Challenges in the Evaluation and Management of the Thrombocytopenic Neonate

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Disclosure

- I am receiving an honorarium from Sysmex for today’s presentation.
Patients in the Neonatal Intensive Care Unit

Approx. 450,000 infants per year

Platelet Counts in Newborn Infants of Different Gestational Ages

Incidence of Thrombocytopenia

- Among all neonates: 0.7 - 0.9%
  - 10% of cases are alloimmune

- In the Neonatal Intensive Care Unit: 20 - 30%
  - 20-25% have severe thrombocytopenia (4-6% of all admissions)
  - Incidence is inversely proportional to gestational age
    (75% among infants with birth weight <1,000g)

Evaluation of the Thrombocytopenic Neonate

- Consider
  - Infant’s age (gestational and postnatal)
  - Severity of the thrombocytopenia
  - Clinical condition (sick or well?)
  - Maternal pathology (platelet counts?)
  - Physical exam
    - Small for gestational age?
    - Syndromic features?
    - Hepatosplenomegaly?
  - Medications
# Early-onset Thrombocytopenia (<72 hrs)

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Severity of thrombocytopenia</th>
<th>Differential diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sick</td>
<td>Variable</td>
<td>Sepsis (bacterial, viral) TORCH Perinatal Asphyxia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placental insufficiency Genetic disorders Congenital thrombocytopenia Thrombosis (renal) Autoimmune</td>
</tr>
<tr>
<td>Well appearing</td>
<td>Mild to moderate</td>
<td>Alloimmune thrombocytopenia Genetic disorders Congenital thrombocytopenia Autoimmune</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
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</table>

# Late-onset Thrombocytopenia (>72 hrs)

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sick</td>
<td>Sepsis (bacterial, viral, fungal) Necrotizing enterocolitis Congenital errors of metabolism</td>
</tr>
<tr>
<td>Well appearing</td>
<td>Drug-related thrombocytopenia</td>
</tr>
</tbody>
</table>
Placental Insufficiency

- Common cause of thrombocytopenia
  - 30-50% of preterm infants with intrauterine growth restriction or born to mothers with pre-eclampsia
- Thrombocytopenia usually mild to moderate
- Nadir at 2-4 days of life
- Nearly resolved by 10-14 days of life
- Associated with transient defect in platelet production

If the thrombocytopenia is severe
- Consider other causes
  - Alloimmune thrombocytopenia (present as early as 20 weeks gestation)
If the thrombocytopenia is prolonged
- Consider congenital viral infections (CMV)
- Consider genetic disorders
  - In particular if associated with dysmorphic features or other congenital malformations.
Alloimmune Thrombocytopenia

- Pathogenesis similar to Rh hemolytic disease of the newborn
- Due to incompatibility in Human Platelet Antigen System (most commonly HPA-1)
- Most common scenario:
  - Mother is HPA-1b (formerly PLA-1 negative)
  - Father and fetus are HPA-1a (PLA-1 positive)
  - Mother develops antibodies against HPA-1a
  - Antibodies cross the placenta and attack fetal platelets → Thrombocytopenia

- Usually severe
- Should be suspected in any neonate with platelet count <50x10⁹/L on the first day of life
- Present before 24 wks gestation
- Intracranial hemorrhage in 10-15%
- Resolves in 1-4 weeks
Chromosomal Disorders

Table 1 Human platelet antigens (HPAs)

<table>
<thead>
<tr>
<th>System</th>
<th>Antigen</th>
<th>Original names</th>
<th>Glycoprotein</th>
<th>CD</th>
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</thead>
<tbody>
<tr>
<td>HPA-1</td>
<td>HPA-1a</td>
<td>Zw, Pk^a</td>
<td>GPIIia</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-1b</td>
<td>Zw, Pk^b</td>
<td></td>
<td>GPIbα</td>
<td>CD42b</td>
</tr>
<tr>
<td>HPA-2a</td>
<td>Kr^a</td>
<td></td>
<td>GPIbα</td>
<td>CD42b</td>
</tr>
<tr>
<td>HPA-2b</td>
<td>Kr^b, Sb^b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPA-3a</td>
<td>Ba^a, Le^a</td>
<td></td>
<td>GPIIia</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-3b</td>
<td>Ba^b</td>
<td></td>
<td>GPIIb</td>
<td>CD41</td>
</tr>
<tr>
<td>HPA-4a</td>
<td>Yk^a, Pkn^a</td>
<td></td>
<td>GPIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-4b</td>
<td>Yk^b, Pkn^b</td>
<td></td>
<td>GPIb</td>
<td>CD41</td>
</tr>
<tr>
<td>HPA-5a</td>
<td>Br^a, Zuv^a</td>
<td></td>
<td>GPIa</td>
<td>CD49a</td>
</tr>
<tr>
<td>HPA-5b</td>
<td>Br^b, Zuv^b, Hc^b</td>
<td></td>
<td>GPIb</td>
<td>CD49a</td>
</tr>
<tr>
<td>HPA-6a</td>
<td>Ca^a, Tu^a</td>
<td></td>
<td>GPIIia</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-7a</td>
<td>Mo^a</td>
<td></td>
<td>GPIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-8a</td>
<td>Sr^a</td>
<td></td>
<td>GPIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-9a</td>
<td>Max^a</td>
<td></td>
<td>GPIIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-10a</td>
<td>La^a</td>
<td></td>
<td>GPIIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-11a</td>
<td>Gru^a</td>
<td></td>
<td>GPIIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-12a</td>
<td>ly^a</td>
<td></td>
<td>GPIIIb</td>
<td>CD42a</td>
</tr>
<tr>
<td>HPA-13a</td>
<td>Sl^a</td>
<td></td>
<td>GPIIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-14a</td>
<td>Oe^a</td>
<td></td>
<td>GPIIa</td>
<td>CD61</td>
</tr>
<tr>
<td>HPA-15a</td>
<td>Gov^a</td>
<td></td>
<td>CD109</td>
<td>CD109</td>
</tr>
<tr>
<td>HPA-15b</td>
<td>Gov^b</td>
<td></td>
<td>CD109</td>
<td>CD109</td>
</tr>
<tr>
<td>HPA-16a</td>
<td>Duv^a</td>
<td></td>
<td>GPIIa</td>
<td>CD61</td>
</tr>
</tbody>
</table>

Chromosomal Disorders

Trisomy 18: 83%  
Trisomy 13: 75%
Chromosomal Disorders

- **Trisomy 21**
  - 66% of patients have thrombocytopenia
  - 6% have platelets <50x10⁹/L
  - Resolves spontaneously at 2 to 3 weeks of life

*Henry et al., Am.J.Med Gen., 2007*

Evaluating the Mechanisms of Thrombocytopenia

- **Available parameters**
  - Bone marrow aspiration/biopsy
    - Technically difficult, particularly in preterm infants
  - Mean Platelet Volume (MPV)
    - Young platelets are bigger
      - A high MPV suggests platelet destruction (i.e. ITP)
    - Useful parameter in the evaluation of congenital thrombocytopenias
Evaluating Platelet Size: The Peripheral Blood Smear

Drachman JG, Blood, 2004

Algorithm for Diagnosis of Familial Thrombocytopenia

PlATELET SIZE

SMALL

NORMAL

LARGE

Eczema, X-linked WAS
No eczema, X-linked XLT
AR, High TPO CAMT
Radial defects TAR, ATRUS
AD, FHx AML Runx1
11q deletion Paris Trousseau
AD, minimal bleeding Cytochrome C ANKRD26
Flow for GPIb/IX BSS
AD, WBC inclusions MYH9
VWF multimers, RIPA Type IIb VWD, TTP
GPIb mutation
Red cells abnl GATA1
ABCG5/8
EM Granule disorder

Geddis A., Blood 2011
Thrombocytopenia and Absent Radius (TAR) Syndrome

- Autosomal recessive
- Severe thrombocytopenia
- 25% mortality, in first year of life.
- Platelet count improves prior to school age
- Inadequate response to thrombopoietin

Amegakaryocytic Thrombocytopenia with Radio-Ulnar Synostosis (ATRUS)

- Congenital Amegakaryocytic Thrombocytopenia
- Inability to rotate forearm
- Mutations found in Hox-A11 gene
Evaluating the Mechanisms of Thrombocytopenia

- **New tests**
  - Thrombopoietin (Tpo) concentrations
    - Inversely proportional to megakaryocyte mass
    - Not clinically available
  - Glycocalicin concentrations
    - Not clinically available
  - **Reticulated Platelet Percentage**

**Reticulated Platelet Percentages (RP%)**

- Reticulated platelets: Newly released platelets (<24 hrs old), which contain residual RNA
- RP% reflects platelet production (Similar to the reticulocyte count for red cells)
- Clinically not practical: Requires flow cytometry, not standardized test
- **Clinical equivalent:** Immature Platelet Fraction (IPF), measured in Sysmex XE-Series
Reference Ranges for IPF% and A-IPF in Adults and Cord Blood

Table 2: Reference intervals for platelet counts and immature platelet fractions in health individuals and umbilical cord blood

<table>
<thead>
<tr>
<th></th>
<th>Healthy individuals</th>
<th>Umbilical cord blood (n = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 2132)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men (n = 1252)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women (n = 900)</td>
<td></td>
</tr>
<tr>
<td>Platelet count (x10^9/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference interval</td>
<td>162–347</td>
<td>191–392</td>
</tr>
<tr>
<td>Lower limit (95% CI)</td>
<td>160–164</td>
<td>160–169</td>
</tr>
<tr>
<td>Upper limit (95% CI)</td>
<td>168–208</td>
<td>168–208</td>
</tr>
<tr>
<td>%-IPF (%)</td>
<td>0.5–3.3</td>
<td>0.7–3.8</td>
</tr>
<tr>
<td>Reference interval</td>
<td>0.5–3.3</td>
<td>0.7–3.8</td>
</tr>
<tr>
<td>Lower limit (95% CI)</td>
<td>0.5–0.8</td>
<td>0.5–0.9</td>
</tr>
<tr>
<td>Upper limit (95% CI)</td>
<td>3.3–3.5</td>
<td>3.0–3.8</td>
</tr>
<tr>
<td>A-IPF (x10^9/L)</td>
<td>1.25–7.02</td>
<td>1.94–9.69</td>
</tr>
<tr>
<td>Reference interval</td>
<td>1.30–6.80</td>
<td>1.66–2.58</td>
</tr>
<tr>
<td>Lower limit (95% CI)</td>
<td>1.20–1.41</td>
<td>1.10–1.27</td>
</tr>
<tr>
<td>Upper limit (95% CI)</td>
<td>6.49–7.16</td>
<td>7.96–10.57</td>
</tr>
</tbody>
</table>

IPF: immature platelet fraction; A-IPF: absolute immature platelet fraction.


IPF in Neonates with Early-onset Thrombocytopenia: Placental Insufficiency vs. Sepsis

Cremer et al., Thrombosis and Haemostasis, 2010
IPF in Neonates with Sepsis or NEC, Relative to Platelet Count

Treatment of Thrombocytopenia
Platelet Transfusions
RBC and Platelet Transfusions Among NICU Patients (Iowa)

Fig 1 A) Transfusions Among Iowa NICU Infants By BWt: 2000 to 2005

Widness J and Strauss, Personal Communication

RBC and Platelet Transfusions Among NICU Patients (U.S.)

Fig 1 B) Estimated Number of Transfusions in US in 2006*

* Based on 2000-2005 Iowa NICU data

* Based on US Birth Vital Statistics & 2000-2005 Iowa NICU data
At What Platelet Counts Are NICU Patients Transfused?

- Electronic Survey sent to 2700 neonatologists in USA
  - Members of the AAP Neonatal/Perinatal Section
- 1006 responses
  - 51.9% medical school faculty
  - 48.1% non-medical school faculty

Josephson et al., Pediatrics 2009

Plt. Transfusion Thresholds: 950 g, 2 days old, well
Plt. Transfusion Thresholds: 950 g, 21 days old, sick (NEC)

Neonatal Platelet Transfusion Thresholds in U.S. and Europe

Cremer et al., Transfusion, 2011.
Platelet Transfusion Thresholds (U.K.)

Stanworth S. et al, Pediatrics, 2009

Variability in Platelet Transfusion Practices

- U.S. neonatologists transfuse at significantly higher platelet counts than European neonatologists

- Estimated to result in administration of 1.8 times more platelet transfusions in U.S. vs. European NICUs
  - Based on practice differences alone

Cremer et al., Transfusion, 2011.
What is the rationale for transfusing neonates at these relatively high platelet counts?

Bleeding in Neonates

- 25-31% of infants with birth weight <1,500 g have intracranial bleeding, most commonly intraventricular hemorrhage (IVH)
- Nearly all IVHs occur in first 10 days of life
  - Associated with significant neurodevelopmental consequences
Platelet Aggregation in CB of Healthy Full-term Neonates

Israels et al., Platelets, 2000

How Severe is the Bleeding Phenotype?

Bleeding times are shorter in healthy full term neonates than in healthy adults (Andrew M., Am J Hematol, 1989)
Neonatal Platelet Hyporeactivity: Part of a Balanced System

- High Hct
- High MCV
- High VWF levels
- Ultralarge VWF polymers

Shorter bleeding times
Shorter closure times (PFA-100)
Adequate primary hemostasis
Is there a correlation between platelet count and risk of bleeding?

Severe Thrombocytopenia and Bleeding Risk (Stanworth, Pediatrics, 2009)

- Prospective multicenter observational study of thrombocytopenic neonates
  - 169 Neonates (platelet counts <60 x 10⁹/L)
  - 9% (15/169) had major bleeding
    - 60% (9/15) were IVH
    - 87% (13/15) during first two wks of life
    - 87% (13/15) in neonates <28 wks gestation
Severe Thrombocytopenia and Bleeding Risk (Stanworth, Pediatrics, 2009)

Severe Thrombocytopenia and Bleeding Risk (Baer et al., Pediatrics 2009)

<table>
<thead>
<tr>
<th>Episodes of Severe Thrombocytopenia</th>
<th>n</th>
<th>% With</th>
<th>% With</th>
<th>% With GI</th>
<th>% With IVH</th>
<th>% With Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest Platelet Count on Study (×10^9/L)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Count</td>
<td>n</td>
<td>% Culaneous</td>
<td>% Pulmonary</td>
<td>% Hemorrhage</td>
<td>% (All Grades)</td>
<td>% 3or4IVH</td>
</tr>
<tr>
<td>Recorded, / L</td>
<td></td>
<td>Hemorrhage</td>
<td>Hemorrhage</td>
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<tr>
<td>&lt; 20 000</td>
<td>78</td>
<td>12</td>
<td>8</td>
<td>5</td>
<td>29</td>
<td>17</td>
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<tr>
<td>20 000–30 000</td>
<td>78</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>31 000–50 000</td>
<td>11</td>
<td>7</td>
<td>6</td>
<td>2</td>
<td>32</td>
<td>19</td>
</tr>
</tbody>
</table>
Relationship Between AM Platelet Count and Bleeding ≥ Grade 2

Conclusions

- Thrombocytopenia is associated with IVH in neonates (and with bleeding in pediatric patients), but there is no relationship between degree of thrombocytopenia and bleeding risk
  - Factors other than platelet count determine bleeding risk?
  - Thrombocytopenia is marker of severity of illness?

- Large proportion of platelet transfusions are given to VLBW infants with platelet counts >50 x10^9/L, particularly in first week of life
Do platelet transfusions in high-risk neonates decrease the incidence/severity of bleeding?

Best Clinical Evidence

One randomized trial (Andrew et al., 1993)

- 152 VLBW infants, 0-7 days old
- Randomized to platelet transfusions for platelet counts <150 x 10^9/L or <50 x 10^9/L
- Most infants in second group were transfused at <60 x 10^9/L
- No difference in frequency or severity of IVH
  - Treated group: 28%
  - Control group: 26%
Conclusions from Single Randomized Trial (Best Evidence)

- Transfusing VLBW infants with plt counts $\geq 60 \times 10^9$/L in the first week of life does not reduce incidence or severity of IVH

Randomized Controlled Trials

- **PLANET II**: Study comparing safety of transfusing at plt. counts <25 vs. <50 $\times 10^9$/L (UK)
  - Enrolling patients
Major Questions When Making Platelet Transfusion Decisions

- What is this infant’s bleeding risk?
- Will the platelet count recover in next 24 hours?

- Platelet Function Analyzer-100 (PFA-100)?
- Will the platelet count recover in next 24 hours?
Platelet Function Analyzer (PFA-100)

- Measures closure times (CTs)
  (CTs in vitro equivalent to BTs)
  - Highly reproducible
  - NOT operator dependent

CT-ADP and Platelet Counts in Thrombocytopenic Neonates

Major Questions When Making Platelet Transfusion Decisions

- What is this infant’s bleeding risk?

- Will the platelet count recover in next 24 hours?
  - Immature Platelet Fraction (IPF)

IPF in Neonates as a Predictor of Resolution of Thrombocytopenia

Cremer et al., BJH, 2008
THANK YOU!