Thrombocytopenia in the NICU: More Common Than You Think

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Presenter Disclosures
Martha Sola-Visner, MD

- The following relationships with commercial interests related to this presentation existed during the past 12 months
  - No relationships to disclose

- The following FDA disclosures related to this presentation exist
  - Romisplatin- FDA approved- Off-label use
  - Eltrombopag- FDA approved- Off-label use
Platelet counts in neonates

Christensen et al., 2009
How common is neonatal thrombocytopenia?

- In the overall population: 0.7 to 0.9%
  - 20 to 25% severe thrombocytopenia (plt. count <50,000/µL)

- In the NICU: 20-30%
  - 25% (or 6% of all admissions) have severe thrombocytopenia

- Among ELBW infants: 73%
  - 38% have severe thrombocytopenia
Diagnosing the cause of the thrombocytopenia

- **History**
  - Neonatal
    - Time of onset of thrombocytopenia?
    - Sick or well?
    - Medications?
  - Familial
    - Siblings with severe neonatal thrombocytopenia?
    - Other family members?
  - Maternal
    - ITP, lupus, bleeding disorder

- **Physical Exam**
Classification

- **Early Onset**
  - Immune-mediated
  - Chronic intrauterine hypoxia
  - Infectious (bacterial or non-bacterial)
  - Genetic
  - Perinatal asphyxia

- **Late onset**
  - NEC
  - Infections/DIC
  - Thrombosis
  - Drug-related
Immune thrombocytopenias

- **Hallmark:** Severe thrombocytopenia in an otherwise healthy neonate.
- **Two types**
  - Alloimmune thrombocytopenia (NAIT)
  - Autoimmune thrombocytopenia
Alloimmune thrombocytopenia

- Pathogenesis similar to Rh disease
- Can affect first pregnancy
- Most common scenario (75%):
  - Mother is PLA1-negative (HPA-1b)
  - Father is PLA1-positive (HPA-1a)
  - Mother develops antibodies against PLA1
  - Antibodies cross the placenta
  - PLA1-positive fetus develops thrombocytopenia
Alloimmune thrombocytopenia

- Usually severe (<50x10^9/L)
- Present before 24 wks gestation
- Intracranial hemorrhage in 10-15% of neonates
Autoimmune thrombocytopenia

- Antibody binds *both* maternal and fetal platelets ➔ Thrombocytopenia in the mother and the neonate
- Most common maternal underlying disease is ITP
- 7-14% of neonates have severe thrombocytopenia
- Incidence of intracranial hemorrhage is low
Chronic intrauterine hypoxia

- Thrombocytopenia in 30-50% of neonates born to mothers with PIH or with chronic intrauterine hypoxia (i.e. IUGR secondary to placental insufficiency)
- Mild to moderate
- Nadir at 3-4 days
- Resolution at 7-10 days
Infections

- Most common cause of thrombocytopenia (always rule out!)
- Neonates usually sick
- More frequent and severe in gram-negative or fungal sepsis
- Very frequent in congenital viral infections

Courtesy of M. McGinnis
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Genetic disorders

- **TAR Syndrome**
  - Autosomal recessive
  - Severe thrombocytopenia early in life (< 4 months)
  - 25% mortality (first year)
  - Thrombocytopenia resolves prior to school-age
Genetic disorders

- **Down’s Syndrome**
  - Mild to moderate thrombocytopenia (Plt. count >40,000)
  - Affects 7-28% of patients
  - Resolves spontaneously at 2 to 3 weeks of life
Genetic disorders: Trisomies
Causes of late-onset thrombocytopenia

- Necrotizing enterocolitis (NEC)
  - Thrombocytopenia in 80-90% of cases
  - Associated with high levels of PAF
  - Severity of thrombocytopenia reflects severity of enterocolitis
Sepsis/Disseminated Intravascular Coagulation (DIC)

- DIC usually complicates severe illness in neonates (sepsis, asphyxia, cold stress, etc.)
- Other laboratory abnormalities
  - Prolonged PT and PTT
  - Increased fibrin degradation products
  - Increased D-dimers
  - Low fibrinogen
Drug-induced thrombocytopenia

Drugs administered to the infant

- Heparin
- Antibiotics
- Antivirals: Gancyclovir
Causes of thrombocytopenia

- Thrombosis
  - Renal vein
  - Right atrium/SVC
  - Associated with an indwelling catheter
If diagnosis still unclear…

- Determine the mechanism of thrombocytopenia
  - Accelerated platelet consumption?
  - Decreased platelet production?
  - Combination?
Evaluating the mechanisms of thrombocytopenia

- Readily available parameters
  - Mean platelet volume (MPV)
    - Younger platelets are larger
    - High MPV (>10 fL) suggests plt. destruction
    - Congenital thrombocytopenias (i.e. small platelets in WAS, large platelets in familial macrothrombocytopenias).
Evaluating the mechanisms of thrombocytopenia

- **Time between transfusions**
  - Decreased production ➔ Approx. 7 days
  - Increased consumption ➔ 2.7 ± 0.9 days
Evaluating the mechanisms of thrombocytopenia

- New Tests (less readily available)
  - Thrombopoietin (Tpo) concentrations
  - Circulating megakaryocyte progenitors
  - Bone marrow studies of megakaryocytes
  - Reticulated platelet percentage (Immature Platelet Fraction, IPF)*
Platelet production

Tpo Concentration
TPO PRODUCTION

MK Progenitors
PROLIFERATION

Bone Marrow
Megakaryocytes

MK MATURATION

PLATELET RELEASE

Reticulated Platelets

Tpo Concentration

TPO PRODUCTION
Tpo concentrations

- Most potent stimulator of platelet production
- Mostly produced in the liver
- Circulating levels reflect
  - Availability of receptors (platelet and megakaryocyte mass)
  - Tpo production
    - Increased in infection/inflammation (IL-6)
    - Decreased in liver failure
Platelet production

- **Tpo Concentration**
- **MK Progenitors**
- **Bone Marrow Megakaryocytes**
- **Reticulated Platelets**

**TPO PRODUCTION**
**PROLIFERATION**
**MATURATION**
**RELEASE**
Circulating MK progenitors
Circulating MK progenitors

Saxonhouse et al., 2004
Platelet production

Tpo Concentration → MK Progenitors

TPO PRODUCTION

PROLIFERATION

MK MATURATION

PLATELET RELEASE

Bone Marrow Megakaryocytes

Reticulated Platelets
Neonatal bone marrow clot section
MK size in thrombocytopenic neonates and adults

Sola-Visner et al., 2007
Platelet production

Tpo Concentration → TPO PRODUCTION

MK Progenitors → PROLIFERATION

Bone Marrow Megakaryocytes → MK MATURATION

Reticulated Platelets → PLATELET RELEASE

TPO PRODUCTION PROLIFERATION MK MATURATION PLATELET RELEASE
Reticulated platelet percentage (RP\%) 

- Platelets newly released from the bone marrow, which contain residual RNA
- Analogous to reticulocytes
- The RP\% in the blood reflects platelet production
- Clinical equivalent: Immature platelet fraction (IPF)
Can these tests help determine the cause of neonatal thrombocytopenia?
Thrombocytopenia of unknown etiology

- Term neonate, SGA
- Platelet count <50,000/µL since birth
- Mild respiratory distress – improved with antibiotics.
- Splenomegaly
- Post-transfusion platelet half-life <48 hours
- Blood cultures, CMV and toxoplasma titers, viral swabs, and anti-platelet antibodies negative
Thrombocytopenia of unknown etiology

<table>
<thead>
<tr>
<th></th>
<th>Values</th>
<th>TPO Conc (pg/ml)</th>
<th>MK Prog (per 5x10^5 LDMNC)</th>
<th>MK Conc (per 250 µ^2 BM)</th>
<th>MK Size (µ)</th>
<th>MK Mass (Conc X Size)</th>
<th>RP%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>497</td>
<td>340</td>
<td>16.8</td>
<td>15.1</td>
<td>254</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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Tighe et al., 2005
Bone marrow clot section
CD61 staining

Tighe et al., 2005
Ineffective platelet production

Tpo Concentration → MK Progenitors → Bone Marrow Megakaryocytes

TPO PRODUCTION → PROLIFERATION → MK MATURATION → PLATELET RELEASE

Tpo Concentration
Congenital HIV infection

Ineffective Platelet Production in Thrombocytopenic Human Immunodeficiency Virus-Infected Patients

By James L. Cole, Ulla M. Marzec, Clifford J. Gunthel, Simon Karpatkin, Lydia Worford, I. Birgitta Sundell, Jeffrey L. Lennox, Janet L. Nichol, and Laurence A. Harker

Blood 91:3239-3246, 1998
Thrombocytopenia of unknown etiology

- 37 weeks gestation, seven weeks old.
- Severe thrombocytopenia since birth. Otherwise healthy. No HSM.
- Time between transfusions: 7-8 days.
- Physical exam: Restricted pronation of both arms.
# Thrombocytopenia of unknown etiology

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<tbody>
<tr>
<td>1260</td>
<td>↑↑</td>
<td>↓↓↓↓</td>
<td>No MKs</td>
<td>No MKs</td>
<td>No MKs</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Thrombocytopenia of unknown etiology
Platelet production

- **Tpo**
- **Bone Marrow Megakaryocytes**
- **Tpo Concentration**
- **MK Progenitors**
- **TPO PRODUCTION**
- **PROLIFERATION**
- **MK MATURATION**
- **PLATELET RELEASE**
Congenital Amegakaryocytic Thrombocytopenia with Proximal Radio-ulnar Synostosis (ATRUS)
# Mechanisms of thrombocytopenia in neonates

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<th>Tpo (pg/ml)</th>
<th>MK prog</th>
<th>RP%</th>
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<tbody>
<tr>
<td>Non-thrombocytopenic Neonates</td>
<td>&lt;162</td>
<td>107 ± 81</td>
<td>2.7 ± 1.6</td>
</tr>
<tr>
<td>Thrombocytopenic liver failure (n=3)</td>
<td>93 ± 20.6</td>
<td>93 ± 133</td>
<td>2.2 ± 1.5</td>
</tr>
<tr>
<td>Thrombocytopenic infection (n=8)</td>
<td>389 ± 292</td>
<td>150 ± 76</td>
<td>5.5 ± 4.1</td>
</tr>
<tr>
<td>Thrombocytopenic other/idiopathic (n=6)</td>
<td>390 ± 294</td>
<td>230 ± 161</td>
<td>4.2 ± 2.1</td>
</tr>
</tbody>
</table>
Immature Platelet Fraction (IPF): Coming soon to a lab near you!

Immature platelet fraction as novel laboratory parameter predicting the course of neonatal thrombocytopenia

*British Journal of Haematology, 2008*
Treatment of severe thrombocytopenia
Therapy of the future: “First Generation” thrombopoietic growth factors

- Recombinant IL-11
- Recombinant Tpo
rIL-11 (Neumega)

- FDA approved for prevention of chemotherapy-induced thrombocytopenia

- Never investigated in neonates

- Positive aspects
  - Experimental benefits for NEC and sepsis in animal models

- Negative aspects
  - Significant toxicity (arrhythmias, fluid retention)
  - Lack of efficacy in certain varieties of thrombocytopenia (pediatric ITP)
Recombinant Tpo

- Most potent stimulator of thrombopoiesis in animal models and adult patients
- First isolated in 1994
- Decreased nadir of chemotherapy-induced thrombocytopenia
- Synergistic effects with G-CSF and Epo
Dose-response of PEG-rHuMGDF on the platelet count of newborn Rhesus monkeys

*Sola et al., 2000*
Recombinant Tpo

- 2004: All rTpo clinical trials interrupted
  - Development of neutralizing antibodies against endogenous Tpo
    - Severe thrombocytopenia
    - Aplastic anemia
“Second generation” thrombopoietic agents: Tpo-mimetics

- Compounds with no sequence homology to Tpo
- Bind to Tpo-receptor (c-mpl) and have Tpo-like effects
- FDA approved for adults with refractory ITP (2008)
  - AMG531 (Romiplostin, Nplate®, Amgen)
  - SB-497115 (Eltrombopag, GlaxoSmithKline)
AMG-531 (Romiplostin)

**AMG 531, a Thrombopoiesis-Stimulating Protein, for Chronic ITP**

James B. Bussel, M.D., David J. Kuter, M.D., D.Phil., James N. George, M.D., Robert McMillan, M.D., Louis M. Aledort, M.D., George T. Conklin, M.D., Alan E. Lichtin, M.D., Roger M. Lyons, M.D., Jorge Nieve, M.D., Jeffrey S. Wasser, M.D., Israel Wiznitzer, M.D., Reggie Kelly, B.S., Chien-Feng Chen, Ph.D., and Janet L. Nichol, M.S.

**Bussel et al., NEJM, Oct. 2006**

An open-label, unit dose-finding study of AMG 531, a novel thrombopoiesis-stimulating peptibody, in patients with immune thrombocytopenic purpura

Adrian Newland,¹ Marie T. Caulier,² Mies Kappers-Klunne,³ Martin R. Schipperus,⁴ Francois Lefrere,⁵ Jaap J. Zwaginga,⁶ Jenny Christal,⁷ Chien-Feng Chen⁸ and Janet L. Nichol⁹

**Newland et al., BJH, Nov. 2006**
Eltrombopag for the Treatment of Chronic Idiopathic Thrombocytopenic Purpura

Bussel et al., NEJM, Nov. 2007

Eltrombopag for Thrombocytopenia in Patients with Cirrhosis Associated with Hepatitis C
John G. McHutchison, M.D., Geoffrey Dusheiko, M.D., Mitchell L. Shiffman, M.D., Maribel Rodriguez-Torres, M.D., Samuel Sigal, M.D., Marc Bourliere, M.D., Thomas Berg, M.D., Stuart C. Gordon, M.D., Fiona M. Campbell, B.Sc., Dickens Theodore, M.D., M.P.H., Nicole Blackman, Ph.D., Julian Jenkins, M.Sc., Nezam H. Afzhal, M.D., for the TPL102357 Study Group

McHutchison et al., NEJM, Nov. 2007
Current treatment: Platelet transfusions
What to transfuse?

- 10-15 mL/Kg of any platelet suspension (random-donor unit or platelet pheresis)
- CMV-safe
  - CMV-negative, and/or
  - Leukoreduced
- Irradiated in cases of
  - Immunodeficiency
  - Intrauterine or exchange transfusion
  - Transfusion from a relative or HLA-matched donor
When to Transfuse?
Platelet transfusion thresholds in neonatology: Evidence

Andrew et al., 1991

- 152 VLBW infants, 0-7 days old
- Randomized to platelet transfusions for platelet counts <150 x 10⁹/L or <50 x 10⁹/L
- No difference in frequency or severity of IVH
Platelet transfusion thresholds in neonatology: Evidence

Murray et al., 2004

- Retrospective review of 53 neonates with platelet counts <50 x 10⁹/L
- 51% transfused
  - Platelet counts <30 x 10⁹/L
  - Platelet counts 30-50 x 10⁹/L and previous hemorrhage or clinically unstable
- No major hemorrhage, regardless of whether platelet transfusions were given or withheld
Platelet transfusion practices world-wide

- Platelet transfusions (% of all NICU admissions):
  - Del Vecchio et al. (USA, 2001): 9.4%
  - Garcia et al. (Mexico, 2001): 2%
  - Murray et al. (England, 2002): 3%
  - Kahn et al. (USA, 2003): 10-fold difference in platelet transfusion usage among VLBW infants in 10 NICUs in USA
  - Christensen et al. (USA, 2006): 45% of ELBW infants (92% not bleeding).
Nationwide survey of platelet transfusion practices

- 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
Platelet transfusion practices: 950 g, 2 days old, well
Platelet transfusion practices:
950 g, 2 days old, sick
Platelet transfusion practices: 950 g, 9 days old, well
Conclusions

- Great practice variability among neonatologists

- Evidence:
  - Platelet transfusions for counts >60,000/uL do not decrease IVH.
  - 30,000/uL might be appropriate threshold for stable non-bleeding neonates

- Literature: NICUs in USA transfuse more platelets

- Are liberal transfusion practices decreasing severe hemorrhagic events, or are they increasing risks?
Risks/Complications of platelet transfusions

- **TRALI (Transfusion Associated Lung Injury)**
  - Most common cause of transfusion-related fatalities
  - Incidence: 1 in 5000 Units
  - Presentation: Acute onset of hypoxemia during or within 6 hrs of transfusion + bilateral CxR infiltrates

- **TACO (Transfusion Associated Circulatory Overload)**
  - Respiratory distress due to circulatory overload causing pulmonary edema
Risks/Complications of platelet transfusions

- **Bacterial Sepsis**
  - Incidence: 1:24,000-1:500,000 plt transfusions
  - **Greatest infectious threat from transfusions**
  - Under-recognized and under-reported

- **TA-GVHD**
  - Skin lesions, elevated liver enzymes, pancytopenia
  - High mortality rate (90%)
  - Preventable by irradiating blood products
Risks/Complications of platelet transfusions

- Emerging pathogens (i.e. Chagas)

- Cytokine/plasma protein mediated reactions
  - Platelet suspensions contain Platelet Activating Factor (PAF)
  - PAF induces intestinal necrosis and thrombocytopenia in animal models, and contributes to the pathogenesis of NEC
Conclusions

- Studies to establish safe platelet transfusion thresholds in neonates are imperative

- Second generation thrombopoietic growth factors might be useful in selected neonates in the future
  - Should only be used in well-designed trials
  - Effects likely to be different in neonates and adults
Thank you!

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- Lisa Rimsza, MD
- Cassandra Josephson, MD
- Robert Christensen, MD
Platelet counts in neonates

Christensen et al., 2009