When should I transfuse platelets and plasma for children?

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When should I transfuse platelets and plasma in children?

1. Platelet Transfusion in children:
   - Background
   - Evidence & uncertainties
   - Recommendations

2. FFP use in neonates & children:
   - Background
   - Evidence & uncertainties
   - Recommendations
Platelet use in the UK

• Increasing use of a scarce resource
  – 25% increase between 2007/8 - 2014/15 (England – all ages)

• Paediatric clinical settings
  – Haematology-oncology, cardiac surgery, PICU

• Therapeutic vs Prophylactic use
  – Prophylaxis : 60%

• Efficacy
  – Historical & more recent evidence of benefit
  – Optimal use not well defined
    • Prophylaxis strategies, Thresholds, Doses

• Safety - consequences of inappropriate use
  – Adverse reactions, platelet refractoriness, blood product exposure
Platelet Support: Evidence

• Evidence base limited:
  – Significant extrapolation from adult studies
  – Consensus opinion

• Recent systematic reviews & other studies –
  – Prophylactic vs transfusion only strategies - support prophylaxis
  – Thresholds - may vary between individuals & disease groups
  – Platelet dose – lower dose may be as effective but may require more frequent transfusion

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Platelet Support: Evidence

- **PLADO study (post hoc paediatric subgroup)**
  - Children (n=198) with treatment induced hypoproliferative thrombocytopenia
  - Daily haemostatic assessment

<table>
<thead>
<tr>
<th>Age range</th>
<th>≥ Grade 2 bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 0-5 yrs</td>
<td>86%</td>
</tr>
<tr>
<td>Child 6-12 yrs</td>
<td>88%</td>
</tr>
<tr>
<td>Child 13-18 yrs</td>
<td>77%</td>
</tr>
<tr>
<td>Adult</td>
<td>67%</td>
</tr>
</tbody>
</table>

- Higher risk of bleeding in children vs adults
- More days with ≥ Grade 2 bleeding
- Risk highest in the autologous HSCT group
- Bleeding occurred at a range of counts

*Josephson, Blood 2012*
Platelet Thresholds: Survey of Practice in ALL 2014

What is your usual threshold for platelet transfusion in the following groups of children/adolescents with ALL?

<table>
<thead>
<tr>
<th></th>
<th>$10 \times 10^9$</th>
<th>$20 \times 10^9$</th>
<th>$30 \times 10^9$</th>
<th>$50 \times 10^9$</th>
<th>$70-80 \times 10^9$</th>
<th>$100 \times 10^9$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well patient</td>
<td>88.9%</td>
<td>11.1%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Febrile patient</td>
<td>15.8%</td>
<td>84.2%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Patient with bleeding</td>
<td>0.0%</td>
<td>0.0%</td>
<td>16.7%</td>
<td>66.7%</td>
<td>11.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Prior to LP</td>
<td>5.3%</td>
<td>10.5%</td>
<td>26.3%</td>
<td>52.6%</td>
<td>5.3%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Prior to CVL Insertion</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>52.6%</td>
<td>36.8%</td>
<td>10.5%</td>
</tr>
</tbody>
</table>

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Platelet Support: Evidence

- Well patient with no bleeding
- Adults & adolescents with AML
- Threshold of $20 \times 10^9$ vs $10 \times 10^9$

Supported by Cochrane Systematic Review 2015 – low quality evidence
Platelet Support: Evidence Prior to LPs

- Cochrane review 2016
  - No evidence from RCTs to determine the correct threshold
  - Would likely require a very large study
- Cohort study data support safety of lower thresholds
- van Veen BJH 2010 Review concluded platelet count of 40 x10^9 was safe for LPs
- Howard et al JAMA 2000
  - 941 LPs in Children with ALL
  - Variable platelet counts – majority: 21-50 x10^9/l
  - No serious bleeding events
  - CI calculated for different thresholds
Platelet Support: Evidence Prior to CVL Insertion

- Cochrane review 2010
  - No RCT evidence on platelet support or thresholds pre CVL insertion
- Most guidelines recommend a platelet count of 50x10^9/l

- Zeidler et al 2011
  - Adult study n= 193
  - 604 CVL placements
  - Un-tunnelled CVL

<table>
<thead>
<tr>
<th>Platelet count (x10^9)</th>
<th>OR</th>
<th>95% CI</th>
<th>(p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>2.88</td>
<td>1.23-6.75</td>
<td>(0.015) *</td>
</tr>
<tr>
<td>20-49</td>
<td>1.27</td>
<td>0.77-2.18</td>
<td>(0.38)</td>
</tr>
<tr>
<td>50-99</td>
<td>1.60</td>
<td>0.98-2.63</td>
<td>(0.062)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>1.0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

* Significant bleeding only in those with platelets < 20

Zeidler K, Transfusion 2011
<table>
<thead>
<tr>
<th>Platelet count (x $10^9$/l)</th>
<th>Clinical situation to trigger platelet transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>Irrespective of other issues (excluding ITP, TTP/HUS, HIT)</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>Severe mucositis</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Laboratory evidence of DIC in the absence of bleeding*</td>
</tr>
<tr>
<td></td>
<td>Anticoagulant therapy</td>
</tr>
<tr>
<td></td>
<td>Risk of bleeding due to a local tumour infiltration</td>
</tr>
<tr>
<td></td>
<td>Insertion of a non-tunnelled central venous line</td>
</tr>
<tr>
<td>&lt; 40</td>
<td>Prior to lumbar puncture**</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Moderate haemorrhage (e.g. gastrointestinal bleeding) including bleeding in association with DIC</td>
</tr>
<tr>
<td></td>
<td>Surgery, unless minor (except at critical sites)</td>
</tr>
<tr>
<td></td>
<td>-including tunnelled central venous line insertion</td>
</tr>
<tr>
<td>&lt; 75 - 100</td>
<td>Major haemorrhage or significant post-operative bleeding (e.g. post cardiac surgery)</td>
</tr>
<tr>
<td></td>
<td>Surgery at critical sites: central nervous system including eyes</td>
</tr>
</tbody>
</table>

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FFP use in neonates & children

• FFP use static or increasing
  – 4% increase in use documented in UK audit (*Stanworth 2011*)

• Evidence base for FFP currently inadequate
  – Lack of supporting evidence for many indications
  – Variations in clinical practice
    • Range of FFP use 0.99 – 5.84% (*Puettz, 2012*)
  – Data suggest some use likely ineffective/inappropriate
CONCLUSION: Combined with the 2004 review, 80 RCTs have investigated FP with no consistent evidence of significant benefit for prophylactic and therapeutic use across a range of indications evaluated.
UK Paediatric and neonatal FFP transfusions

**FFP National Comparative Audit 2009**

Age ranges:
- 4635 - 16+
- 114 - 1-15 yrs
- 220 < 1 yr

**EASTR study, 2016**

- 9% of FFP recipients paediatric (<16 yrs)
- 63% of paediatric FFP recipients < 1yr of age

Stanworth et al, *Transfusion* 2011

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[Graph showing age distribution of FFP recipients]

Main reason for transfusion in Children (1 – 15 yrs old)

- Bleeding:
- Before or during invasive procedure or surgery with abnormal coagulation:
- Abnormal coagulation with no bleeding:
- Other:
- Not known

FFP National Comparative Audit 2009
Age ranges: 16yrs+ (4635) 1-15 yrs (114) < 1 yr (220; 4%)
Main reason for transfusion in Infants (< 1 yr old, n=220)

- Bleeding
- Before or during invasive procedure/surgery with abnormal coagulation
- Abnormal coagulation no bleeding
- Other
- Not known

FFP National Comparative Audit 2009

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Indications and Effects of Plasma Transfusions in Critically Ill Children

Oliver Karam\textsuperscript{1,2}, Pierre Demare\textsuperscript{3}, Alison Shefler\textsuperscript{4}, Stéphane Leteurtre\textsuperscript{2,5}, Philip C. Spinella\textsuperscript{6}, Simon J. Stanworth\textsuperscript{7}, Marisa Tucci\textsuperscript{8}; on behalf of the Canadian Critical Care Trials Group (CCCTG), Pediatric Acute Lung Injury and Sepsis Investigators (PALISI), BloodNet, and the PlasmaTV Investigators\textsuperscript{*}

Primary indication for plasma transfusion

- Critical bleeding: 34%
- Minor bleeding: 22%
- Preparation: 21%
- Post-op risk of bleeding: 11%
- No bleeding, no procedure: 12%

\textit{n = 443}
FFP Use in infants: UK National Comparative Audit 2011

- Median INR pre FFP
  - Children with bleeding: 1.5 (1.2-1.9)
  - Children with no bleeding: 1.6 (1.2-1.8)

- Is this predictive of bleeding?

Coagulation Screening – PT & APTT
- Initially developed as tests for patients with a high pretest probability of coagulation factor deficiency

- PT/APTT became screening tool to predict bleeding risk in a variety of clinical situations
Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedures: an evidence-based review

Volume 45, September 2005 TRANSFUSION 1413

Jodi B. Segal and Walter H. Dzik on behalf of the Transfusion Medicine/Hemostasis Clinical Trials Network

Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities

Volume 46, August 2006 TRANSFUSION 1279

Omar I. Abdel-Wahab, Brian Healy, and Walter H. Dzik

• Pre-transfusion INR 1.1 – 1.85
  • Normalisation of PT/INR: 0.8%
  • Reduction in INR (50%): 15%
  • Median decrease in INR: 0.2 sec

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PT/INR

Stanworth S et al. Transfusion 2011; 51: 62-70

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## Neonatal Haemostasis

### Defining abnormal coagulation in neonates

<table>
<thead>
<tr>
<th>AGE</th>
<th>I, V, VIII/vWF</th>
<th>Vitamin K-dependent factors (U/ml)</th>
<th>Contact factors (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
<td>V</td>
<td>VIII</td>
</tr>
<tr>
<td>ADULT</td>
<td>3.40</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Term (37-41 WEEKS)</td>
<td>2.40</td>
<td>1.00</td>
<td>1.50</td>
</tr>
</tbody>
</table>

- Coagulation parameters are affected by gestational/postnatal age
- Physiological prolongation of PT and APTT in neonates
- Age adjusted normal ranges
- Problems of defining normal ranges and interpreting results

*Andrew, 1988*
# Preterm normal ranges

<table>
<thead>
<tr>
<th>Test</th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (secs)</td>
<td>13.0 (10.6-16.2)</td>
<td>12.5 (10.0-15.3)</td>
<td>11.8 (10.0-13.6)</td>
</tr>
<tr>
<td>APTT (secs)</td>
<td>53.6 (27.5-79.4)</td>
<td>50.5 (26.9-74.1)</td>
<td>44.7 (26.9-62.5)</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.43 (1.50-3.73)</td>
<td>2.80 (1.60-4.18)</td>
<td>2.54 (1.50-4.14)</td>
</tr>
</tbody>
</table>

Figures for healthy preterm infants (30-36 weeks gestation) during the first month of life.

Data from M. Andrews et al, 1988, 1990. All infants had had vitamin k
BSH recommendations - neonates

• FFP may be of benefit in neonates with clinically significant bleeding (including massive blood loss) or prior to invasive procedures with a risk of significant bleeding, and who have an abnormal coagulation profile
  – PT/APTT significantly above the normal gestational and postnatal age-related reference range (taking into account local reference ranges where available) (2C)

• There is no evidence to support the routine use of FFP to try to correct abnormalities of the coagulation screen alone in non-bleeding neonates (1C)

• FFP should not be used for simple volume replacement or routinely for prevention of IVH (1B).
BSH recommendations – Children

- FFP may be beneficial in children with DIC who have a significant coagulopathy (PT/APTT >1.5 times the mid-point of the normal range or fibrinogen <1g/l) associated with clinically significant bleeding or prior to invasive procedures.
- Early use of FFP is also recommended in the management of major haemorrhage.
- FFP should not be administered to non-bleeding children with minor prolongation of the PT/APTT (including prior to surgery unless to critical sites).
- Other specific indications: TTP; coagulation deficiencies; vitamin K deficiency bleeding.

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Platelet & FFP transfusions in Children: Conclusions

• Optimal strategies for platelet use in children remain to be defined – thresholds recommended for treatment & prophylaxis
  – Thresholds largely unchanged from previous guideline

• Doubt exists on the efficacy of FFP in a range of settings & there is evidence to suggest inappropriate
  – Extensive use in non-bleeding children with abnormal coagulation
  – Poor predictive value of PT/APTT to predict bleeding
  – Problems defining abnormal coagulation in neonates
  – Limited correction of abnormal parameters by FFP

• Likely that more restrictive use would be appropriate

• Clear need for ongoing research