Pediatric Transfusion Medicine – What’s HOT?

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Lifestream’s Transfusion Medicine Forum
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Conflict of Interest

• None

• Special thank you to the organizers for kind invitation to speak
Objectives

1. Define Pediatric Transfusion Medicine
2. Understand metabolic and storage lesion concerns in children receiving massive transfusion support
3. Understand best practices around massive transfusion support of children
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What is Pediatric Transfusion Medicine?

- ‘Children are not just little adults’
- ‘Aliquots do not a safe transfusion make’
Why is transfusion practice different in children?

- Children have *unique* pathophysiology, diseases, risks of blood transfusions
- Sicker and complex in modern era
- Long life ahead of them
A new sub-specialty is born

- In the late 1990’s, US National Institutes of Health (NIH) began a campaign, and changed policy, stressing the vital inclusion of children in research endeavors.
- In 2002, at the commencement of the Transfusion Medicine/Hemostasis Clinical Trials Network funded by the National Heart, Lung, and Blood Institute (NHLBI), pediatric working groups were formed.
- In 2002, Herman and Manno published an important textbook entitled *Pediatric Transfusion Therapy*.
- In 2004, Hillyer, Strauss, and Luban published the *Handbook of Pediatric Transfusion Medicine*.

Definition of Pediatric Transfusion Medicine by Dr. Christopher Hillyer

• ‘Pediatric transfusion medicine encompasses the collection, processing, and testing of an adequate number of blood units and their manufacture into a variety of safe and available blood components and the appropriate provision of these components, for intra- or extrauterine transfusion to fetuses, neonates, infants, children, and adolescents’
  – Expanded definitions may include the appropriate manufacture and use of plasma derivatives or concentrated proteins, recombinant coagulation factors, hematopoietic progenitor cells, and other regenerative technologies, encompassed under the titles of cellular therapies and tissue banking.

• Additionally, the practice of Pediatric Transfusion Medicine may require the use of a variety of specialized procedures and technologies including extracorporeal membrane oxygenation (ECMO), apheresis, and intraoperative cell salvage, amongst others

Huge breadth of topics in Pediatric Transfusion Medicine

- Testing differences, including small volume samples and neonatal screens
- Smaller components/Aliquots
- Metabolic concerns, including hyperkalemia, risks of additive/preservative solutions especially with massive transfusions
- Infectious concerns, mainly cytomegalovirus (CMV), but recently Zika!
- Immune tolerance, i.e. ABOi heart transplantation
- Special situations, i.e. exchange transfusions and intrauterine transfusions
- Landmark studies (TRIPICU study, multiple studies in neonates)
• One overarching theme: ‘More studies on transfusion therapy for pediatric patients, and separately on neonates, are *urgently* required’

NHLBI SOS on Pediatric Transfusion Medicine

- Goal: to identify important research questions that can be answered in the next 5-10 years, and would have the potential to transform the clinical practice of pediatric transfusion medicine
- Addressed by basic, translational, and/or clinical research studies
- Focused in six areas:
  - Neonatology and Perinatology - Devices and Surgery
  - Oncology and Transplant - Intensive Care and Trauma
  - Chronic Transfusion - Teenage Blood Donation

https://www.nhlbi.nih.gov/research/reports/2016-scientific-priorities-pediatric-transfusion-medicine
NHLBI SOS on Pediatric Transfusion Medicine, continued

- Meeting was attended by 80 participants representing multiple stakeholders, including academic medicine, researchers, clinicians and government
  - Chaired by Dr. Naomi Luban, Chief of Laboratory Medicine & Pathology, Children’s National Medical Center
  - Sponsored by Dr. Simone Glynn, Branch Chief Blood Epidemiology and Clinical Therapeutics Branch, Division of Blood Diseases & Resources, NHLBI

- Expertise in multiple relevant disciplines and included transfusion medicine, pediatrics, neonatology, hematology, surgery, critical care, trauma, internal medicine and basic and translational science

https://www.nhlbi.nih.gov/research/reports/2016-scientific-priorities-pediatric-transfusion-medicine
Overarching themes

• Lack of baseline data and databases for retrospective and longitudinal studies in neonates to young adults receiving blood products
  • Such data would inform the ability to successfully plan, implement and complete future clinical studies in pediatric transfusion medicine
  • Many of the participants recommended the need to have a REDS (Recipient Epidemiology and Donor Study Evaluation)-like program with a focus on pediatric research
  • Overall, all participants agreed that this was a major area of need in order to move the field forward and to develop future studies to tailor the utilization of blood products in pediatric populations according to age and disease state

https://www.nhlbi.nih.gov/research/reports/2016-scientific-priorities-pediatric-transfusion-medicine
Overarching themes, continued

• Need for novel in vitro and in vivo models to study impact of transfusion in specific diseases/conditions
• Meeting participants noted that in-vitro and in-vivo models need to be developed to answer basic research questions in pediatric transfusion medicine
• This may require modification of existing models or creation of new models

https://www.nhlbi.nih.gov/research/reports/2016-scientific-priorities-pediatric-transfusion-medicine
Overarching themes, continued

- Well designed, well controlled clinical trials are needed to improve clinical guidelines and therapies in pediatric transfusion medicine
- A few areas were identified where clinical trials could be done in a relatively short period of time, but most would require baseline epidemiological data and more translational research before a clinical trial could be developed and successfully implemented
- All participants agreed that mechanistic questions and translational science components should be included as part of the clinical trial when possible to maximize the efficiency and impact of the trial

https://www.nhlbi.nih.gov/research/reports/2016-scientific-priorities-pediatric-transfusion-medicine
Objectives

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Storage lesion of RBCs

- RBCs lose viability & function with increasing duration of storage
- Decrease in pH
- Increase in plasma K⁺
- Decrease in glucose consumption
- Decrease in ATP
- Decrease in 2,3-DPG
- Increase in % of hemolysis

Concerns of treating pediatricians

- Age of the blood, reflected in the quantity of intra-erythrocytic ATP and 2,3-diphosphoglyceric acid and, hence, oxygen offloading
- Potassium content, which increases over storage time
- Solute load from the anticoagulant solutions, which might result in osmotic diuresis with subsequent alteration of cerebral microcirculation and resultant periventricular hemorrhage
- Transfusion-associated viral diseases and graft-versus-host-disease resulting from passive transfer of viral-infected monocytes and engraftable lymphocytes, respectively
Depletion of 2,3-DPG (generally over 1-2 weeks of storage) will cause L shift

- Greater O2 affinity
- Less O2 to tissues

Repletion of 2,3-DPG

- p50 value drops from about 27 mmHg in fresh blood to 18 mmHg in stored RBCs at the time of outdate
  - Corresponds to the normally low p50 value obtained from the blood of many healthy preterm infants at birth, due to the effects of high fetal Hb levels
- Older adult transfused RBCs provide an advantage over the infant’s own RBCs in that 2,3 DPG and the p50 of transfused adult RBCs (but not endogenous infant RBCs) increase rapidly after transfusion, i.e. within hours
More to the 2,3-DPG story

• Moreover, in the small-volume (15 mL/kg) RBC transfusion setting, 2,3 DPG levels were maintained in infants given stored RBCs.

• In fetuses with >80% circulating adult RBCs given via intrauterine transfusions, 2,3 DPG levels were normal in sampling by cordocentesis.

• When stored blood was used for exchange transfusions (massive), the p50 in infant blood increased from 17 mmHg 2 hours after exchange to 23 mmHg 24 hours after exchange, whereas it rose to 26 mmHg at 24 hours after exchange when fresh blood stored <24 hours was used.

In massive transfusion setting

- Impaired oxygen offloading has been shown in infants given stored RBCs by measurements of 2,3-DPG and p50
- Thus ‘fresh’ blood generally is used in this setting
Massive transfusion of the pediatric patient

- Definition: large-volume transfusion of RBCs >20mL/kg (physician’s discretion)
- Common clinical scenarios include:
  - Intrauterine transfusion/exchange transfusion
  - ECMO
  - Complex congenital heart surgeries (more to come)
  - Liver transplantation
  - Craniosynostosis repair
  - Other surgical procedures, such as large tumor removal
  - Trauma (including blunt trauma)


Age of blood *not* well studied in massive transfusion setting in pediatrics

- Age of Red Cells in Premature Infants (ARIPI) study
- Age of Blood Evaluation (ABLE) trial
- Tissue Oxygenation by Transfusion in Severe Anemia with Lactic Acidosis (TOTAL) study


Transfusion-associated hyperkalemic cardiac arrest

• When massive transfusion is anticipated, a Transfusion Medicine consult is beneficial in determining the transfusion policy for the hospital and what effective measures are available to reduce the potassium delivered in stored RBCs. These measures are institution-dependent and may include the following:
  – Use of ‘fresh’ RBCs for massive transfusion. The definition of ‘fresh’ is arbitrary and often refers to RBC units that are within 7 days of collection
  – Plasma volume reduction
  – Reduction of additive solution
  – Washing of RBCs either by the Blood Bank or by using an intraoperative cell salvage machine
  – Minimizing the time interval between irradiation and transfusion
Hyperkalemia calculations

• After 42 days of storage in extended-storage media (AS-1, AS-3, AS-5) at Hct ~60%, extracellular K\(^+\) levels approximate 50 mEq per L (0.05 mEq/mL)

• Daily potassium requirement for normal infants is 2 to 3 mEq/kg/24 hrs
  – Infusion rate for intravenous maintenance potassium is 3 mEq/kg ÷ 1440 min = 0.002 mEq/kg/min
  – For hypokalemic infants, the therapeutic infusion rate will be higher, but generally not above 0.004 mEq/kg/min
HyperK⁺ calculations, continued

- Assume 10mL/kg transfusion of a 1 kg infant over 3 hours (180 minutes)
- Assume that a 10 mL transfusion from RBC unit consists of 5.7 mL RBCs + 4.3 mL extracellular fluid (Hct ~60%)
- Thus, the potassium “dose” is 4.3mL × 0.05 mEq/mL = 0.215 mEq/kg
- 0.215 mEq/kg potassium ÷ 180 min = 0.001 mEq/kg/min
- A similar RBC transfusion given as 20 mL/kg will deliver twice the potassium dose (0.002 mEq/kg/min).
- Either potassium dose does not exceed the normal maintenance infusion rate
Large volume transfusions

- Potassium that increases in the extracellular fluid during RBC storage poses a significant danger for transfusions >25mL/kg
- Whenever possible, fresh RBC units (stored no more than 7 days since collection) should be issued for large volume RBC transfusions
- Alternatively, older RBC units can be washed before transfusion
- Remember K+ continues to leak after washing, so should be transfused within 6 hours in my opinion (though have 24 hour expiration time)
Future directions: a potassium adsorption filter?

- Recent RCT in adults showed efficacy in treating anemia with pRBCs transfused via potassium adsorption filter (available for use at the bedside in Europe)
- Kawasumi Laboratories, Inc (Tokyo, Japan) claims the filter is capable of removing at least 80% of the K+ from 2 pRBC-SAGM units at a flow rate of less than 50mL/min
- Obvious implications in pediatric massive transfusions (especially in the OR setting)

RBC additive/preservative solutions

- Historically, children received RBCs stored in CPDA-1 anticoagulant-preservative solution
- Additive solutions offer extended shelf life & decreased donor exposure for neonates

TABLE 1. Formulation of anticoagulant-preservative solutions in blood collection sets

<table>
<thead>
<tr>
<th>Constituent</th>
<th>CPDA*</th>
<th>AS-1†</th>
<th>AS-3†</th>
<th>AS-5†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td>63</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Sodium chloride (mg)</td>
<td>None</td>
<td>900</td>
<td>410</td>
<td>877</td>
</tr>
<tr>
<td>Dextrose (mg)</td>
<td>2000</td>
<td>2200</td>
<td>1100</td>
<td>900</td>
</tr>
<tr>
<td>Adenine (mg)</td>
<td>17.3</td>
<td>27</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Mannitol (mg)</td>
<td>None</td>
<td>750</td>
<td>None</td>
<td>525</td>
</tr>
<tr>
<td>Trisodium citrate (mg)</td>
<td>1660</td>
<td>None</td>
<td>588</td>
<td>None</td>
</tr>
<tr>
<td>Citric acid (mg)</td>
<td>206</td>
<td>None</td>
<td>42</td>
<td>None</td>
</tr>
<tr>
<td>Sodium phosphate (monobasic) (mg)</td>
<td>140</td>
<td>None</td>
<td>276</td>
<td>None</td>
</tr>
</tbody>
</table>

* Approximately 450 mL of donor blood is drawn into 63 mL of CPDA. A unit of RBCs (Hct =70%) is prepared by centrifugation and removal of most plasma.
† When AS-1 or AS-5 is used, 450 mL of donor blood is first drawn into 63 mL of CPDA, which is identical to CPDA except it contains 1610 mg of dextrose per 63 mL and has no adenine. When AS-3 is used, donor blood is drawn into CP2D, which is identical to CPD except it contains double the amount of dextrose. After centrifugation and removal of nearly all plasma, RBCs are resuspended in 100 mL of the additive solution (AS-1, AS-3, or AS-5) at a Hct =55 to 60 percent.

TABLE 2. Quantity (total mg/kg) of additives infused during a transfusion of 15 mL per kg of AS-1 or AS-3 RBCs at Hct of 60%

<table>
<thead>
<tr>
<th>Additive</th>
<th>AS-1</th>
<th>AS-3</th>
<th>Toxic dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaCl</td>
<td>42</td>
<td>7.5</td>
<td>137 mg/kg/day</td>
</tr>
<tr>
<td>Dextrose</td>
<td>129</td>
<td>23</td>
<td>240 mg/kg/hr</td>
</tr>
<tr>
<td>Adenine</td>
<td>0.6</td>
<td>0.6</td>
<td>15 mg/kg/dose</td>
</tr>
<tr>
<td>Citrate</td>
<td>9.8</td>
<td>12.6</td>
<td>180 mg/kg/hr</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.0</td>
<td>5.6</td>
<td>&gt;60 mg/kg/day</td>
</tr>
<tr>
<td>Mannitol</td>
<td>33</td>
<td>0</td>
<td>360 mg/kg/day</td>
</tr>
</tbody>
</table>

* Accuracy of toxic dose is difficult to predict for transfusions to individual infants because infusion rates generally are slow, permitting the metabolism and distribution of additives from blood into extravascular sites. Moreover, dextrose, adenine, and phosphate enter RBCs and are somewhat sequestered and not immediately available in the extracellular solution. Potential toxic doses taken from Luban NLC et al. Transfusion 1991; 31:229-35.

Massive transfusions

- Multiple trials demonstrate safety & efficacy for *small-volume* transfusion
- Safety of AS-preserved RBCs in trauma-related massive transfusions, cardiac surgery or exchange transfusions has not been well investigated
  — CPDA preferred

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## Variability in practice internationally

<table>
<thead>
<tr>
<th>Country</th>
<th>National Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>Common practice to remove the additive solution when RBCs are to be used for exchange transfusions, cardiac surgery and ECMO (usually replaced by FFP from same RBC donor)</td>
</tr>
<tr>
<td>UK</td>
<td>Use of CPD units discouraged (except for exchange transfusion) because they contain more plasma, increasing the risk of vCJD. In Northern Ireland, additive solutions removed &amp; replaced with FFP</td>
</tr>
<tr>
<td>Netherlands</td>
<td>Common practice to remove the additive solution when RBCs are to be used for exchange transfusions, cardiac surgery and ECMO (usually replaced by plasma, FFP or saline)</td>
</tr>
<tr>
<td>US</td>
<td>Washington, DC – CPDA-1 units mostly used; Iowa – additive solution removed and replaced with FFP from same RBC donor</td>
</tr>
</tbody>
</table>

## Variability in the US

<table>
<thead>
<tr>
<th>Center</th>
<th>AS RBC in large volume transfusions?</th>
<th>AS RBC in Cardiac surgery / ECMO?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dallas Children’s</td>
<td>Yes</td>
<td>Yes / ?</td>
</tr>
<tr>
<td>Cincinnati Children’s</td>
<td>Yes</td>
<td>No, CPDA1</td>
</tr>
<tr>
<td>CHOP</td>
<td>Yes</td>
<td>Yes / Yes</td>
</tr>
<tr>
<td>Children’s National</td>
<td>Yes</td>
<td>Yes / Yes</td>
</tr>
<tr>
<td>Texas Children’s</td>
<td>Yes</td>
<td>Yes / Yes</td>
</tr>
<tr>
<td>Denver</td>
<td>No</td>
<td>No / ?</td>
</tr>
<tr>
<td>Brigham</td>
<td>Volume reduced or CPDA</td>
<td>?</td>
</tr>
<tr>
<td>Michigan</td>
<td>CPDA1, CPD</td>
<td>?</td>
</tr>
</tbody>
</table>
So what is best practice?

• Much variability even amongst well-respected children’s hospitals
• No accepted practice nationwide for use of additive containing RBC products
• Read evidence/seek education
• Institution-specific protocols with subject matter experts
Summarize objectives

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