1. INTRODUCTION

- 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.

- Thrombocytopenia (e.g. platelets <100) should be investigated and may be a symptom of underlying disease.

- 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.

- 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.

- 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.

2. CAUSES OF THROMBOCYTOPENIA

Isolated thrombocytopenia (i.e. normal Hb, WCC and differential) is almost always due to shortened platelet survival. The Causes of neonatal thrombocytopenia can usually be determined by the clinical history and presentation. In particular, the timing of the onset of thrombocytopenia. The causes (common emboldened) of thrombocytopenia are below.
Early <72 hours

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Chronic fetal hypoxia</td>
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<tr>
<td>Perinatal asphyxia</td>
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<tr>
<td>Perinatal infection e.g. E.Coli, GBS</td>
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<td>Disseminated intravascular coagulation</td>
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<tr>
<td>Neonatal alloimmune thrombocytopenia (NAIT)</td>
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<tr>
<td>Neonatal autoimmune thrombocytopenia (ITP, SLE)</td>
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<tr>
<td>Congenital infection e.g. CMV, toxoplasma, rubella, Coxsackie</td>
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<tr>
<td>Thrombosis e.g. renal, aortic</td>
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<td>Bone marrow replacement e.g. congenital leukaemia</td>
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<tr>
<td>Kasabach Merritt syndrome</td>
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<tr>
<td>Metabolic disease e.g. propionic and methylmalonic acidaemia</td>
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<tr>
<td>Chromosomal disorders e.g. T21, T18, T13</td>
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<tr>
<td>Inherited e.g. congenital amegakaryocytic thrombocytopenia</td>
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</tbody>
</table>

Late >72 hours

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Late onset sepsis</td>
</tr>
<tr>
<td>NEC</td>
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<tr>
<td>Congenital infection e.g. CMV, toxoplasma, rubella, Coxsackie</td>
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<tr>
<td>Autoimmune</td>
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<tr>
<td>Kasabach Merritt syndrome</td>
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<tr>
<td>Metabolic disease e.g. propionic and methylmalonic acidaemia</td>
</tr>
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</tr>
</tbody>
</table>

3 MANAGEMENT OF THROMBOCYTOPENIA

3.1 HISTORY AND EXAMINATION

- **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**
3.2 INVESTIGATION

Infants with platelets persistently < 100 should have the following;

1. Repeat FBC: confirm low platelets, assess trends in Hb / WCC. Is the platelet count stable or falling?

2. Peripheral blood film

3. Consider blood cultures (consider starting antibiotics if unwell baby or severe thrombocytopenia). Consider full septic screen. A platelet count <50 or abnormal clotting is a contraindication to lumbar puncture.

4. Coagulation screen (NB. A coagulation sample reported as ‘clotted’ reflects an activated sample but not necessarily normal clotting. This sample must be repeated). D-dimers and fibrinogen should be specifically requested, as they may provide the only sign of low grade DIC and so may explain increased platelet consumption.

5. Consider maternal platelet count

6. Consider screening for congenital infection.

If unexplained thrombocytopenia in baby with no other obvious risk factors;

7. Maternal serum (EDTA and red-top clotted) for anti HPA-1a and anti HPA-5b antibodies, plus sample of platelets from father (EDTA tube) and sent to NBS Bristol, Filton (turn around 5 days). If antibody –ve but strong clinical suspicion, repeat maternal serum sample 2 – 4 weeks later. Treat without waiting for serology results (but they may be relevant for future pregnancies). A sample from the baby and a form completed (Form 3D- Platelet immunology FRM1010 available from here: [http://hospital.blood.co.uk/diagnostic-services/hi/hi-test-request-forms/](http://hospital.blood.co.uk/diagnostic-services/hi/hi-test-request-forms/)) to accompany the samples to blood bank in a transfusion form.

8. Bone marrow aspirate is rarely necessary. It may help in the assessment of persistent severe thrombocytopenia where there is no evidence for peripheral consumption. Discuss with Haematology Consultant.

3.3 TREATMENT

- At any given platelet count, risk of bleeding is increased by a coexisting coagulopathy or a platelet function disorder (e.g. DIC).

- Risk of bleeding also depends on mechanism of thrombocytopenia. Aplastic disorders, though rare, have a greater risk of acute haemorrhage than consumptive thrombocytopenias.

- The significance of moderate thrombocytopenia, (ie. platelets 50 – 100), is controversial. In such cases, low platelets may reflect a sick baby rather than independently altering outcome.

- Prophylactic platelet transfusions for preterm infants with platelets < 150 have been shown not to reduce the incidence or severity of IVH. The exact risk of intracranial haemorrhage in thrombocytopenia is unknown but the following guidelines are based on accepted professional consensus.

- Platelets must be requested from the on-call haematology registrar (out of hours) or the paediatric haematology registrar (in hours) on bleep 780 7166. If there is no paediatric
haematology registrar available during working hours, contact one of the paediatric haematology consultants.

3.3.1 **Treat cause**, e.g. cover for sepsis until cultures –ve

3.3.2 **Transfuse 10 ml/kg platelets if**
   a) clinically bleeding and platelet count < 50
   b) platelets < 50 preoperatively, though a higher threshold may be required for spinal or neurosurgery
   c) platelets < 30 in sick term or preterm infant
   d) platelets < 30 in NAIT
   e) 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 table III in ref. 12).

Bag of platelets should be hung vertically for 10 minutes before transfusion to allow most platelets to settle in the volume being transfused. The bag should then be sampled vertically into the syringe used for administration.

Platelets need to be ABO and Rh compatible but not cross-matched.

In alloimmune disease need to give fully compatible platelets.

In autoimmune disease, platelets of limited value as maternal antibodies also attack transfused donor platelets. However, in acute bleeds an increased dose (15ml/kg) of platelets may be given along with immunoglobulin.

3.3.3. **See sections on alloimmune and autoimmune disease for details on immunoglobulin and steroids.**

4 **SPECIFIC PROBLEMS**

4.1 **NEONATAL ALLOIMMUNE THROMBOCYTOPENIA (NAIT)**

- In Caucasian populations the two most common platelet alloantigens are HPA-1a and HPA-5. Challenge by antigen positive platelets to a mother who is HPA antigen negative will result in generation of anti-HPA antibodies in the maternal circulation which are transferred transplacentally to the fetus causing platelet destruction. About 80% of NAIT is caused by anti-HPA and 15% by anti-HPA 5b antibodies, the remaining cases are caused by other HPA antigen-antibody incompatibilities. Severe thrombocytopenia is most often seen with HPA 1A antibodies.

- In addition to thrombocytopenia, platelet aggregation is reduced and antibody-mediated endothelial damage occurs. This may account for the high incidence of severe bleeding and why a higher transfusion threshold is recommended\textsuperscript{12}.

- Screening is not currently practised, and sensitisation can occur in a first pregnancy.

- In subsequent pregnancies, recurrence risk is 50 or 100% depending on partner’s genotype. Antenatal management is controversial, and should be carried out in a specialist centre.

4.1.1 **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.

4.1.2 **Treatment:**

- 1. **Transfuse HPA 1a–ve, 5b–ve platelets if platelet count < 30 x10\(^9\)/L \textsuperscript{12}**.
- These will be compatible in 95% of cases. Any infant who has been transfused platelets in utero and then needs postnatal transfusion should have irradiated blood products.
Only use **HPA-random platelets** as a last resort, as they are rapidly consumed.

Babies who are well, with mild to moderate thrombocytopenia (>30 in term and > 50 in preterm) can be observed, with daily platelets counts, until they start to rise.

Babies who are well with severe unexplained thrombocytopenia should be treated (pending serology) as having alloimmune disease.

FBC should be repeated **1 hour post-platelet transfusion**, as a poor increment may help in diagnosis. The mean platelet increment following compatible platelets is 116 x10^9/L (range 7207 x10^9/L) and with incompatible platelets is lower (68 x10^9/L) and they have shorter survival. But both strategies result in an acceptable absolute platelet count.

Siblings of a baby previously affected by NAIT should have a platelet count checked on cord blood, at 24 and 48 hours of age.

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

- Give 1 g/kg/dose on 2 consecutive days. This is effective in 65% of cases, 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.

### 4.2 INFANTS OF MOTHERS WITH LOW PLATELET COUNT

There are a significant number of mother’s that will have a low platelet count during pregnancy (4-8%). The causes are numerous, including pre-existing platelet conditions such as ITP/SLE (see below), or pregnancy specific conditions – including gestational thrombocytopenia, pre-eclampsia, HELLP etc.

#### 4.2.1 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. If there is an immune mediated pathology for maternal low platelet count, see section 4.3. For non-immune mediated thrombocytopenia in mother, cord blood should be taken for FBC. If the cord platelet count is low, this should be confirmed with a sample from the infant.

#### 4.2.2 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. Should severe thrombocytopenia ensue, the criteria for transfusion should be followed as per section 3.3.

### 4.3 INFANTS OF MOTHERS WITH AUTOIMMUNE ITP

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%. This can occur in any mother with a history of adult (not childhood) ITP even if her FBC is now normal.

Mothers who have had symptomatic ITP needing treatment have a greater risk of an affected infant (40% risk of thrombocytopenia, <10% risk of significant bleeding). Even in such babies, the morbidity is much less than in alloimmune disease and antenatal haemorrhage is rare.

Maternal and fetal platelet counts do not necessarily correlate. Antenatal steroids or immunoglobulin can be used effectively for maternal reasons, but do not raise neonatal platelet count significantly.

#### 4.3.1 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 so**
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.

4.3.2 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.

No randomised controlled trials on use of immunoglobulin / steroids.

- **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).

SEE FLOW CHART ON NEXT PAGE

REFERENCES:


10. Approach to the newborn who has thrombocytopenia. Wong W, Glader B: Neoreviews 2004; 5, 445-449


Audit Points

- All sick preterm infants with a platelet count <50 receive platelet transfusion
- All babies with a platelet count <50 requiring surgery receive platelets pre-operatively
- No baby with a platelet count <50 has an LP
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

Maternal serum
Paternal platelets

Treat if platelets <30
HPA1a –ve, 5b –ve platelets
Check FBC 1 hour afterwards and assessment increment achieved

Platelets Unobtainable?

HPA1a+ve, 5b +ve platelets
Immunoglobulin

Treat if platelets <30

Immunoglobulin
Steroids 2nd line

Transfuse
According to threshold given in 3.3.2

(Platelet count must be >50 prior to surgery)