Transfusion of Blood Products in Neonatal Unit - Paediatric Full Clinical Guideline - Derby only

Reference no.: NIC NN HA01

Introduction:

A) Blood transfusion:

Haemoglobin (Hb) decreases during the first few weeks of life in all infants usually in the absence of clinical signs or symptoms of anaemia [1,2]. There is considerable controversy about the 'trigger' points for transfusions in preterm babies and this is because the Hb is not a good indicator of the degree of significant anaemia [3], There are significant adverse effects of transfusions [4], therefore transfusions should be limited to the minimum number required for the infants' optimal well-being. It is useful to note however that simple approaches such as reducing the frequency of blood sampling are effective [5].

B) Platelet transfusion:

Normal platelet count for neonates is 150–400 x 10 9/L. Population based studies on cord blood suggest 2% of term infants have a platelet count < 150, and 0.2% have platelets < 50. The natural history of thrombocytopenia in sick infants is very consistent. Platelets fall by day 2 of life in 75% of affected babies, and usually reach their nadir around day 4. By day 10, the platelet count has recovered to normal in 90% of cases.

C) Clotting factors:

Bleeding or thrombosis occurs more frequently in sick infants who are preterm. More rarely, an otherwise healthy infant with a congenital coagulation defect may present clinically in the newborn period

Aim and Scope

To ensure a baby receives a blood transfusion, platelets and clotting factors (fresh frozen plasma (FFP)/ Cryoprecipitate) appropriately and safely.

Summary of contents

A) BLOOD TRANSFUSION:

Indications:

Post natal age	Suggested transfusion threshold Hb (g/L)		
	Ventilated	Oxygen/NIPPV†	Off Oxygen
1st 24 hours	<120	<120	<100
≤ week 1 (day 1-7)	<120	<100	<100
week 2 (day 8 -14) ≥ week 3 (day 15 onwards)	<100	<95 <85	<75*

If transfusions are being considered for the latter category always check reticulocyte count. Avoid transfusion if reticulocytes are >2% (or >100,000/ml) except if symptoms are severe.

Prescription and Administration of Blood Transfusion:

- Blood transfusion can be given either using the formula below or 20mls/kg (whichever is lower in volume).

Required raise in Hb (g/L) x Body weight (kg) x 0.45 = mls packed cells

Required raise = 140 - actual Hb (g/l)

- Blood is transfused over 3.5 hours to ensure the transfusion is completed within four hours of being removed from the fridge. So allowing for 30 mins to collect the blood and check the cannula etc.
- Blood transfusions may be given through peripheral or central lines but not through the arterial or long lines.
- Drugs are never added to blood or blood products. TPN may not be given through the same catheter as a blood transfusion. However, separate lumens of a double lumen catheter may be used for these infusions.
- Feeds are to be discontinued during a transfusion.
- Furosemide is not given routinely as a slow transfusion is well tolerated. Furosemide may be given cautiously (1mg/kg) only when there is a significant risk of fluid overload, e.g. in presence of a PDA/Congenital heart disease/CLD. Where indicated it should be clearly prescribed as a single dose on prescription chart.

a) HAEMOLYTIC TRANSFUSION REACTION:

A hemolytic transfusion reaction is a serious complication that can occur after a blood transfusion. The reaction occurs when the red blood cells that were given during the transfusion are destroyed by the person's immune system. It may present with fever, rigor, utricaria/rash, hypertension/hypotension, tachyc ardia/bradycardia, tachypnoea/apnoea. It may result in acute pulmonary odema and circulatory collapse.

Management:

Urgent action is warranted. However, these are rare may be rare in the neonates, as neonates do not produce its own is agglutinins (anti-A, anti-B)

- Stop the transfusion
- Maintain IV access
- Inform Blood Bank.
- Monitor urine output (catheterise if necessary). Test urine for presence of haemoglobin and urobilinogen.
- Send baseline FBC, Coag (PT/APTT/FIBRINOGEN), U&E's and LFT's.
- Frequent observations should be continued until the patient's condition is stable.
- Take a fresh cross-match sample and send to Blood Bank along with the blood pack and administration set. Also return any empty or unused blood packs to Blood Bank.
- Discuss further management with the on-call Haematology Medical Staff, (who will have already been notified by Blood Bank staff)
- Complete an incident form

B) NEONATAL THROMBOCYTOPENIA

Causes of Thrombocytopenia:

The commonest cause of a falsely low platelet count is a clot in the sample. Repeat if in doubt, especially if capillary sample or difficult peripheral venepuncture.

In an otherwise well term infant, the commonest cause of thrombocytopenia is alloimmune. In a preterm or systemically unwell baby, the commonest cause is sepsis. The causes (common emboldened) of thrombocytopenia are below [34].

Early <72 hours	**Chronic fetal hypoxia**
	Perinatal asphyxia
	Perinatal infection e.g. E.Coli, GBS
	Disseminated intravascular coagulation
	Neonatal alloimmune thrombocytopenia (NAIT)
	Neonatal autoimmune thromobocytopenia (ITP, SLE)
	Congential infection e.g. CMV, toxoplasma, rubella, Coxsackie
	Thrombosis e.g. renal, aortic
	Bone marrow replacement e.g. congenital leukaemia
	Kasabach Merritt syndrome
	Metabolic disease e.g. proprionic and methylmalonic acidaemia
	Chromosomal disorders e.g. T21, T18, T13
	Inherited e.g. congenital amegakaryocytic thrombocytopenia
Late >72 hours	**Late onset sepsis**
	NEC
	Congential infection e.g. CMV, toxoplasma, rubella, Coxsackie
	Autoimmune
	Kasabach Merritt syndrome
	Metabolic disease e.g. proprionic and methylmalonic acidaemia
	Inherited e.g. congenital amegakaryocytic thrombocytopenia

Management of Thrombocytopenia:

- Family history:
  -Affected siblings

- Maternal factors in this pregnancy:
  - Symptoms suggestive of congenital infection
  - Autoimmune disease
  - Platelet count
  - Drugs taken during pregnancy

- Infant factors:

- Is the infant haemorrhagic? (Petechiae, purpura, mucosal bleeding)
- Is the infant dysmorphic?
- Cranial USS should be part of this assessment.

- Symptoms/ signs of current infection
- Congenital anomalies, e.g. TAR, capillary haemangioma
- Central venous catheters

Investigations:

Infants with platelets persistently < 100 should have the following;

- Repeat FBC: confirm low platelets, assess trends in Hb / WCC. Is the platelet count stable or falling?
- Peripheral blood film
- Consider blood cultures (consider starting antibiotics if unwell baby or severe thrombocytopenia).
- Coagulation screen (NB. A coagulation sample reported as 'clotted' reflects an activated sample but not necessarily normal clotting. This sample must be repeated). Fibrinogen should be specifically requested, as they may provide the only sign of low grade DIC and so may explain increased platelet consumption.
- Consider maternal platelet count
- Consider screening for congenital infection

Treatment:

1. Treat the cause

Amount of platelets to be transfused = 10mls/kg over 30min

2. Transfuse if:

a) clinically bleeding and platelet count < 50
b) platelets < 30 in sick term or preterm infant
c) platelets < 30 in NAIT
d) platelets < 20 in well term baby with no clinical bleeding

Very well babies with platelet counts 20 – 50 may be observed rather than given platelets, so long as they have no clinical signs of bleeding (thresholds adapted from ref 37)

SPECIFIC PROBLEMS:

a) <u>NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)</u>

In Caucasian populations the two most common platelet alloantigens are HPA-1a and HPA-5. Severe thrombocytopaenia is most often seen with HPA 1A antibodies. In addition to thrombocytopenia, platelet aggregation is reduced and is antibody- mediated.

Presentation:
-Intracranial haemorrhage (10-30% have antenatal intracranial bleed)

-Obvious petechiae/ mucosal bleeding
-Most often an incidental diagnosis in an otherwise well child with petechial rash.

Treatment:

Transfuse HPA 1a–ve, 5b–ve platelets if platelet count < 30 x109 /L [37].

- Only use HPA-random platelets as a last resort, as they are rapidly consumed
- FBC should be repeated 1hour post-platelet transfusion, as a poor increment may help in diagnosis.
- Babies who are well with severe unexplained thrombocytopenia should be treated (pending serology) as having alloimmune disease.

As 2nd line if HPA1-ve, 5b-ve platelets not available use high dose immunoglobulin with random platelets.

- Give 1g/kg/dose on 2 consecutive days. This is effective in 65% of cases [32]. but there is a significant delay in achieving a 'safe' platelet count compared to platelet transfusion but the evidence is based on case series data.
- Steroids were used historically but there is no evidence to support their use.

b) INFANTS OF MOTHERS WITH LOW PLATELET COUNT

Presentation:
Most infants will be born with a normal platelet count, and will not be affected by the maternal platelet count. 0.5-1.5% will have a low platelet count as a consequence. The highest risk infants are those born to mothers with severe thrombocytopenia, male gender and low birth weight [35]. If there is an immune mediated pathology for maternal low platelet count. For nonimmune mediated thrombocytopenia in mother, cord blood should be takenfor FBC. If the cord platelet count is low, this should be confirmed with a sample from the infant.

Treatment (for non-immune mediated causes):
IM injections should be avoided until the platelet count is known. If thrombocytopenia is confirmed, the blood count should be monitored until platelet counts start to recover.

c) INFANTS OF MOTHERS WITH AUTOIMMUNE ITP [38].

Most mothers with anti-platelet antibodies deliver healthy infants with normal platelet counts. However, maternal antibody will cross react with neonatal platelets and leads to their increased destruction in a minority of babies, incidence varies in studies from 10-29%.

Presentation:

- Most affected infants have normal platelet count at birth.
- Check FBC on cord blood, then at 24 and 48 hours. If platelets are normal at 48 hours, they are unlikely to fall rapidly
- Monitoring can be stopped. In affected babies, the platelet count may not reach its trough until day 5, and typically recover by day 7 to day 14 [36].

Management:

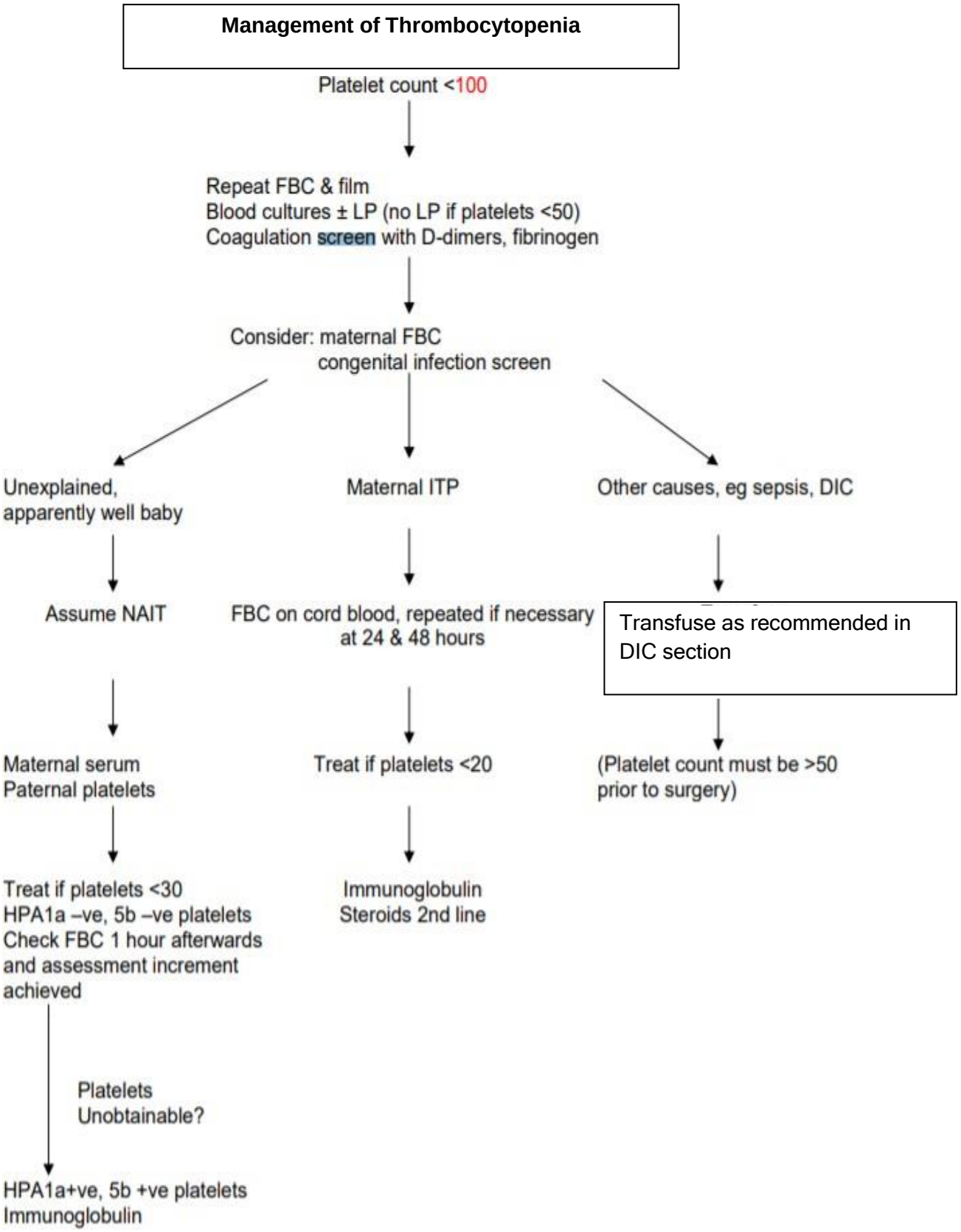
- Cranial ultrasound in those with a platelet count <50
- Neonatal thrombocytopenia secondary to ITP may last for months.

- Severe neonatal thrombocytopenia and bleeding are rare due to maternal so when present NAIT should be excluded.

Treatment:

- Give immunoglobulin 1 g/kg/day for as first line treatment. Shown to have 80% response rate in small studies. Response to immunoglobulin faster than response to steroids. Repeat once if necessary

- Prednisolone 2 mg/kg/day Used alone or with immunoglobulin if no response after 2 days. Unclear whether steroids add to the response from immunoglobulin alone.
- In life-threatening situations, give a double dose of platelet transfusions with immunoglobulin.
- Unfortunately, platelets produce a poor increment and the platelet count rapidly falls back to pre-transfusion levels (this can help support the diagnosis).


Management of Thrombocytopenia
Platelet count <100
Repeat FBC & film
Blood cultures ± LP (no LP if platelets <50)
Coagulation screen with D-dimers, fibrinogen
Consider: maternal FBC
congenital infection screen
Unexplained, apparently well baby
Maternal ITP
Other causes, eg sepsis, DIC
Assume NAIT
FBC on cord blood, repeated if necessary at 24 & 48 hours
Transfuse as recommended in DIC section
Maternal serum
Paternal platelets
Treat if platelets <20
(Platelet count must be >50 prior to surgery)
Treat if platelets <30
HPA1a –ve, 5b –ve platelets
Check FBC 1 hour afterwards and assessment increment achieved
Immunoglobulin
Steroids 2nd line
Platelets Unobtainable?
HPA1a+ve, 5b +ve platelets
Immunoglobulin

C) TRANSFUSION OF CLOTTING FACTORS:

Normal neonatal clotting values:

The newborns' haemostasis system matures during the early weeks and months of life with most parameters reaching adult values by 6 months of age. Although preterm infants show accelerated maturation of clotting and fibrinolytic systems [16,17], they may be unable to compensate when systemically unwell [17,18].

We have used conservative normal ranges [21], based on 5th-95th centiles of 168 neonates, which correlate with the values given in the Neonatal Formulary 7th Edition (see table below), with the exception of the upper limit for APTT.

	<28 weeks	**28-34 weeks**	**36-40 weeks**
PT (sec)	14.5-20.9	13.9-20.6	11-15.8
APTT (sec)	27-64	30-57	25-54.5
Fibrinogen (g/dl)	0.71-5.35	0.87-4.7	2.0-3.99

Indications for Clotting screen testing of newborn infants:

- Haemorrhage i.e. purpura, mucosal bleeding, pulmonary haemorrhage, IVH, prolonged oozing from venepuncture or heelprick site.
- Severe metabolic disease, severe respiratory distress syndrome, liver disease (including hepatic impairment in HIE), or sepsis in the presence of active bleeding or evidence of DIC. There is no increased risk of coagulopathy in infants undergoing neuroprotective hypothermia.
- Unwell infants born to mothers who have received medications that interfere with vitamin K metabolism. These include anticonvulsants (phenytoin, barbiturates or carbamazepam), antitubercular drugs (rifampicin or isoniazid) and vitamin K antagonists (warfarin and phenprocoumarin).
- All neonates undergoing surgery.
- A family history of an inherited bleeding disorder. Discuss appropriate investigations with Haematologist first if antenatal alert plan not already made.

Do not check clotting *routinely* in preterm infants: there is evidence that abnormal clotting values are not predictive of IVH, pulmonary haemorrhage or GI bleeding in the first week of life [21], and that routinely checking clotting values increases the use of FFP and clotting products with no evidence of benefit [25,26].

Interpreting laboratory results in neonatal coagulation disorders: (23)

Condition	PT	APTT	Fibrinigen	Platelets
Vitamin K Deficiency	↑	N/↑	N	N
DIC	↑	↑	↓	↓
Liver disease	↑	↑	N/ ↓	N/ ↓
Haemophilia A	N	↑	N	N
Haemophilia B	N	↑	N	N
VWD	N	↑	N	N

PT *Prothrombin time*

APTT A*ctivated partial thromboplastin time*

N Normal

DIC Disseminated intravascular coagulation;

VWD Von Willebrand disease.

Clinical Problems:

a) VITAMIN K DEFICIENCY:

- Concentration of the vitamin K dependent factors (FII, FVII, FIX, FX) are reduced in the newborn period and are functionally inactive in the absence of Vitamin K.

- *Laboratory findings:* Isolated prolongation of the PT is the earliest laboratory evidence of vitamin K deficiency, followed by prolongation of APTT. The diagnosis is confirmed by correction of these parameters by Vitamin K, or by assay of the specific factors.

Management:

- Any infant suspected of Vitamin K deficiency should receive immediate slow IVVitamin K (1 mg) (to avoid haematoma after IM injection), which will usually result in correction within a few hours.

- In infants who are actively bleeding, FFP 10-15 ml/kg should be given in addition to vitamin K. Subsequent Vitamin K may be required if there is no improvement.

b) DISSEMINATED INTRAVASCULAR COAGULATION (DIC):

- DIC always occurs as a secondary event, and is associated with a number of perinatal and neonatal problems such as birth asphyxia, acidosis, RDS, sepsis, necrotizing enterocolitis (NEC) and meconium aspiration syndrome.

- Intravascular activation of coagulation results in consumption and depletion of coagulation factors, which may be accompanied by capillary microthrombi. Bleeding or rarely thrombosis may occur, along with end organ damage due to ischaemia.
- *Laboratory findings*: Prolonged APTT, PT and TCT. Fibrinogen and platelets are low, with red cell fragmentation on blood film though not always. Raised D-Dimers are a sensitive marker of early DIC but are not routinely monitored.

Management:

- The priority should be to identify and correct the underlying cause and to treathypoxia, acidosis, and hypotension. In compensated low grade DIC, in the absence of *active* bleeding, management of the cause and observation is appropriate [27].

- However, blood product replacement is indicated for the treatment of clinical bleeding in the presence of DIC [17,23,28]:

If fibrinogen <1g/l, give Cryoprecipitate (5-10 ml/kg) which contains a higher concentration of FVIII and Fibrinogen per unit volume than FFP.

If Fibrinogen >1g/l, give FFP (10-15 ml/kg over 30 minutes)

- The indication for requesting cryoprecipitate must be discussed with the Blood bank/on-call haematology consultant**.**
    - If platelet count < 50x 10_9/l, give platelets (10-15 ml/kg)
    - FFP (10-15 ml/kg over 30 minutes) (unless cryoprecipitate and platelets have both been given, since if the cryoprecipitate plus platelets are indicated (as above) there is usually no need to give FFP in addition).
    - Red cell transfusion may be required.

- Further management should be guided by the clinical picture and the repeated clotting screen.

- Careful consideration should be given to the overall volume of fluid being administered to the baby, particularly in pulmonary haemorrhage.

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Documentation Controls

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Training and Dissemination: BU Newsletter				
Development of Guideline: Dr Bala Subramaniam Consultant Paediatrician				
In Consultation with: (Relevant peer review) NICU consultants RDH Consultant Paediatricians RDH and the wider neonatal team.				
Linked Documents: (Nice guidance/Current national guidelines)				
Keywords: (Search term for KOHA)				
Business Unit Sign Off			**Group:** Paediatric Guidelines Group **Date:** 15th May 2023	
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