Red blood cell transfusions in the PICU: What & When

Canada Critical Care Forum
November 8th 2018
Toronto, CA

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Conflict of Interest Disclosure
Marisa Tucci M.D.

None
Objectives

What we transfuse

- Prevalence of RBC transfusion in PICU
- Current practices and beliefs with regard to RBC storage time

When we transfuse:

- RBC transfusion thresholds in PICU
- Anemia tolerance
WHAT DO WE TRANSFUSE?
Red blood cell (RBC) units

- Packed RBC units, also known as packed cells, are RBCs that have been separated for blood transfusion and stored for periods that can range from 2 to 42 days.
- RBC concentrates slightly vary in contents of residual platelets, plasma and additive solution.
- All RBC units are leukocyte-depleted prior to storage in Canada.
- Storage of RBCs outside the body leads to complex changes - storage-related changes may have clinical relevance.
Red blood cell storage lesion

Changes in red blood cell
Increases in:
- Osmotic fragility
- Microvesicles
- Membrane rigidity
- Oxygen affinity of hemoglobin
- Vascular endothelium adherence

Decreases in:
- Oxygen delivery
- Na-K-ATPase
- RBC deformability

Changes in additive solution
Increases in:
- Cell free hemoglobin
- Free heme and iron
- Cytokines (IL-1, 6, 8, and TNF α)
- Potassium
- Hydrogen ion

Decreases in:
- pH
- Opsonization ability

Metabolic changes
Increase in:
- Lactate production

Decreases in:
- 2,3 DPG
- ATP
- Nitric oxide
- Phosphate

Oxidative stress
Increases in:
- Protein oxidation
- Lipid peroxidation
- Prostaglandins

Remy et al Curr Opin Pediatrics 2015
RBC transfusions are frequent in PICU

- 8% of all RBC transfusions are given in intensive care
- Prevalence of transfusion in critically ill children
  - 49% of children admitted to PICU for > 48 hours (Bateman et al. AJRCCM 2008)
  - In consecutive PICU admissions at Sainte-Justine
    - 14% in 2001 (Armano et al. CCM 2001)
    - 18% in 2009 (Lacroix, unpublished observation)
    - 14% in 2013-2018 (Jutras et al)
## Storage time of RBC units given in PICU

<table>
<thead>
<tr>
<th>Number of children</th>
<th>Study Details</th>
<th>Storage time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>977 children in 30 PICUs</td>
<td>Bateman, AJRCCM 2008</td>
<td>17.2</td>
</tr>
<tr>
<td>842 children admitted to Sainte-Justine PICU</td>
<td>Demaret PCCM 2009</td>
<td>15.8</td>
</tr>
<tr>
<td>Patients in ABC-PICU trial usual practice arm</td>
<td>Spinella, Tucci et al 2014-2018</td>
<td>17-20</td>
</tr>
</tbody>
</table>
Age of RBC units in pediatrics

- **Standard practice of blood banks:**
  - **For most patients:** delivery of oldest available RBC unit first
  - **For certain critically ill pediatric patients:**
    - Belief that shorter storage improves outcomes
    - Agreements with blood banks to routinely use fresher RBCs even though there is no evidence to support such practice.
### RBC age policies survey

<table>
<thead>
<tr>
<th>Restriction on max RBC storage age?</th>
<th>≤ 7 days</th>
<th>8-14 days</th>
<th>15-29 days</th>
<th>42 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate card surgery ICU</td>
<td>51.2%</td>
<td>20.9%</td>
<td>2.3%</td>
<td>25.6%</td>
</tr>
<tr>
<td>Neonate card medical ICU</td>
<td>27.9%</td>
<td>16.3%</td>
<td>4.7%</td>
<td>51.1%</td>
</tr>
<tr>
<td>Non-neonatal cardiac, surgical ICU</td>
<td>25.6%</td>
<td>18.6%</td>
<td>4.7%</td>
<td>51.2%</td>
</tr>
<tr>
<td>Non-neonatal cardiac, medical ICU</td>
<td>11.6%</td>
<td>11.6%</td>
<td>4.7%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Sickle cell patients</td>
<td>9.3%</td>
<td>14%</td>
<td>11.6%</td>
<td>65.1%</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>11.6%</td>
<td>9.3%</td>
<td>7%</td>
<td>72.1%</td>
</tr>
<tr>
<td>Severe traumatic brain injury</td>
<td>4.7%</td>
<td>7%</td>
<td>4.7%</td>
<td>83.7%</td>
</tr>
<tr>
<td>Post cardiac arrest</td>
<td>7%</td>
<td>4.7%</td>
<td>4.7%</td>
<td>83.7%</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>4.7%</td>
<td>4.7%</td>
<td>7%</td>
<td>83.7%</td>
</tr>
<tr>
<td>Post bone marrow transplant</td>
<td>4.7%</td>
<td>4.7%</td>
<td>4.7%</td>
<td>86%</td>
</tr>
<tr>
<td>ARDS</td>
<td>7%</td>
<td>2.3%</td>
<td>2.3%</td>
<td>88.3%</td>
</tr>
</tbody>
</table>

*Spinella et al, Transfusion 2010*
If older RBC units do cause adverse consequences, then such practice raises ethical concerns regarding inequitable use of available RBC units.

Emotional overtones complicate decision-making processes at bedside and blood bank.
Older blood in the sickest children

Is there really a concern?
Is older worse, better or just as good?
4 large RCTs in adults have compared RBC transfusions aged less than 10 days with transfusion of 14- to 32-day-old RBC units in various critically ill populations:

- Age of Blood Evaluation (ABLE) randomized controlled trial
- Red Cell Storage Duration Study (RECESS) trial
- Informing Fresh versus Old Red Cell Management (INFORM) trial
- Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) trial

No survival advantage in transfusing fresher RBC units in over 10000 participants.
No high quality evidence presently available that can answer this question in critically ill PICU patients.

Numerous retrospective studies have been published to address this issue in various critically ill pediatric populations including general PICU, cardiac surgery, neonatal, and sickle cell patients.

Some report an association between older RBC units and risk of adverse outcomes

Others find no association between longer RBC storage and worse clinical outcomes.

Most are secondary analyses undertaken in databases from RCTs or observational studies with other primary aims
Results are conflicting largely due to the nature of the study design.

RCTs needed to really answer the question.
Mortality in a systematic review and meta-analysis of 16 RCTs

Transfusion of fresher RBCs was not associated with decreased mortality. No difference in any of the subgroups analyzed (ICU, Cardiac surgery, Pediatric).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Fresh or fresher Events</th>
<th>Total</th>
<th>Old or standard-issue Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauss 1996</td>
<td>0</td>
<td>21</td>
<td>1</td>
<td>19</td>
<td>0.0%</td>
<td>0.30 [0.01, 7.02]</td>
<td>1996</td>
</tr>
<tr>
<td>Schulman 2002</td>
<td>4</td>
<td>8</td>
<td>2</td>
<td>9</td>
<td>0.1%</td>
<td>2.25 [0.55, 9.17]</td>
<td>2002</td>
</tr>
<tr>
<td>Hebert 2005</td>
<td>5</td>
<td>20</td>
<td>4</td>
<td>29</td>
<td>0.2%</td>
<td>1.81 [0.55, 5.93]</td>
<td>2005</td>
</tr>
<tr>
<td>FerandesdaCunha 2005</td>
<td>9</td>
<td>26</td>
<td>10</td>
<td>26</td>
<td>0.5%</td>
<td>0.90 [0.44, 1.85]</td>
<td>2005</td>
</tr>
<tr>
<td>Bennett Guerrero 2009</td>
<td>1</td>
<td>12</td>
<td>0</td>
<td>11</td>
<td>0.0%</td>
<td>2.77 [0.12, 61.65]</td>
<td>2009</td>
</tr>
<tr>
<td>Fergusson 2012</td>
<td>30</td>
<td>188</td>
<td>31</td>
<td>189</td>
<td>1.3%</td>
<td>0.97 [0.61, 1.54]</td>
<td>2012</td>
</tr>
<tr>
<td>Kor 2012</td>
<td>17</td>
<td>49</td>
<td>22</td>
<td>50</td>
<td>1.1%</td>
<td>0.79 [0.48, 1.29]</td>
<td>2012</td>
</tr>
<tr>
<td>Heddle 2012</td>
<td>35</td>
<td>309</td>
<td>61</td>
<td>601</td>
<td>1.8%</td>
<td>1.12 [0.75, 1.65]</td>
<td>2012</td>
</tr>
<tr>
<td>Aubron 2012</td>
<td>5</td>
<td>25</td>
<td>2</td>
<td>26</td>
<td>0.1%</td>
<td>2.60 [0.55, 12.19]</td>
<td>2012</td>
</tr>
<tr>
<td>Dhabangi 2013</td>
<td>1</td>
<td>37</td>
<td>0</td>
<td>37</td>
<td>0.0%</td>
<td>3.00 [0.13, 71.34]</td>
<td>2013</td>
</tr>
<tr>
<td>Lacroix 2015</td>
<td>448</td>
<td>1211</td>
<td>430</td>
<td>1219</td>
<td>25.1%</td>
<td>1.05 [0.94, 1.17]</td>
<td>2015</td>
</tr>
<tr>
<td>Dhabangi 2015</td>
<td>7</td>
<td>145</td>
<td>5</td>
<td>145</td>
<td>0.2%</td>
<td>1.40 [0.45, 4.31]</td>
<td>2015</td>
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<tr>
<td>Steiner 2015</td>
<td>23</td>
<td>538</td>
<td>29</td>
<td>560</td>
<td>1.0%</td>
<td>0.83 [0.48, 1.41]</td>
<td>2015</td>
</tr>
<tr>
<td>Schreiber 2015</td>
<td>3</td>
<td>82</td>
<td>2</td>
<td>85</td>
<td>0.1%</td>
<td>1.55 [0.27, 9.07]</td>
<td>2015</td>
</tr>
<tr>
<td>Heddle 2016</td>
<td>634</td>
<td>6936</td>
<td>1213</td>
<td>13922</td>
<td>33.4%</td>
<td>1.05 [0.96, 1.15]</td>
<td>2016</td>
</tr>
<tr>
<td>Cooper 2017</td>
<td>687</td>
<td>2410</td>
<td>678</td>
<td>2414</td>
<td>34.8%</td>
<td>1.01 [0.93, 1.11]</td>
<td>2017</td>
</tr>
</tbody>
</table>

Total (95% CI) 12017 19342 100.0% 1.04 [0.98, 1.09]

Total events 1909 2490

Heterogeneity: Tau² = 0.00; Chi² = 7.82, df = 15 (P = .93); I² = 0%

Test for overall effect: Z = 1.28 (P = .20)
2.3.3 Paediatric

**Strauss 1996:**
Randomized single-blind clinical trial conducted to assess donor exposure and safety in VLBW infants

<table>
<thead>
<tr>
<th></th>
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<td>2015</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>47</td>
<td>417</td>
<td>47</td>
<td>416</td>
<td>2.1%</td>
<td>0.99 [0.69, 1.42]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 47
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.46$, df = 4 ($P = .83$); $I^2 = 0$
Test for overall effect: $Z = 0.06$ ($P = .95$)

**Fergusson 2012:**
Age of Red blood cells In Premature Infants (ARIPI) trial was carried out in 377 premature infants weighing ≤ 1250 g. A composite outcome not applicable to older children (necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, intraventricular hemorrhage and/or death) was used.

**Dhabangi 2013, 2015:**
Pilot and then final results of the Tissue Oxygenation by Transfusion in severe Anemia with Lactic acidosis (TOTAL) RCT conducted in Uganda in children severe anemia most of whom had malaria (81%) or sickle cell disease (13%).
Data from these pediatric subpopulations cannot be generalized to all critically ill children.
Pediatric evidence needed to change practice

- No high level evidence available data (RCTs) for general population of PICU patients
- Data from currently existing RCTs in children not applicable to PICU.
- Data from adult trials
  - Cannot be transposed to children
  - Not perceived as relevant to children
- Only a definitive study in children would provide needed evidence to guide care / policy and change practice.
Age of Blood in Children in PICU (ABC-PICU)
Multicenter international double blind superiority RCT
Principal investigators: M Tucci, P Spinella, J Lacroix
Primary question:
Will fresh RBC units (≤ 7 days of storage) improve outcomes in critically ill children compared to older standard delivery RBC units?
Enrollment finished in August 2018
Trial has enrolled 1538 critically ill children from 5 countries who required transfusion in PICU
WHEN DO WE TRANSFUSE?

ANEMIA TOLERANCE IN THE CRITICALLY ILL PATIENT?
IMPACT OF ANEMIA?
Anemia in the critically ill child

- Anemia = one of the most common medical complications encountered in critically ill children – almost 50%!
- RBC transfusions can be lifesaving but are associated with several risks (including transmission of infectious diseases, immune suppression, ARDS, circulatory overload and errors in administration)
- Should only be given when true benefits are likely
Decision to transfuse RBCs

- In principle, RBCs are given when there is evidence of inadequate oxygen delivery to the tissues and therefore an inadequate supply of oxygen to support cellular metabolism.
- **Goal = restoration of tissue oxygenation**
- In ICU, RBC transfusion generally occurs when:
  - Clinical evidence of hypoxia/dysoxia (hypoperfusion, including lactic acidosis, increased base deficit, decreased central venous oxygen saturation) after appropriate volume expansion, use of pressor agents, etc.
  - **Active hemorrhage** associated with shock
  - Hemorrhage that cannot be immediately controlled
RCTs on threshold hemoglobin (Hb) for RBC transfusion

- 31 RCTs
- 12,587 participants
- Compared restrictive vs. liberal red blood cell (RBC) transfusion strategy
- Outcome measure: mortality

Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion (2016)
Carson JL, Stanworth SJ, Roubinian N, Fergusson DA, Triulzi D, Doree C, Hebert PC
Only 1 RCT in children

28 or 30-day mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Restrictive Events</th>
<th>Liberal Events</th>
<th>Weight</th>
<th>Risk Ratio (M-H, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacroix 2007</td>
<td>14</td>
<td>14</td>
<td>4.7%</td>
<td>0.99 [0.48, 2.04]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total (95% CI) 5221 5316 100.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total events 470 497</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heterogeneity: Tau² = 0.04; Chi² = 29.75, df = 21 (P = 0.10); I² = 29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Test for overall effect: Z = 0.29 (P = 0.77)</td>
</tr>
</tbody>
</table>
Findings provide good evidence that transfusions with allogeneic RBCs can be avoided in most patients with Hb thresholds above 7 to 8 g/dL.

Transfusing at a restrictive Hb concentration of 7 to 8 g/dL decreases exposure to RBC transfusion by up to 43% across a broad range of clinical specialities.

No evidence that a restrictive transfusion strategy impacts 30-day mortality or morbidity compared with a liberal transfusion strategy.

Insufficient data to inform the safety of transfusion policies in certain clinical subgroups, including acute coronary syndrome, myocardial infarction, neurological injury/traumatic brain injury, acute neurological disorders, stroke, thrombocytopenia, cancer, hematological malignancies, and bone marrow failure.
RCTs on threshold hemoglobin (Hb) for RBC transfusion in children

<table>
<thead>
<tr>
<th>Population</th>
<th>637 hemodynamically stable critically ill children 88% of eligible patients not enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>New Progressive MODS</td>
</tr>
<tr>
<td>Restrictive arm</td>
<td>Hb ≤ 7.0 g/L</td>
</tr>
<tr>
<td>Liberal arm</td>
<td>Hb ≤ 9.5 g/dL</td>
</tr>
<tr>
<td>Results</td>
<td>Restrictive transfusion strategy noninferior to liberal transfusion strategy and reduces exposure to blood products</td>
</tr>
</tbody>
</table>

TRIPICU
Lacroix et al NEJM 2007
RCTs on threshold hemoglobin (Hb) for RBC transfusion in children

<table>
<thead>
<tr>
<th></th>
<th>TRIPICU Lacroix et al NEJM 2007</th>
<th>Cholette et al Ann Thorac Surg 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>637 hemodynamically stable critically ill children 88% of eligible patients not enrolled</td>
<td>162 infants weigh less than 10 kg undergoing biventricular repair or palliative (nonseptated) operation</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>New Progressive MODS</td>
<td>Lactate, arteriovenous oxygen difference ([avO_{2} \text{ diff}])</td>
</tr>
<tr>
<td><strong>Restrictive arm</strong></td>
<td>Hb ≤ 7.0 g/L</td>
<td>Biventricular repair Hb &lt; 7.0 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palliative repair Hb &lt; 9.0 g/dL</td>
</tr>
<tr>
<td><strong>Liberal arm</strong></td>
<td>Hb ≤ 9.5 g/dL</td>
<td>Biventricular repair Hb &lt; 9.5 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Palliative repair Hb &lt; 12.0 g/dL</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Restrictive transfusion strategy noninferior to liberal transfusion strategy and reduces exposure to blood products</td>
<td>No evidence of impaired oxygen delivery Clinical outcome similar. Volume of transfusions lower.</td>
</tr>
</tbody>
</table>
Transfusion thresholds in PICU

Despite these 2 seminal studies, multiple surveys and studies indicate that pediatric intensivists have only partially adopted a restrictive transfusion strategy:


Observed Hb thresholds are higher than the evidence indicates, which may expose some children to potential complications without any expectation of benefit.

Uses a stratified probability sample of 20% of all inpatient discharges (representing approximately 96% of the US population).
The need to update guidance for RBC transfusion decision-making in critically ill children prompted TAXI conference series.

Goals were to bring together international, multidisciplinary experts to develop evidence-based, and when evidence lacking, expert consensus-based recommendations regarding decision-making for RBC transfusion management and research priorities for transfusion in critically ill children.

Experts focused on 9 specific populations of critically ill children: general, respiratory failure, non hemorrhagic shock, non life threatening bleeding or hemorrhagic shock, acute brain injury, acquired/congenital heart disease, sickle cell/oncology/transplant, extracorporeal membrane oxygenation/ventricular assist/ renal replacement support, and alternative processing.

Developed 56 clinical recommendations and 45 research recommendations.
TAXI recommendations

Consensus Recommendations for RBC Transfusion Practice in Critically Ill Children From the Pediatric Critical Care Transfusion and Anemia Expertise Initiative

Stacey L. Valentine, MD, MPH, FCCP; Melania M. Rembea, MD, PhD; Jennifer A. Muszynski, MD, MPH; Jill M. Cholette, MD; Allan Doctor, MD; Phillip C. Spinella, MD; Marie E. Steiner, MD; Marisa Tucci, MD; Nabil E. Hassan, MD; Robert I. Parker, MD; Jacques Lacoix, MD; Andrew Argent, MD, MBChB; Jeffrey L. Carson, MD; Kenneth E. Remy, MD; Pierre Demaret, MD, MSc; Guillaume Emeriaud, MD, PhD; Martin C. J. Kneyber, MD, PhD, FCCM; Nina Guzzetta, MD; Mark W. Hall, MD; Duncan Macrae, MBChB; Oliver Karam, MD, PhD; Robert T. Russell, MD, MPH; Paul A. Stricker, MD; Adam M. Vogel, MD; Robert C. Tasker, MA, MBBS, MD; Alexis F. Turgeon, MD, MSc; Steven M. Schwartz, MD; Ariane Willems, MD; Cassandra D. Josephson, MD; Naomi L. C. Luban, MD; Leslie E. Lehmann, MD; Simon J. Stanworth, MD; Nicole D. Zantek, MD; Timothy E. Bunchman, MD; Ira M. Chelifetz, MD; James D. Fortenberry, MD; Meghan Delaney, DO, MPH; Leo van de Watering, MD; Karen A. Robinson, PhD; Sara Malone, LCSW; Katherine M. Steffen, MD; Scot T. Bateman, MD; for the Pediatric Critical Care Transfusion and Anemia Expertise Initiative (TAXI), in collaboration with the Pediatric Critical Care Blood Research Network (BloodNet), and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

What next?

- Question remains: Is it safe to use a restrictive RBC transfusion strategy in these excluded patients?
  - Bleeding patients
  - Severe trauma
  - Unstable patients, etc.

- Optimizing Transfusion Thresholds in Critically-ill Children with Anemia (OpTTICCA) – Jacques Lacroix and Marisa Tucci
  - Upcoming RCT to inform us on whether it is safe to not to administer RBC transfusion in the vast majority of PICU patients.
  - Will exclude a small minority of eligible patients (≤ 12%)
  - Will be pragmatic and have a minimal number of exclusion criteria
  - Data collection: electronically (> 95%)
Transfusing RBCs versus tolerating anemia is a major and daily clinical dilemma in PICU

- 74% of patients in PICU more than 48 hours are anemic
- 50% are anemic at discharge

Permissive anemia has been proven to be safe during the acute illness in stabilized children in ICU

Little is known about the ramifications of such practices on long-term well-being post PICU

Chronic anemia may have a significant long-term negative impact on developing children and in particular on their neurocognitive function
Impact of anemia post PICU

- Anemia research group – international collaboration
- Studies currently ongoing to assess the causes of post-PICU stay anemia, its course and its association with post-PICU outcomes.
- These research questions are particularly relevant in an era where PICU mortality is very low and post-PICU outcomes have become an important focus for all PICU physicians.
Thank you :)
Acknowledgements