Thresholds for transfusion of platelets in preterm and term infants

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Definition of Thrombocytopenia

Normal circulating platelet count: 150/nl – 450/nl

Mild thrombocytopenia: 100 - 150/nl
Moderate thrombocytopenia: 50 - 150/nl
Severe thrombocytopenia: < 50/nl
Controversies on Platelet Reference Data

Wiedmeier SE et al. J Perinatol 2009; 29:130-6
Incidence of Neonatal Thrombocytopenia

0.12 – 0.24% of all neonates at birth

0.1 – 2% of all children during the neonatal period

but:

18 – 35% of all neonates admitted to the NICU

73 % of ELBW infants have one or more platelet counts < 150/ during hospital stay

Are major bleedings associated with thrombocytopenia?
And if so, to which extent?
Prospective Outcome Study for Neonates with Platelet Counts < 60/nL (PlaNet-1)

UK, n = 7 NICU, n = 3,652 patients

Platelet count < 60/nL: n = 194 (5%)
Median GA: 27 wks [IQR 24 – 32 wks]
Median BW: 822g [IQR 671 – 1300g]

Outcome
n = 31 (18%) no hemorrhage
n = 123 (73%) minor hemorrhage (hematuria 40%, endotracheal tube 21%, naso-gastric tube 10%, skin 15%)

n = 15 (9%) major hemorrhage
(defined by hemorrhage requiring prompt, sustained nursing or medical intervention (eg pulmonary hemorrhage, n = 3) or IVH °III/IV (n = 9))

Platelet count
< 20/nL: n = 58 (34%)
20 – 39/nL: n = 64 (39%)
40 – 59/nL: n = 47 (28%)

Cause of thrombocytopenia
Sepsis: 43%
Maternal preeclampsia/IUGR: 25%
NEC: 7%

Gestational Age Distribution of Infants with and without Major Hemorrhage.

Lowest Platelet Counts in Neonates with and without Major or Minor Hemorrhage.

Age at First Platelet Transfusion for Infants Who Received ≥1 Transfusion.

Response Curves to Platelet Transfusions (15 ml/kg)

Median (IQR) platelet count:
- prior to transfusion: 27 /nl (19-36 /nl)
- after transfusion: 79 /nl (47-127 /nl)

Incidence of sepsis: 72%

Further Considerations for Defining Thresholds of Clinical Significant Thrombocytopenia

- Origin of thrombocytopenia
- Developmental differences in megakaryopoiesis
- Platelet lifespan
- Ability to increase platelet production
- Platelet function
Course of Acquired Neonatal Thrombocytopenia in an Extremely-Low-Birth-Weight Infant

Cremer M. & Dame C., Monatsschr Kinderheilkd 2006; 154:522-532
Thrombopoietin (Thpo): higher plasma concentrations

Response to Thpo: progenitors more sensitive to low Thpo concentrations

Megakaryocyte (MK) progenitors: highly proliferative (10-fold)

MK size and ploidy: low ploidy (mostly 2N/4N in vitro)

MK maturation: cytoplasmatically mature at low ploidy levels

Platelet Life Span and Production Rate
In Neonatal vs. Adult Mice

Platelet Function and Primary Hemostasis

Platelet function in healthy full-term neonates:

• less responsive to platelet agonists
  > fewer $\alpha_2$ adrenergic receptors
  > impairment of calcium mobilization
  > differences in signaling downstream of thromboxane receptors

• but shorter bleeding time, shorter closure time in PFA-100 analyzers
  > higher hematocrit, higher MCV, higher vWF concentrations,
  > predominance of longer vWF polymers

Platelet hypo-reactivity of healthy full-term neonates is an integral part of a delicately balanced neonatal hemostatic system, rather than a developmental deficiency.
Platelet Function and Primary Hemostasis

Platelet function in preterm neonates:

• more pronounced platelet hypo-reactivity than in full-term neonates

• decreased platelet adhesion, but still better than in healthy adults
  > not related to vWF or ristocetin activity

• bleeding times and closure-time inversely correlate with gestational age

Despite the pronounced platelet hypo-reactivity preterm infants do have adequate primary hemostasis.

Saxonhouse MA et al., Neonatology 2010
Platelet Function and Primary Hemostasis

Platelet hypo-reactivity

• still present 3 to 4 days after birth
• significant improvement during the first 10 to 14 days
• GA-dependent differences in platelet adhesion persist for at least 10 weeks
• GA-dependent differences in platelet activation and bleeding times disappear by day 10.

Sepsis, maternal hypertension or gestational diabetes can induce a decrease in adhesion properties of neonatal platelets.

Drugs (particularly indomethacin, ibuprofen) can prolong closure and bleeding times.
Survey on Platelet Transfusion Practice

Case Vignette: GA 27 wks, BW 950 g

A  d2, stable condition, no bleeding

B  d9, no bleeding, stable condition

OR (95% CI) US vs. AUT/GER/SUI: 3.79 (2.64 – 5.38)
P < 0.0001

OR (95% CI) US vs. AUT/GER/SUI: 3.34 (2.34 – 4.78)
P < 0.0001

Cremer M et al., Transfusion, 2011
Survey on Platelet Transfusion Practice

Case Vignette: GA 27 wks, BW 950 g

d2, sepsis, mechanical ventilation, vasopressors, IVH

OR (95% CI) US vs. AUT/GER/SUI: 3.95 (2.72 – 5.73)
P < 0.0001

OR (95% CI) US vs. AUT/GER/SUI: 5.05 (3.52 – 7.26)
P < 0.0001

Cremer M et al., Transfusion, 2011
Survey on Platelet Transfusion Practice

Case Vignette: Term neonate

A d1, healthy, suspected AITP

OR (95% CI) US vs. AUT/GER/SUI: 1.71 (1.20 – 2.43)
P < 0.001

B d1, Gram-negative sepsis, mechanical ventilation, vasopressors*

OR (95% CI) US vs. AUT/GER/SUI: 4.59 (3.20 – 6.58)
P < 0.0001

Cremer M et al., Transfusion, 2011
**Evidence of Efficacy of Prophylactic Platelet Transfusions**

Multicenter RCTs:

Andrew M et al., J Pediatr 1993;123:285-91

Inclusion criteria: preterm infants GA < 33 wks, BW 500 – 1500 g platelet count < 150/nl within the first 72 hrs

Exclusion criteria: platelet count < 50/nl

Transfusion criteria:

Arm 1: to maintain platelets > 150/nl within the first 7 days, blood examinations every 12 hrs, single donor package, volume 10 ml/kg BW, within 1 h.

Arm 2: platelet count >50/nl and < 150/nl, or if bleeding occurred

<table>
<thead>
<tr>
<th></th>
<th>Arm 1 (n = 78)</th>
<th>Arm 2 (n = 74)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Overall increase of IVH</td>
<td>22 (28.2 %)</td>
<td>19 (25.7 %)</td>
<td>0.73</td>
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<td>(all stages, over 7 d)</td>
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<td>IVH °III/IV</td>
<td>11 (8.6 %)</td>
<td>5 (3.9 %)</td>
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<td>RBC (ml/kg)</td>
<td>15.7</td>
<td>18.8</td>
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<td>FFP (ml/kg)</td>
<td>10.3</td>
<td>17.2</td>
<td></td>
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<tr>
<td>Platelets (ml/kg)</td>
<td>16.4</td>
<td>6.0</td>
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PlaNet-2: RCT Towards Platelet Transfusion Thresholds

Introduction
Platelets are the cells that help the blood to clot. Platelet transfusions are given to babies with low levels of platelets and signs of bleeding, but we do not know when best to give platelet transfusions to babies with low platelet levels and no signs of bleeding.

The aim of this study is to understand better when to give transfusions of platelets to babies with low platelet counts. For babies with low platelets and no evidence of bleeding, we would like to find out which platelet levels we should transfuse babies at. We have therefore designed a new clinical study to compare outcomes for babies transfused at two different platelet levels. Babies are randomised in to one of two groups:

One group of babies will receive a platelet transfusion whenever their platelet count drops below 50.

Arm 1 (n = 330): if platelets < 25/nl.
Arm 2 (n = 330): if platelets < 50/nl.

Plt transfusion volume: 15 ml/kg
Risks of Platelet Transfusions

- Suppression of megakaryopoiesis by binding of Thpo to transfused platelets
- Transmission of infections (bacterial, but also viral or protozoal)
- Errors in administration
- Micro-embolisms
- Transfusion-related acute lung injury (TRALI)
- Hepatic dysfunction after NEC
- Imbalance of the hemostatic system – ‘developmental mismatch‘

The Immature Platelet Fraction (IPF)  
A novel diagnostic tool of the megakaryopoietic activity
Immature Platelet Fraction during the first week after birth

Cremer M et al., Br J Haematol, 2009
Predictive value of IPF on a consecutive severe decrease (>50 × 10^9/l) of neonatal platelet counts within 24 h.
Indication for platelet transfusion in neonates according to the current guideline of the German Medical Association (*Querschnittsleitline Bundesärztekammer, 2011*):

- acute massive or threatening hemorrhage
- liver dysfunction, if platelet counts are < 20/nL
- prior to major surgery, if platelet counts are < 100/nL
- prophylactically prior to elective lumbar puncture, if platelet counts are < 50/nL

For details see:
Current Best Practice for Prophylactic Platelet Transfusions in Neonates

Consider always the cause and the course of neonatal thrombocytopenia!
Choose rather restrictive thresholds!
Substitute with FFP to maintain the hemostatic balance!

A. Preterm infants, BW < 1500g, GA < 34+0 weeks

- No signs of bleeding
  > maintain platelet counts > 20/nl
- No signs of bleeding, but positive laboratory signs of infection
  > maintain platelet counts > 50/nl

B. ELBW infants, particularly if BW < 800 g

- Maintain platelet counts > 80/nl, if positive laboratory signs of infection or neutropenia occurs (IUGR)
- Maintain platelet counts > 100/nl, if starting indomethacin or ibuprofen

Dame C, Checkliste Neonatologie, 2015 (in press)
Current Best Practice for Prophylactic Platelet Transfusions in Neonates

C. Neonatal alloimmune thrombocytopenia (NAIT)

• Transfuse compatible HPA-1a-, 5b-negative platelets
  > to maintain platelet counts > 30/nl in term neonates
  > to maintain platelet counts > 50/nl in preterm neonates

If hemorrhage occurs or platelets are < 30/ nl, but HPA-1a-, 5b-negative platelets are not available, transfusion of non-selected platelets is allowed.
Best Practice for Prophylactic Platelet Transfusions in Neonates

- AB0-identical platelets, also considering the Rhesus factor
- Apheresis product (preferentially)
  - better recovery, lower refractory, single donor exposure,
    higher platelet number per ml volume of the package
- Transfusion volume: 15 – 20 ml/kg over 30 – 60 min, separate i.v. line
- Max. storage time 5 d, if adequately handled
- Baby-packages to reduce donor exposure
Thank you!

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