Neonatal Thrombocytopenia & Platelet Transfusion – 
An Update

Dr V C Manoj
Assoc Professor & Head
Dept of Neonatology
Jubilee Mission Medical College & Research Institute
Thrissur, Kerala
Scope

1. How good is the **Definition** of Thrombocytopenia in neonates?

2. What are the **differences between neonatal and adult** thrombopoiesis?

3. What is the **Diagnostic Approach**?

4. What are the current **guidelines for Platelet Transfusion**?
A Case ......
Looks familiar?

- 36 weeks late preterm SGA 2.1 kg male infant born vigorous and roomed in with mother, noticed to be lethargic on day 3 and investigated:
  - Haemogram: Hb: 15, PCV: 46, TLC: 9600, **Platelet Count: 55,000**
  - CRP: Neg, Blood Culture: Sterile

How do we manage this baby?
Defining Thrombocytopenia ....

- A symptom of a variety of congenital or acquired conditions in the neonatal period

- **Platelet count <150,000 /uL**
  - Mild Thrombocytopenia: 100-150,000
  - Moderate: 50-99,000
  - Severe: <50,000

- **Basis:**
  - Pl production starts in fetus @ 5 wks
  - Count reaches adult level by 22 wks

Therefore traditionally, Neonatal value = Adult Value

**Neonate = Adult ?**
Challenging the Definition in Neonates ....

Recent large population study involving 47,291 neonates in 8 hospitals in US:

Lower limit of platelet
- late preterm & term: **123,000/μL**
- 32 weeks’: **104,000 /μL**

Significance?

Magnitude of the Problem

• ~18-32% of infants admitted to NICU

• more preterm infants.

• Increased risk for
  – ICH,
  – mortality, and
  – long term neurodevelopmental disability.
Platelet production:

All blood cells originate from stem cells in the red bone marrow

Platelets: tiny cellular fragments produced by megakaryocytes
Short half life in circulation (7 - 10 days)
Mechanism of Platelet Production: 4 Steps

1. Production of Thrombopoietin (Tpo):
   Less in neonates
Mechanism of Platelet Production: 4 Steps

1. Production of Thrombopoietin (Tpo)

2. Proliferation of megakaryoblasts
   More sensitive to Tpo stimulation
Mechanism of Platelet Production: 4 Steps

1. Production of Thrombopoietin (Tpo)

2. Proliferation of megakaryocytes progenitors

3. Megakaryocyte maturation
   - Increase in nuclear ploidy (the number of sets of chromosomes in a given cell)
   - Generation of large polyploid (8N–64N) megakaryocytes
     - more in number but
     - smaller and
     - have lower ploidy than adults
Mechanism of Platelet Production: 4 Steps

1. Production of Thrombopoietin (Tpo)

2. Proliferation of megakaryocytes progenitors

3. Megakaryocyte maturation

   ✓ by bursting of megakaryocyte
Response to increased platelet demand:

**Adult BM:** first increases the MK size and ploidy and then increases the MK number.

**Limitation in Neonates:** can increase the number, but not the size of their MKs.

Various Factors Influence Platelet Production:

Measures of platelet production like serum Tpo or reticulate platelet % (RP%)
- not reliable in the neonates!
How do I approach a neonate with thrombocytopenia?
# Thrombocytopenia – 3 Periods of Presentation

<table>
<thead>
<tr>
<th>Time of Onset</th>
<th>Type</th>
</tr>
</thead>
</table>
| **Fetal**           | • **Immune:** Alloimmune (NAIT) / Autoimmune  
                       • Congenital Infections (TORCH, HIV)  
                       • Chromosomal (Aneuploidy)            |
| **Early (<72 hrs)** | • All above  
                       • **Placental Insufficiency** (Eg: IUGR)  
                       • Asphyxia  
                       • Sepsis (DIC)                         |
| **Variable**        | • Sepsis Thrombosis  
                       • Vascular tumor  
                       • Metabolic (Proprionic acidemia, methylmalonic acidemia)  
                       • ECMO                                        |
| **Late (>72 hrs)**  | • NEC  
                       • **Drug** Induced (Penicillin and derivatives, vancomycin, metronidazole, Phenytoin, phenobarbital) |
Early Onset <72 hrs

Well Baby:
- IUGR;
- Autoimmune thrombocytopenia
  - Mild to moderate thrombocytopenia
  - Nadir on postnatal day 4-5
  - Usually resolves by 7-10 days.

Sick Baby:
- Neonatal Alloimmune Thrombocytopenia (NAIT)

Variable (Sick / Well):
- Sepsis (Bacterial or viral), TORCH, DIC
Neonatal Autoimmune Thrombocytopenia

- Early onset
- Moderate severity
- Maternal history: +/-
  - Usually H/O ITP or autoimmune disease (2 in 1000 pregnancies)
    Any infant born to a mom with autoimmune disease should have a platelet count (10%).
  - Sometimes - Presenting sign of maternal autoimmune disease
    Any mother having a neonate with thrombocytopenia should have a platelet count!

- Treatment: +/- (IVIG, Platelet transfusion)
- Evaluate for ICH (~1%).
- Lasts from days to months.
Neonatal Alloimmune Thrombocytopenia (NAIT)

- Severe (<50,000)
- Increased risk for ICH (8-22%)
- Antenatal Presentation: ICH, severe hydrocephalus, hydrops fetalis.
- Incidence 1 in 1500 pregnancies
Neonatal Alloimmune Thrombocytopenia (NAIT)

- Due to maternal Ab (to paternal Ag) present in fetal platelets
- Can occur in first pregnancy
- Testing of Mother and Father for Human Platelet antigen (HPA 1a, 5b, and 15b)
  - sixteen HPAs identified but only three cause 95% of the NAIT cases
Neonatal Alloimmune Thrombocytopenia (NAIT)

• Requires Transfusion
• Resolves within 2 weeks
• Platelet count: needs to be followed until normalized and stable.
• If persists longer may be a different diagnosis.
• Monitoring for future pregnancies and possibly treatment with maternal IVIG/steroids.
Late-Onset Thrombocytopenia

• Ill Appearing:
  – Sepsis (Viral & Fungal – Earlier)
  – NEC,
  – IEM (Propionic Acidemia, isovaleric acidemia, methylmalonic acidemia, Gaucher Disease)

• Well Appearing:
  – Drug induced,
  – thrombosis,
  – Fanconi’s Anemia
The bleeding pattern

- Mucocutaneous.

- Petechiae, bruises, or bleeding from the mucous membranes

- Look out for: IVH / ICH!
Physical Exam

Keeping in Mind:

1. **Time of onset**: early & late

2. **Gestational age**: Term Vs preterm

3. **Possible underlying mechanism**
   (consumption, increased destruction, decreased production),
   Due to maternal or infant factors or individualized to the particular infant.

- Ill or Well
- Petechia, bruising
- Fontonelle
- Liver size
- Abdominal masses (renal vein thrombosis)
- Dysmorphic features
- Forearm or thumb abnormalities (TAR syndrome or Fanconi anemia)
When do we need to treat?
Diagnostic approach

Thrombocytopenia
(Platelet count < 150,000 µL)

Term

< 100,000/µL

Sick

Consider causes in the table

> 100,000/µL

Healthy

Observe

Persistent

Preterm

< 100,000/µL

NAIT

Yes

Treat

No

Consider causes in the table

> 100,000/µL

Observe

Persistent

NeoReviews Vol.14 No.2 February 2013
Diagnostic approach

Thrombocytopenia
(Platelet count < 150,000 μL)

- Term
  - <100,000/μL
    - Sick
      - Consider causes in the table
    - Healthy
      - Observe
- >100,000/μL
  - Observe

- Preterm
  - <100,000/μL
    - NAIT
      - Yes
        - Observe
      - No
        - Persistent
        - Consider causes in the table
  - >100,000/μL
    - Observe

Observe or treat?
When is the right time to transfuse Platelets?

Platelet transfusion thresholds selected by neonatologists in German-speaking European countries versus U.S. neonatologists in 2 different clinical scenarios!

Transfusion 2011;51:2636–7
When is the right time ???

Various prospective, observational trials strongly suggest that factors other than the platelet count determine the risk for major ICH!!
Platelet Count and Risk of Bleeding (US)

Risk:
• 100,000 – 20,000/uL: Minimal or mild risk of bleeding
• 20,000 – 5,000/uL: Moderate Risk
• <5,000/ Ul: severe Risk

Transfusion Threshold:
• Lower for preterm (Higher incidence IVH & “immaturity of the hemostatic system”) - 50,000/uL?
• When platelets < 30,000/Ul: Trauma & stress of birth can precipitate ICH

Formulating a Guideline: NeoReviews Vol.14 No.2 February 2013
Defining Threshold for Transfusion: (UK)

- < 150000 vs <50,000 no differences in freq or severity of ICH
  (Andrew et al 1993)

- Transfuse platelets: (volume reduction not necessary)
  - <100,000: Any infant if ICH or signs of active bleeding.
  - <50,000: Ill term / preterm (<33weeks) in 1\textsuperscript{st} week of age.
  - <30,000: stable term / preterm > 1 week of age
    (Murray et al 2002: no major hemorrhage in infants if platelets >30,000)

Chakravorty S, Roberts I. How I manage neonatal thrombocytopenia.
NAIT: Management Guidelines:

• If platelets <50,000- Suggest cerebral imaging (US, MRI)

• Transfuse platelets:
  – trial of random donor platelets first.
  – If ineffective: Antigen negative platelets should be used (maternal platelets or known PL A1 or PL A5 negative platelets)

• Consider IVIG 1g/kg q 24hrs x 2 doses (+/- in combination with random donor transfusions)

• Consider methylprednisolone (1mg/kg q 8hrs) with IVIG.
Before deciding to transfuse ......

• Any doubt - repeat sample
  – Errors from improper collection or unrecognized platelet clumping

• Blood culture +/- antibiotics depending on history, clinical picture and severity.

• Review peripheral smear and MPV
  – (Jacobsen and Fechtner syndromes present with large platelets and Wiskott-Aldrich syndrome and X-linked thrombocytopenia present with small platelets)
Remember when you Transfuse ......

- **Dose:** 10-15ml/kg random-donor platelets
  - Either CMV neg or leukoreduced
  - Irradiation to reduce GVHD

- **Adv Effects:** Platelet transfusions associated with **TRALI (Transfusion Related Acute Lung Injury)** and increased mortality ??

- **Multiple Transfusion Requirement:**
  - on a **weekly basis** - decreased platelet production (congenital amegakaryocytic thrombocytopenia)
  - every **1-2 days** - increased platelet consumption.
Which is more suitable platelet for transfusion in neonates?

**Adult Vs Neonatal Platelets:**
Effects of platelet transfusions on neonatal primary hemostasis

Is there a developmental mismatch associated with platelet transfusions?

**Closure times after stimulation with CT-EPI** (closure time epinephrine) –

Significantly shorter in neonatal blood “transfused” in vitro with adult platelets compared with blood “transfused” with neonatal platelets.

*P < 0.05.

Ongoing RCT comparing two different platelet transfusion thresholds and aims to establish whether a lower platelet transfusion threshold is as good as a higher threshold in preterm infants < 34 weeks POG

Randomisations to date = 532 / 660
Platelet transfusion cut off: Arm A : < 25; Arm B < 50
Primary Outcome: Death or severe IVH in 1ST 28 days

Dr Simon Stanworth, et al, University of Cambridge.
Thank you!

jubileenicu@gmail.com,
Genetic Disorders Associated With Thrombocytopenia

- **Chromosomal:**
  - Trisomy 13: Aplasia cutis, CHD, cleft lip and palate, polydactyly
  - Trisomy 18: IUGR, CHD, rocker-bottom feet, overlapping digits, hypertelorism, small mouth, clinodactyly
  - Trisomy 21: CHD, single palmar crease, hypotonia, short neck, w/ redundant posterior folds
  - Turner syndrome: CHD, cubitus valgus, webbed posterior neck, broad chest, with wide-spaced nipples, lower extremity edema
- **11 q terminal disorder** (Jacobsen syndrome): CHD, GU anomalies, facial anomalies, abnl brain imaging, limb anomalies
- **Familial:**
  - May-Hegglin anomaly (Sebastian syndrome): Giant platelets, neutrophilic inclusions
  - Fechtner syndrome: Giant platelets, sensorineural hearing loss, cataracts, nephritis, neutrophilic inclusions
  - Bernard-Soulier syndrome: Anemia, genitourinary abnormalities (cryptorchidism)
  - Congenital amegakaryocytic thrombocytopenia: Abnl head size and shape, developmental delay, CHD, cleft and high-arched palate, abnormal kidneys, optic atrophy, valgus and varus deformities, vertebral anomalies, coloboma, scoliosis, absent bone marrow megakaryocytes
- **Wiscott-Aldrich syndrome:** Immunodeficiency, small platelets, eczema
- **Amegakaryocytic thrombocytopenia:** Restricted forearm pronation, proximal radioulnar synostosis in forearm, and radioulnar synostosis absent bone marrow megakaryocytes
- **Fanconi anemia:** Hypopigmented and hyperpigmented skin lesions, urinary tract abnormalities, microcephaly, upper extremity radial-side abnormalities involving the thumb, pancytopenia (usually with onset in childhood)
- **Thrombocytopenia and absent radii:** Shortened/absent radii bilaterally, nm thumb, ulnar and hand abnormalities, abnormalities of the humerus, CHD, eosinophilia, leukemoid reaction
- **Neonatal primary hemophagocytic lymphohistiocytosis:** Fever, HSM, hyperferritemia, hypertriglyceridemia, hypofibrinogenemia

**Metabolic:**
- Propionic acidemia, methylmalonic acidemia: FTT, developmental delay, ketoacidosis, hyperglycinemia, hyperammonemia
- Isovaleric acidemia: Odor of sweaty feet, poor feeding, hypotonia, hyperammonemia, metabolic acidosis
- Gaucher disease: Hepatosplenomegaly, Gaucher cells in bone marrow
<table>
<thead>
<tr>
<th>Categories</th>
<th>Subtypes</th>
<th>Differential Diagnoses (Where Applicable)</th>
<th>Severity</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Illnesses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td>Autoimmune</td>
<td>Neonatal autoimmune thrombocytopenia, Maternal ITP, lupus, other collagen vascular disorder</td>
<td>Severe</td>
<td>Early</td>
</tr>
<tr>
<td>Infected</td>
<td>Bacterial</td>
<td>GBS, Gram-negative rods, <em>Staphylococcus</em>, etc.</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Viral</td>
<td>CMV, HSV, HIV, enteroviruses</td>
<td>Variable</td>
<td>Usually early</td>
</tr>
<tr>
<td></td>
<td>Fungal</td>
<td><em>Candida</em>, other</td>
<td>Severe</td>
<td>Usually early</td>
</tr>
<tr>
<td></td>
<td>Parasite</td>
<td>Toxoplasmosis</td>
<td>Variable</td>
<td>Early</td>
</tr>
<tr>
<td>Placental</td>
<td></td>
<td>Preeclampsia, eclampsia, chronic hypertension, Intrauterine growth restriction due to placental insufficiency</td>
<td>Mild-moderate</td>
<td>Early</td>
</tr>
<tr>
<td>Insufficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIC</td>
<td></td>
<td>Asphyxia, Sepsis, Congenital ITP (rare)</td>
<td>Severe</td>
<td>Early</td>
</tr>
<tr>
<td>Genetic</td>
<td>Chromosomal</td>
<td>Trisomy 13, Trisomy 18, Trisomy 21, Turner syndrome, Jacobsen syndrome</td>
<td>Severe</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Familial</td>
<td>Macrothrombocytopenias, Wiskott-Aldrich syndrome, X-linked thrombocytopenia, Amegakaryocytic thrombocytopenia, TAR, Fanconi anemia*</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Metabolic</td>
<td>Proprionic acidemia, methylmalonic acidemia, etc.</td>
<td>Mild-moderate</td>
<td>Variable</td>
</tr>
<tr>
<td>Medication</td>
<td>Antibiotics</td>
<td>Penicillin and derivatives, vancomycin, metronidazole, etc.</td>
<td>Variable</td>
<td>Late</td>
</tr>
<tr>
<td>Induced</td>
<td>Heparin</td>
<td></td>
<td>Variable</td>
<td>Late</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsants</td>
<td>Phenytoin, phenobarbital</td>
<td>Variable</td>
<td>Late</td>
</tr>
<tr>
<td></td>
<td>H2 receptor antagonists</td>
<td></td>
<td>Variable</td>
<td>Late</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Thrombosis</td>
<td>RVV, line-associated thrombosis, sagittal sinus thrombosis</td>
<td>Moderate</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>Vascular tumor</td>
<td>Kasabach Kasabach-Merritt, hepatic hemangiendothelioma</td>
<td>Moderate</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>NEC</td>
<td></td>
<td>Severe-moderate</td>
<td>Usually late</td>
</tr>
<tr>
<td></td>
<td>ECMO</td>
<td></td>
<td>Variable</td>
<td>Variable</td>
</tr>
</tbody>
</table>