text{(observed Hct - desired Hct)}}{\text{observed Hct}}$$

e.g. 3 kg infant with Hct of 70%
Blood volume = 80 ml/kg = 240 ml

$$51 \text{ ml} = 240 \text{ a } \frac{(70-55)}{70}$$

The exchange is performed in 10 ml aliquots (smaller aliquots of 5 ml may be necessary in VLBW infants, although polycythaemia is rare in this group). This is ideally done through peripheral lines as there is an increased risk of necrotising enterocolitis in polycythaemic infants.
Keep a record of volume of blood removed and 0.9% saline given as you carry out the dilution exchange to keep track of the volume. This procedure usually takes about 30 mins (depending on the volume to be removed and the rate at which it can be withdrawn).

Feeds may be restarted after 12 hours and should be reintroduced slowly (breast milk if possible).

MEASURING THE HAEMATOCRIT
The following affect the viscosity of whole blood

a) deformability of the red cells
b) plasma viscosity
c) haematocrit

The most important in the neonate is the haematocrit.

The haematocrit reaches a maximum at about 8 hours of age and this is therefore the ideal time to measure it. (This allows for the absorption of excess plasma following birth, and the accompanying rise in red cell concentration and blood viscosity). If polycythaemia is clinically suspected before this then there is no need to wait, do a haematocrit immediately, it will get higher the longer you wait!

Below a haematocrit of 65%, the relationship between viscosity and haematocrit is almost linear. However, above this level there is an exponential rise in viscosity. The blood of all infants with a central venous haematocrit of over 65% can be shown on in vitro testing to be hyperviscous; in contrast it is never demonstrated with a haematocrit of less than 60%.

Peripheral venous samples give a higher haematocrit than central (umbilical) samples, thus there is a tendency to over diagnose the problem if these samples are routinely used. Capillary samples are even higher, hence the recommendation that a high capillary result is checked with a free flowing venous sample.

Measuring Haematocrit continued
There is no significant difference in haematocrit between umbilical venous and arterial samples.

The ONLY recommended method of measuring the haematocrit is by microcentrifugation. The sample should be spun for at least 5 minutes.

It is possible to derive a value using measurements from the coulter counter on the FBC request. Various inaccuracies (in particular in the MCV resulting from the poor deformability of neonatal erythrocytes) lead the calculated value to be significantly lower than the venous haematocrit and for this reason it should not be relied on.

Neonatal Haemostasis
Many of the procoagulants, anticoagulants and proteins involved are gestation dependent. Although this does not usually cause problems in the healthy neonate, it may contribute to morbidity in the sick and pre-term infant. Different factors show different patterns of postnatal maturation and most achieve adult levels by six months.

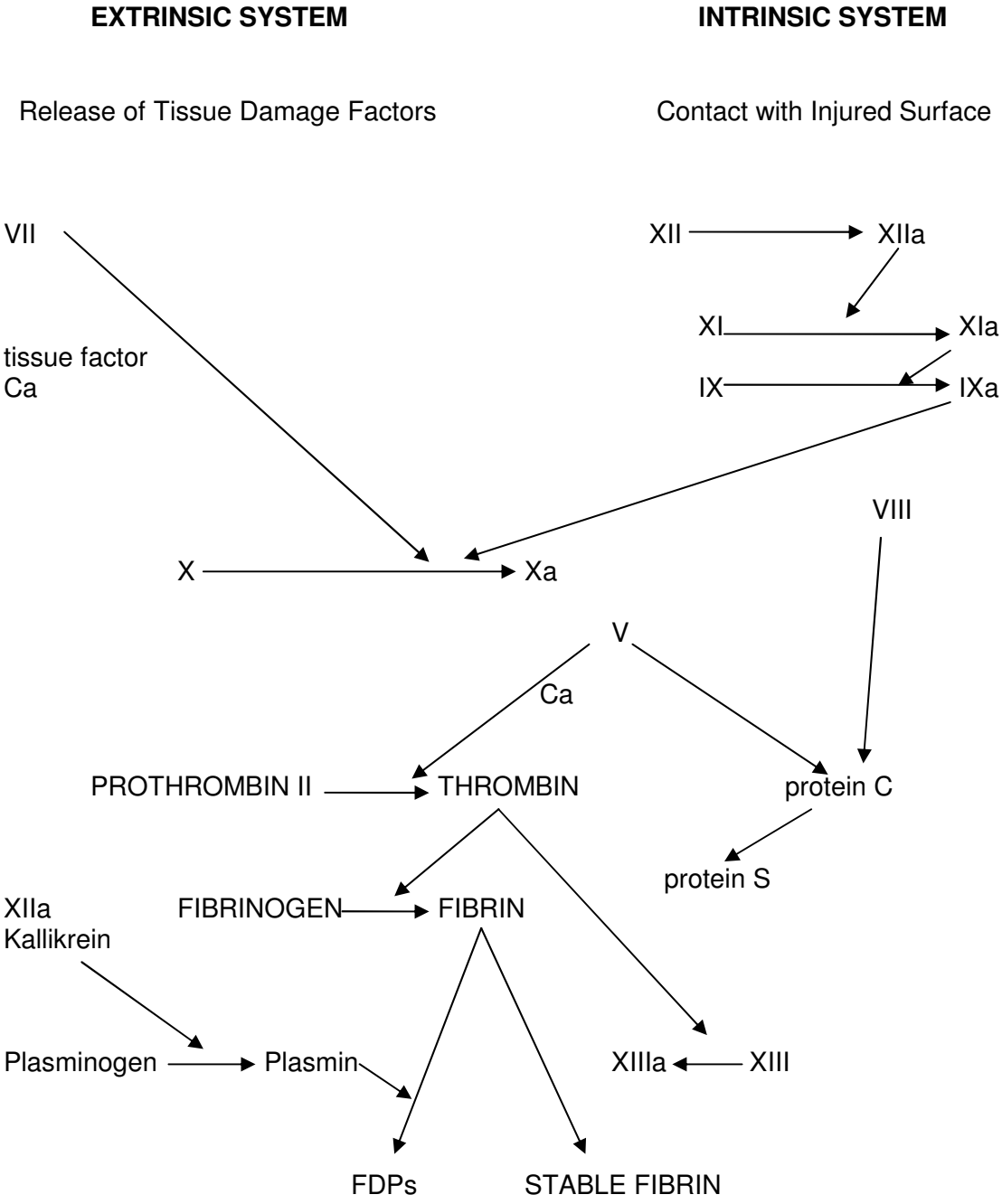
The Coagulation Tests
Use a green top bottle (fill to line - 1.3 mls)
(In exceptional circumstances the lab can make up a special small tube - discuss with lab!)
INR (PT) tests the competence of Factors 11, V11 and X (Vit K Dependent) 1, V, and Fibrinogen.
APTR (APPT) tests the competence of V111, 1X, X, X1, X11, Prekallikrein
Fibrinogen levels are reduced in DIC
FDP's (known as XDPs in SGH lab) result from the breakdown of fibrinogen. These may be increased in many conditions affecting sick neonates as any trauma can cause levels to rise. The levels typical of DIC are however much higher (at least a factor of 10-20) than those caused by any trauma, although neonatal normal values have never been established. The adult assay for XDPs become positive at levels of 250 mcg/l; the diagnosis of DIC is not considered until levels are > 1-2000 mcg/l (and typically > 6000mcg/l).

Platelets. Healthy term and pre-term infants have been shown to have values within the adult range.
Neonates should be considered thrombocytopenic if their platelet count if <150 x 109/l. Bleeding time is prolonged in thrombocytopaenia but in practise this is not usually measured in neonates.

<u>PROBLEMS WITH SAMPLES</u>
There are often problems collecting and interpreting samples and results:
Always fill the tubes exactly

Always repeat an abnormal result
A clot in a FBC may result in an apparently low platelet count (ask for a film and repeat)
There are many sources of error from neonates samples e.g. the tiniest bit of heparin in a sample will affect the result - always remove at least 5 ml from any line before taking a sample for clotting analysis and tell the lab where you took the sample from.
N.B. Heparin Filters
The coagulation lab at SGH does not use these (Hepcheck/Hepabsorb) as they are unreliable. Any sample with an abnormal APTR that does not correct with normal plasma can be assumed to be contaminated with heparin without the use of these expensive tests/filters. This can be confirmed by a thrombin/reptilase test. Any sample taken from a heparinised line should clearly be labelled as such.

The Clotting Cascade



Interpreting Coagulation Test Findings

	Platelets	INR	APTR	Fibrinogen	FDPs	Other tests
Haemophilia VIII & IX deficiency	normal	normal	High	normal	normal	Factor assays
von Willebrands	normal numbers but not function i.e. prlonged bleeding time	normal	High	normal	normal	Factor assays
Vitamin K deficiency	normal	high	High	normal	normal	Treatment corrects INR and APTR
Thrombocytopenia e.g. ITP NAIT	low	normal	Normal	normal	normal	Maternal platelet count and antibodies TORCH/septic screen
acute DIC	low	high	High	low	high	Septic screen
chronic DIC	low	may be slightly increased	May be slightly increased	normal/low	unlikely to be in acute DIC range	Chromosomes/ Dysmorphic features IUGR

Thrombocytopenia

The commonest cause of bleeding problems in the neonate is thrombocytopenia. Neonates should be considered thrombocytopenic if their platelet count is <150x10 9/1 (i.e. same as adults).

Thrombocytopenia in neonates has many causes, the commonest are underlined:

Infection
Viral (Rubella, CMV, HSV, HIV)
Bacterial
Toxoplasmosis
Intravascular coagulation problems
DIC
Maternal PET
Hypothermia, Hypoxia, Sepsis, Shock
Rhesus isoimmunisation
NEC
Congenital heart disease
Giant haemangiomata
Chromosomal/Congenital abnormalities
Trisomy 13 & 18
Fanconis anaemia
Thrombocytopaenia absent radii
Immune mediated Immune mediated
Neonatal alloimmune thrombocytopenia (NAIT)
Maternal ITP or SLE
Drug induced
Marrow infiltration
Congenital leukaemia
Neonatal neuroblastoma
Miscellaneous
Ventilation
Drugs
Metabolic disorders (e.g. hyperglycinaemia)
Post exchange transfusion

INVESTIGATION OF THROMBOCYTOPENIA

Repeat FBC and film to confirm count
Thorough examination
Clotting screen to identify DIC
Cultures
CRP
Viral screen (TORCH)
Maternal platelets and platelet antibodies

If it is not clear which group the baby falls into and neonatal allo-immune thrombocytopenia is still being considered, the following blood samples are required for laboratory investigation at the supra regional centre in Cambridge:

Maternal sample	10-20 mls clotted blood for HPA antibody identification 10 mls EDTA blood for HPA typing
Paternal sample	10 mls EDTA blood for platelet cross matching and platelet typing.

MANAGEMENT OF THROMBOCYTOPENIA

The management of thrombocytopenia depends on the cause. Platelet count is most often increased by platelet transfusion. This should be done with ABO compatible/CMV negative platelets, suspended in as small a volume of plasma as possible. In practise a normal unit of platelets (50 mls) is provided, 10 ml/kg is given and the response monitored. Transfusion is advised if platelet count is less than 25 x 10 9 or if the neonate is actively bleeding.
Platelet transfusion to an infant with immune thrombocytopenia are generally ineffective but may be considered in cases of serious haemorrhage. These infants usually require no treatment but may be treated by exchange transfusion, steroids or immunoglobulins.

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)

This may be distinguished from thrombocytopenia caused by maternal ITP as the mother's platelet count is normal. The commonest platelet antigen involved is P1 A1. The mother would in this case be P1 A1 negative causing destruction of infant platelets by anti P1 A1 Antibodies.

The incidence may be as high as 1 in 2-3000. Intracranial haemorrhage is the greatest risk (and may occur in utero) to these infants who are usually otherwise well, although excessive bruising of the presenting part and oozing from the umbilical stump may occur. Definite diagnosis is by detection of specific antibodies in maternal serum and on the infant's platelets.

Treatment may begin prenatally. Not all infants require treatment but should initially be observed. Any platelet transfusions should be with P1 A1 negative platelets. High dose immunoglobulin and exchange transfusion may also be used.

MATERNAL IDIOPATHIC THROMBOCYTOPENIA (and SLE)

Maternal idiopathic thrombocytopenia and SLE may result in thrombocytopenia in the neonate when maternal antiplatelet IgG crosses the placenta. Unlike the mothers of infants with alloimmune thrombocytopenia these mothers will usually be thrombocytopenic themselves (not if splenectomised).

The main difficulty in these cases is predicting which babies will be affected as not all will be thrombocytopenic. There is no correlation between maternal platelet count and the impact of the disease on the fetus. The fetus may be assessed by cordocentesis or fetal scalp capillary sample although this is rarely practiced for the risk of significant fetal haemorrhage is <1%. If the count is <50 x 10 9/l, then the infant may be delivered by LSCS.

Problems may be confined to bruising with jaundice and secondary anaemia or may be as severe as intracranial haemorrhage. The process is self limiting with the platelet count beginning to rise by the third week and becoming normal by 2-3/12.

There is no good evidence to favour any one particular therapy. The guidelines produced by the National Blood Transfusion Service suggesting 2g/kg of IVIG in total are for ITP in children and adults and not in newborns.

Current recommendations are that in infants with platelets <30 x 10 9/l, 1g/kg of IVIG be given as a single dose. If the platelet count remains <30 x 10 9/l by day 5 of life then a further 1g/kg of IVIG may be given.

Platelets should be transfused only if the infant is haemorrhaging , and not routinely.

*exchange transfusion may also be considered.

(updated June 2006 – Rob Bomont)

Neonatal thrombocytopenia: causes and management
Arch. Dis. Child. Fetal Neonatal Ed., Sep 2003; 88: 359 – 364

http://www.transfusionguidelines.org.uk/index.asp?Publication=HTM&Section=9&pageid=8

DIC

Sepsis acidosis and shock are potent provokers of disseminated intravascular coagulation. The relative imbalance between anticoagulants and procoagulants predisposes the neonate (especially the preterm) to DIC. If the provoking factor is removed and the infant is able to replace the consumed factors readily then the processes may not progress. However if acidosis +/- hypoxia continue then full blown DIC results. Diagnosis should be suspected if bleeding from GI tract or haematuria occur or prolonged bleeding from a blood sampling site.

Chronic DIC may be seen in IUGR infants, Rhesus incompatibility and Downs' Syndrome.

DIC is confirmed by:
Thrombocytopenia
Raised INR and APTR
Reduced Fibrinogen <1 g/l
Elevated FDPs
Schistocytes in peripheral blood film

MANAGEMENT OF DIC
The likely precipitating cause should be identified and addressed in the first instance (i.e. hypoxia, acidosis, sepsis)
Management involves the attempted correction of clotting abnormalities in order to control haemorrhage and the maintenance of adequate tissue perfusion with FFP/cryoprecipitate and platelets within the constraints of careful fluid balance. Exchange transfusion may be considered. Heparin is rarely used as major vessel thrombosis is an unusual complication except in the presence of UVCs or UACs.

NB FFP - contains all clotting factors.
Cryoprecipitate - contains factor VIII and fibrinogen.

Haemorrhagic Disease Of The Newborn
(VIT K DEFICIENCY)
This condition results from a deficiency of procoagulant factors II, VII, IX and X. These factors require Vitamin K to allow normal function. Due to immaturity of the biosynthetic hepatic enzyme system these factors are present in low amounts at birth and the situation may be compounded by a deficiency of vitamin K in the early post natal days and weeks.

This deficiency may cause bleeding problems in the neonate - Haemorrhagic Disease of the Newborn.

Haemorrhagic Disease Of The Newborn may present in one of three ways:
Early - within 24 hours
Classic - 2-5 days
Late - after the first month

EARLY

This is associated with severe and sometimes fatal haemorrhage. The group most at risk are breast fed infants or those whose mothers have been on drugs that interfere with fetal Vitamin K metabolism (e.g. anticonvulsants, rifampicin, isoniazid, warfarin). These infants should receive immediate parenteral Vitamin K.

CLASSIC
This presents at 2-5 days usually as bruising or gastrointestinal bleeding. IVH is an uncommon complication. It is this group in particular that routine prophylactic vitamin K is aimed at preventing.

LATE

This is usually the result of a combination of factors including:
no prophylaxis
poor postnatal intake (breast milk is particularly deficient in vitamin K)
condition predisposing to impaired vitamin K absorption.

Infants with chronic diarrhoea, y or oral antibiotic therapy are at risk. Late onset Haemorrhagic Disease of the Newborn may be the presentation of conditions such as cystic fibrosis, biliary atresia and alpha-1-antitrypsin deficiency. An underlying cause should be sought in all cases.

INVESTIGATION
In vitamin K deficiency an otherwise healthy (if bruised) infant will have:
Prolonged INR and APTR
Normal platelets
Normal fibrinogen
The INR and APTR will improve following vitamin K treatment.

There are more sophisticated tests including functional factor assays and immunological assays that can be used to investigate Haemorrhagic Disease of the Newborn but in practise these are not helpful.

PREVENTION OF HAEMORRHAGIC DISEASE OF THE NEWBORN

Babies at particular risk are:

Preterm infants
Neonates requiring surgery
Infants of mothers on anticonvulsant treatment
Infants admitted to NNU
Infants born by traumatic delivery
Infants in whom onset of feeds is delayed
Infants with obstructive jaundice
Infants with bleeding in the neonatal period

All babies should receive vitamin K to prevent haemorrhagic disease of the newborn and young infant. The guidelines are in accordance with recommendations drawn up by the SE Thames Regional Perinatal Monitoring Group see below.

Inherited Clotting Disorders

Haemophilia A (factor VIII)
Incidence is 1 in 10,000 newborns; <10% present with neonatal bleeding problems.

Can be diagnosed on cord blood as normally present in adult levels in neonates. If treatment is necessary then factor VIII concentrate is given.

Haemophilia B (Factor IX)
1 in 30,000 Classed according to functional Factor IX. Difficult to diagnose in the neonatal period as Factor IX is Vitamin K dependent and is therefore present at low levels at birth.

Von Willebrands
This is characterised by a lack of von Willebrands Factor (vWF) causing platelet dysfunction and sometimes factor VIII deficiency. It is probably the most common inherited disorder affecting haemostasis. It is a heterogeneous condition and its diagnosis in the neonatal period is difficult. This mainly because vWF acts as an acute phase reactant and levels are markedly elevated in the early post natal period in term and preterm infants.

Thrombosis In Neonates
This is a very unusual problem, usually related to the use of lines (both venous and arterial, central and peripheral) and as a feature of severe DIC. Renal vein thrombosis is a particular problems, hypertension and haematuria being the clinical clues to its occurrence.
Polycythaemia is a risk for thrombotic events (see guidelines for treatment).
Infants of diabetic mothers may also be at risk.
Any imbalance between activators and inhibitors of either fibrinolysis or coagulation may predisopose towards thrombosis. Although there seems to be a physiological reduction in natural anticoagulants in neonates this does not seem to contribute to an increased tendency to thrombosis.
There are also some rare with anticoagulant deficiencies e.g. Protein C, that may manifest themselves as neonatal thrombosis.

INVESTIGATIONS
Apart from the exclusion of polycythaemia and sepsis the investigations involve the search for rarities such as protein C and S deficiencies. Accurate diagnosis of heterozygote states of these factors is very difficult as they are present in reduced levels in the normal neonate.

PROTEIN C
This is a vitamin K dependent anticoagulant. It is present in reduced amounts in the normal neonate. It acts by destroying activated factors V and VIII and enhances fibrinolysis. This action is enhanced by protein S which acts as a cofactor.
Protein C deficiency is inherited as an autosomal dominant trait. This appears to cause no predisposition to venous thrombosis until young adulthood. The homozygotic state however presents as fulminant thrombosis in the neonatal period.

PROTEIN S
This is also vitamin K dependent and therefore reduced in the normal neonate.

ANTITHROMBIN III
This is present in about 50% adult levels in the term infant. These levels would be associated with a risk of thrombosis in an adult, but even in congenital anti thrombin III deficiency thrombosis is rare in neonates.

ALPHA-2 MACROGLOBULIN

Levels are above adult range. This may play a protective role against thrombosis at a time when all other anticoagulants are physiologically at low levels.

MANAGEMENT

This involves the removal of any central lines although the need for access must be considered. Anticoagulant therapy, thrombolytic drugs and surgery have all been used in the management of thrombosis depending on the clinical problem.

Vitamin K

1) Normal Term Babies

1. All newborn infants are to be given vitamin K as soon as possible after birth (within 24 hours).

2. Vitamin K will be given as Konakion, 1 mg IM.

3. Parents give consent to this policy during the ante natal period so that they have time to ask questions and read the information sheet that is available.

4. When parents wish for their baby to have oral vitamin K, this must be documented on the obstetric notes.

5. The regimen for oral vitamin K is first dose 2 mg Konakion MM at birth, second dose 2 mg Konakion MM at one week, third dose 2 mg Konakion MM at 6 weeks PO in breastfed babies only..

6. The first dose is given in hospital but the second and third will be given by the community midwife and health visitors via a prescription from the G.P. The prescription should be obtained and the Konakion should be obtained before the birth of the baby. The prescription is as follows:

   2 mgs Konakion MM orally to be given at birth at
   1 week and at 6 weeks of age.

2) Babies at particular risk should receive parenteral vitamin K:

Babies born prematurely (<35 completed weeks gestation)
Babies who require surgery in the neonatal period
Babies who have delayed onset of oral feeds due to illness
Babies admitted to the neonatal unit whose medical condition places them at increased risk of bleeding e.g. sepsis
Babies who develop bleeding in the neonatal period
Babies with obstructive jaundice
Babies of mothers who have been on medication known to interfere with vitamin K metabolism, e.g. Phenytoin and Phenobarbitone
Consideration should be given to supplementing such mothers with vitamin K before the expected delivery date

The recommended parenteral dose of vitamin K is:

Weight >1.5 kg dose = 0.5 mg

Weight < 1.5 kg dose = 0.25 mg

3) Babies who have received oral vitamin K in the neonatal period and are subsequently diagnosed as having a condition affecting liver function or absorption from the gastrointestinal tract e.g. alpha-1 antitrypsin deficiency, cystic fibrosis should receive further vitamin K supplementation.

4) Babies who are solely breast fed and suffer a protracted bout of diarrhoea or are prescribed repeated courses of antibiotics should receive further vitamin K supplementation.

5)Babies who are solely breast fed and require surgery should receive further vitamin K supplementation prior to surgery.

The following points should be noted:

1) Bleeding in the neonatal period may be due to, or may be exacerbated by, vitamin K deficiency. In addition to any other therapeutic and investigative measures such babies should receive parenteral vitamin K.

2) The above policy has been reached using currently available information and takes into account currently available vitamin K preparations. Further changes may therefore be needed in the light of future developments or advice from National bodies.
This is believed to be a safe policy but there is a need for increased awareness among professionals involved in caring for babies of Haemorrhagic Disease of the Newborn.

Bleeding should always be considered a serious symptom in babies and arrangements made for prompt Paediatric assessment and treatment as indicated.

Screening for prothrombotic disorders

Incidence of neonatal thromboses:
Thrombotic events are rare but serious complications in babies receiving intensive care. Two prospective studies of thromboembolism in the neonatal period report 2.4 clinically apparent thromboses per 1000 admissions to intensive care and 5.1 symptomatic thromboses per 100 000 births.[1,2] The incidence of symptomatic thrombosis is probably greater in the neonatal period than in childhood especially in the sick preterm neonate with central vascular catheters.[1] It is likely that neonatal thrombosis is under diagnosed and may become more common with increasing intensive care trearments.[3]

No large multicentre prospective randomised trials are available to guide evaluation and therapy of neonatal thrombosis. In particular the role of inherited factors predisposing to thrombophilia in neonates remains unclear.[1,4,5,6,7] However, in view of the risk of repeat thrombotic episodes and the possibility of other family members being affected prothrombotic disorders should be actively sought in appropriate cases.

Who do we investigate?

The following clinical indicators may alert you to possible candidates for investigation:

Platelet consumption, catheter related problems, cool pale limb (arterial thrombosis), hypertension and anuria (renal artery thrombosis), oedema of body parts eg head and upper limbs (SVC obstruction), haematuria and flank mass (RVT), chylothorax (SVC obstruction), seizures / neurological signs (cerebral sinus thrombosis, intracerebral haemorrhage or infarction), dermal vascular thromboses (purpura fulminans, rare but treatable acutely therefore important to recognise).

Screening should be confined to infants with:

- **objectively documented venous or arterial thrombosis or purpura fulminans.[8]**
- **documented venous sinus thrombosis, focal intracerebral haemorrhage or infarction in a vascular territory[9]**
- **an unusual pattern of intracranial haemorrhage (eg term infants with an intraventricular bleed)**
- **unexplained bleeding / petechiae**

Objective confirmation can almost always be gained in cases of symptomatic thrombosis[1]:

1) Most commonly with ultrasound / doppler
2) Cranial MRI
3) Rarely with angiography when catheter in situ

When should testing be undertaken?
Plasma concentrations and activity of individual clotting factors vary markedly and change from the time of birth throughout the first 6 months of life. Neonatal assessment is possible as reference ranges have been established.[10] However these ranges may not be reliable and early screening is probably only appropriate in cases of purpura fulminans where specific treatment with protein C concentrate may be

beneficial. In other cases screening can wait as therapeutic decisions are made on clinical findings not test results. In any case it may be impossible to obtain sufficient blood for testing, especially from sick premature infants. Investigation should therefore be awaited but not forgotten.
The consequences of screening should be explained, verbal consent gained from parents and documented in the notes. **Beware**, negative results cannot fully exclude a clotting tendency, as further prothrombotic abnormalities are almost sure to be discovered in the future. If a positive finding is made in the index case the whole family will need genetic counselling.

What blood samples should be taken and to whom should they be sent?

- Discuss with Dr Raina Liesner at Great Ormond Street (Phone: 020 7829 8837)
- Alert coagulation laboratory at RSCH (Kevin Crisp or Diane Angus)
- Take blood into four 1.3ml citrated coagulation bottles from each parent and the baby.
- Clearly label samples and take immediately to coagulation laboratory to be double spun
- Send 100 microlitre aliquots of plasma on dry ice, together with the cell fraction by express courier for urgent attention of:

The Coagulation Department,
Camila Botna Laboratories, Hospital for Sick Children,
Great Ormond Street, London WC1N 3JH

- A covering letter should be sent stating the following:

Name / DOB / K No: / Ethnic origin of both parents and baby / Gestational age at birth.
Clinical history including problems of bleeding and thrombosis in the family history,
maternal history, during pregnancy, at birth and in the neonatal period.
Give results of relevant MRI and US investigations and a drug history
For results state the UNIT Consultant and request a copy for Diane Angus (BMS Coagulation RSCH)

- Telephone 020 7829 8837 to inform lab staff that the samples have been sent.

The following tests will be undertaken for the index case and parents[11]
Standard clotting screen and fibrinogen levels
- Antithrombin activity, plasminogen activity
- Factor VIII level, von Willebrand factor antigen
- Protein C and S activities, activated Protein C resistance
- Factor V Liedin gene PCR
- Prothrombin gene PCR
- Methyltetrahydrofolate reductase deficiency (MTHFR), for the thermolabile variant
- Lupus anticoagulant screen (5ml of blood in lithium heparin bottles from mother).

For a complete screen consider measuring a lipoprotein A level.[6,7] Take 1ml of clotted blood and send to St. Georges Hospital via the biochemistry department, RSCH.

All results will be compared with standard postnatal and gestational age reference ranges. Abnormal values should be repeated in several weeks, and family members of neonates whose tests remain abnormal should also undergo testing. Factor V Liedin and prothrombin mutations are genetic tests and positive tests do not need to be repeated although family members should undergo testing.

All patients with positive testing for prothrombotic disorders need long-term follow-up with a paediatric haematologist who is able to counsel the family appropriately.

References:

1 Nowak-GÖttl U, von Kries R, GÖbel U. Neonatal symptomatic thromboembolism in Germany: two-year survey. Archives of disease in childhood 1997; 76: F163-167

2 Schmidt B, Andrew M. Neonatal thrombosis: report of a prospective Canadian and international registry. Pediatrics 1995;96:939-43

3 Evaluation and treatment of thrombosis in the neonatal intensive care unit. Cynthia S. Edstrom, MD, and Robert D. Christensen, MD. Clinics in Perinatology. Volume 27, Number 3, September 2000

4 deVeber G, Monagle P, Chan A, et al: Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurol 55:1539, 1998

5 Hagstrom JN, Walter J, Bluebond-Langner R, et al: Prevalence of the factor V Leiden mutation in children and neonates with thromboembolic disease. J Pediatr 133:777, 1998

6 Nowak-GÖttl U, Debus O, Findeisen M, et al: Lipoprotein (a): Its role in childhood thromboembolism. Pediatrics 99:E11, 1997

7 Nowak-GÖttl U, Dubbers A, Kececioglu D, et al: Factor V Leiden, protein C and lipoprotein (a) in catheter related thrombosis in childhood: A prospective study. J Pediatr 131:608, 1997

8 BPSU protocol for thrombosis in childhood (Age >1 month – 16 years)

9 BPSU protocol for cerebrovascular disease, stroke and stroke-like-illness in childhood thrombosis (at >37 weeks gestation)

10 Andrew M, Vegh P, Johnston M, Bowker J, OfosuF, Mitchell L. Maturation of the hemostatic system during childhood. Blood 80:1998-2005, 1992

11 Mercuri E, Cowan F, Gupte G, Manning R, Laffan M, Rutherford M, Edwards D, Dubowitz L, Roberts I. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 107:1400, 2001

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