Pediatric Transfusion Risks and Guidelines

Jed B. Gorlin, MD
Memorial Blood Centers
Pediatric Transfusion: Risks and Guidelines

- Review of risks of transfusion
  - Pediatric specific complications
- Guidelines for Pediatric Transfusion
  - Red Cell
  - Platelet
  - Plasma
- Improving practice, limiting transfusions, alternatives
Risks of Transfusion

• Infectious Risks
  – Viral
  – Bacterial
  – Protozoa
  – Tick Borne
  – Other
    • Prion

• Non-infectious risks
  – Transfusion Reaction
  – Metabolic
  – Cardiac Overload
  – Dilutional Coagulopathy
  – TAGVHD
  – Alloimmunization
  – T antigen activation
Transfusion Recipient Fatalities FDA 05-13

- TRALI
- HTR (non-ABO)
- HTR (ABO)
- Microbial Infection
- TACO

Fatalities

FY05 FY06 FY07 FY08 FY09 FY10 FY11 FY12 FY13
Transfusion Safety

- Product Safety
  - Donor Recruitment
  - Donor history screening
  - Donor Testing
  - Manufacturing cGMP

- Transfusion Safety
  - Patient blood sample
  - Med indication for Tx.
  - Special Tx needs
  - Select right unit
  - Issue to floor
  - Administration
  - Monitoring & evaluation of reaction
Current Risks Summary (NAT)

- HIV, HCV 1 in ~2,000,000
- Bacteria 1 in 1-10,000
- Mis-transfusion 1 in 500-16,000
- Lung injury 1 in 5000
- TAGVHD 1 in 10,000
- Cardiac 1 in 100-1,000
- Metabolic rxn neonate 1 in 10-100
- Undertransfusion 1 in 50-1000
CMV at risk guideline

- CMV Ab - pregnant women/fetus
- Premature infants (<1200g)
- CMV(-) BMTX/solid organ transplant recipients receiving CMV(-) donor marrow/organ
- CMV(-) HIV or other immunosuppressed patient
- Less established: CMV (-) recipient of + marrow/organ, full term infant, premies of CMV+ mom.
- Note: Boppana NEJM (2001) 344:1366 documents new infection of fetus of CMV Ab+ mom
Non-Infectious Risks

- Transfusion reactions
- Metabolic complications
- Dilutional coagulopathy
- Cardiac overload
- TAGVHD
- Alloimmunization- RBC, platelets
Transfusion Reactions

• Hemolytic
  – Acute hemolytic (typical ABO incompatibility)
  – Delayed (antibodies to minor red cell antigens)

• Febrile

• Allergic
  – Severe: Anaphylaxis, Shock
  – Moderate: Extensive Hives, itching
  – Mild: Few hives
We make antibodies against things we don’t have. Newborns are born without iso-hemagglutinins and develop them over time against intestinal flora with similar antigens.

### The ABO Blood System

<table>
<thead>
<tr>
<th>Blood Type (genotype)</th>
<th>Type A (AA, AO)</th>
<th>Type B (BB, BO)</th>
<th>Type AB (AB)</th>
<th>Type O (OO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell Surface Proteins (phenotype)</td>
<td><img src="image1" alt="A agglutinogens only" /></td>
<td><img src="image2" alt="B agglutinogens only" /></td>
<td><img src="image3" alt="A and B agglutinogens" /></td>
<td><img src="image4" alt="No agglutinogens" /></td>
</tr>
<tr>
<td>Plasma Antibodies (phenotype)</td>
<td><img src="image5" alt="b agglutinin only" /></td>
<td><img src="image6" alt="a agglutinin only" /></td>
<td><img src="image7" alt="No agglutinin" /></td>
<td><img src="image8" alt="a and b agglutinin" /></td>
</tr>
</tbody>
</table>
Metabolic Complications

• Hyperkalemia- K leaks out of cells as they age. Irradiation doubles rate of leak. (see next slide)

• Hypocalcemia- Citrate may result in hypocalcemia if rapidly infused. Met. Alkalosis may follow metabolism of large amounts of citrate.

• Hypothermia- Use blood warmer

• Hemolysis
  – Storage: exposure to freezing or excessive heat
  – Hypo-osmotic: Only use compatible solutions
  – Bacterial contamination may cause hemolysis

• Hypoglycemia- Paradoxical response following receipt of high glucose containing transfusion. When transfusion ceases unbalanced insulin causes hypoglycemia.
Hyperkalemia

• A study of 54 consecutive RBC TX in a PICU showed no clinically significant increase in potassium including 5 infusions at > 5ml/kg in < 10 minutes

• The mean potassium before (3.85 mmol/L) and after (3.94mmol/L) were not significantly different. Of the six given a RBC bolus (> or = 5 mL/kg over < 10 mins),

• CONCLUSIONS: No significant change in patient potassium concentration

• Conversely, a series of hyperkalemic transfusion fatalities included pediatric patients receiving rapid transfusion:

• RESULTS: 16 patients with transfusion-associated hyperkalemic cardiac arrest, 11 adult and 5 pediatric. The mean [K+] was 7.2 +/- 1.4 mEq/L
  – # RBC units before arrest was 1 (in a 2.7 kg neonate) to 54. RBCs were rapidly infused (pressure bags, syringe pumped) most (87.5%) via central venous access. CONCLUSION: Pathogenesis is multifactorial; Hyper[K+] is complicated by low cardiac output, acidosis, hyperglycemia, hypocalcemia, and hypothermia.

Transfusion Associated Graft-Versus Host Disease

- When donor lymphocytes attack the host
- Host Immuno-compromised
- Host Overwhelmed (Premie)
- Host Immune-competent but donor is HLA homozygous for an HLA antigen that the recipient is heterozygous for. Most common setting is related donor.
AABB TAGVHD @ risk guide

- BMTX (stem cell transplant recipient)
- congenital immune deficiency
- Neonates getting intrauterine, during or post exchange
- Hodgkin’s lymphoma
- Directed donor/family member/HLA or platelet cross-match
- other chemo (fludarabine, 2-CDA)
- Premie < 1200g
Transfusion-related lung injury

• Incidence ~1:5,000 but rarely reported in pediatric transfusion recipients
• Pathogenesis: Donor anti-HLA and anti-PMN antibodies causing activation of host leukocytes = pulmonary capillary trapping.
• May be fatal
• Donor is typically multiparous female
• Usually Platelet or Plasma comp. RBC rare
TRAGI?

• Transfusion associated gut injury
• NEC (necrotizing enterocolitis) often follows transfusion and the temporal correlation is statistically significant.
  – Less clear is whether sicker preemies are both more likely to develop NEC and require transfusion or whether the transfusion contributes NEC
  – Patel [JAMA (2016) 315:889-897] found NEC associated with severe anemia not transfusion

http://tragiregistry.com/index/TRAGI_Registry_files/TRAGI%20in%20Jpeds%20Published.pdf
Correlation between per capita chocolate consumption and Nobel laureates/population

While admittedly tongue in cheek, this NEJM article clearly points out that not all statistically significant correlations are causative!
Neonatal T-activation

• Associated with NEC- Necrotizing enterocolitis.
  – Bacteria release sialidases that cleave sialic acid residues creating neoantigens. Naturally occurring complement dependant antibodies cause lysis of the neoantigen labeled red cells
  – But, T activation is common (~13% of NICU infants) but hemolysis is uncommon. Therefore, it is controversial as to whether it is really necessary to provide washed red cells to all neonates with NEC or only those with evidence of hemolysis. (See Hume)
Directed Donations

• Pros:
  – Keeps patient, parents and extended family happy.
  – May result in fewer donor exposures
  – May encourage blood donation by individuals who do not usually donate

• Cons:
  – No study shows that directed donations are safer and many show that directed donor blood is rejected at a greater rate. (first time donation rate higher)
  – Alloimmunization
  – Logistics/$/Error
Neonatal Transfusion

• Many premature newborns require transfusion
• Iatrogenic: Frequent blood sampling, especially for monitoring blood gases may result in requirement to replace “blood out.”
• Blood donor exposures in premature infants < 1kg are typically greater than 5 unless special programs to reduce exposure
Neonatal Anemia

- All infants experience a decline in Hemoglobin/hematocrit over the first weeks
- Termed: “Physiologic Anemia of Infancy”
- Healthy full-term newborns typically nadir > 9g Hgb @ 10-12 weeks
- BW 1-1.5 kg, Nadir ~8 g Hgb.
- BW < 1.0 kg nadir ~7gHgb
Physiologic Factors: Neonatal anemia

• Loss of fetal hemoglobin
  – Different Hbg-O2 dissociation curves: left shifted 1/2 saturation is at 16 to 18mmHg instead of 24-26.
  – Fetal hemoglobin has reduced 2,3 DPG effect

• Decreased production of erythropoietin (Epo) in response to anemia
Phlebotomy Blood Losses

• Mean levels of sampling = 0.8-3.1 ml/kg/day.
• Corresponds to 30%-300% of infant blood volume over course of stay in NICU
• Transcutaneous O2 monitoring, smaller volumes for ABG and lab studies help reduce volume out.
Treatment of Anemia of Prematurity

• Observation- Non-ill infants tolerate significant anemia (see guideline)
  – No need to perform DATs on all infants of either Rh negative or group O mothers. The DAT is often positive (either passive from Rhogam or anti-A,B, but has a very low predictive value for HDN!)

• Transfusion
  – Allogeneic
    • Directed
    • Limited donor program
  – Autologous-harvesting autologous blood from placenta

• Erythropoietin
Guidelines for RBC transfusion*

- Hgb < 13g/dl (Hct <40%) with severe cardiopulmonary disease
- Hgb < 10g/dl (Hct <30%) with moderate cardiopulmonary disease or surgery
- Hgb < 8g/dl (Hct <24%) with symptomatic anemia
- Bleeding or phlebotomy exceeding 25% of red cell volume.

* from Strauss, Chap 20 Neonatal Transfusion in Anderson, Ness Scientific Basis of Transfusion Medicine and Transfusion 48:209
TRIPICU: 7 vs 9.5g Hgb NEJM 356:1609

• Pediatric ICU study-randomized very sick pediatric patients to RBC transfusion trigger of 7 vs. 9.5g Hgb.
• Outcomes measured including MODS (multiple organ dysfunction syndrome) mortality, length of stay, morbidity
• No difference discernable supporting non-inferiority of lower transfusion trigger!
Guidelines for Neonatal RBC Transfusion

• Definitions of severe, moderate, symptomatic must be locally defined
• No proven benefit of replacing iatrogenic blood loss by ml. Instead transfuse to maintain minimum hct
• Few studies guide transfusion triggers
• Transfusion to treat apneic episodes is controversial
“Strict” Guidelines for neonatal RBC transfusion in Sao Paulo!*

- Hgb < 13g/dl (Hct < 40%) with severe cardiopulmonary disease, major surgery
- Hgb < 12g/dl (Hct < 35%) with (6-8 cm H$_2$O) mechanical ventilation
- Hgb < 10g/dl (Hct < 30%) with symptomatic anemia, mild ventilatory support, minor surgery
- Hct < 20% asymptomatic, retic < 2%, or symptomatic
- Adherence to this protocol at 7 public NICUs reduced blood use by 17%  
  * from Miyashiro, dos Santos Vox Sanguinis (2005) 88:107-113
RBC Tx trigger: PINT Study

• STUDY DESIGN: Infants <1000 g were randomized to a low or high hemoglobin transfusion threshold, analogous to Hebert study. Outcomes included: death before home discharge or survival with any of either severe retinopathy, bronchopulmonary dysplasia, or brain injury on cranial ultrasound.

• Superiority trial: Hypothesis = restrictive tx were superior.

• 451 neonates in 10 NICUs, Canada, US, Australia.
  – Inclusion criteria BW <1kg, < 31 wk, <48hr old
  – Groups were similar, with mean birth weight of 770 g and gestational age of 26 weeks.
RESULTS: Fewer infants received one or more transfusions in the low threshold group (89% low versus 95% high, P = .037).

Combined rates of death/severe morbidity were NOT different in low vs. high groups
- There were no statistically significant differences between groups in any secondary outcome. (hgb level, transfusions, donor exposures, rate of growth)

Does NOT demonstrate superiority of low trigger

CONCLUSIONS: In extremely low birth weight infants, maintaining a higher hemoglobin level results in more infants receiving transfusions but confers little evidence of benefit.

Randomized trial of liberal vs restrictive guidelines for red blood cell transfusion in preterm infants

- **Pediatrics 2005 Jun;115(6):1685-91** Bell, Strauss
- Randomized 100 premature infants 500-1300g to liberal vs. restrictive Tx trigger. Higher # of Tx but not donor exposures in liberal group. Higher % with adverse neurologic outcome in restrictive group.

**CONCLUSIONS:** Although both transfusion programs were well tolerated, our finding of more frequent major adverse neurologic events in the restrictive RBC-transfusion group suggests that the practice of restrictive transfusions may be harmful to preterm infants.
ARIPi study: JAMA. 2012;308(14):1443-1451

- Age of blood study: <7 days vs. standard of care (about 14 days)
- ~350 infants <1250 g admitted to Canadian NICU
- The mean age of transfused blood was 5.1d (SD, 2.0) RBC vs 14.6d (SD, 8.3) standard.
- Composite outcomes, infection rate were indistinguishable between groups.

**Conclusion** In this trial, the use of fresh RBCs compared with standard blood bank practice did not improve outcomes in premature, very low-birth-weight infants requiring a transfusion
Effect of transfusion guidelines: Craniofacial surgery

• Single center trial reporting historical experience before and after establishing a procedure based transfusion algorithm

• Institution of guidelines (hgb 7, plt 100K, INR> 1.5) resulted in less Tx (17 vs 42%) especially reduction in FFP

Transfusion: Neonatal Anemia

• How much: 10-20ml/kg
• How fast: Over 2-4 hours
• What: RBC product of choice: Controversial- See summary of Strauss studies
  – Age: # of days since unit donated
  – Anticoagulant
  – Irradiation
Don’t waste blood
Don’t order blood unless needed
Much blood wastage results from blood sent to ER, OR and not used, and returned out of temperature range
Don’t read the Onion, thinking the news is real!!
  - http://literallyunbelievable.org
Neonatal Tx: Anticoagulant

- Dr. Ronald Strauss, University of Iowa has extensively studied anticoagulant-preservative solutions & small volume transfusion.
  - Several studies document the safety of transfusion stored blood (up to 42 days) using AS-1 anticoagulant which contains both Adenine and Mannitol as preservatives. (Note: Adsol units have a lower hct!)
## Additive (mg/kg during 15ml/kg)

<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>137mg/kg/day</td>
</tr>
<tr>
<td>Dextrose</td>
<td>129</td>
<td>23</td>
<td>240mg/kg/hr</td>
</tr>
<tr>
<td>Adenine</td>
<td>0.6</td>
<td>0.6</td>
<td>15mg/kg/dose</td>
</tr>
<tr>
<td>Citrate</td>
<td>9.8</td>
<td>12.6</td>
<td>180mg/kg/hr</td>
</tr>
<tr>
<td>PO4</td>
<td>2.0</td>
<td>5.6</td>
<td>&gt;60mg/kg/day</td>
</tr>
<tr>
<td>Mannitol</td>
<td>33</td>
<td>0</td>
<td>360mg/kg/day</td>
</tr>
</tbody>
</table>

Neonatal Rx: K+ Age of Units

• Extracellular Potassium (K+) rises with extended storage (CPDA-1: 78mmol/L in unit d 35, 45-50 @ d42 in AS); **irradiation doubles rate**

• No significant change in [K+] post small volume (10-20ml/kg) given over 2-3 hours.

• K+ problematic in massive transfusion
  – Cardiac Bypass, ECMO, Neonatal Exch Tx.
  – Give blood less than one week old, or washed
Neonatal 2,3 DPG

• 2,3 DPG levels are depleted during RBC storage
• Formerly used as an argument to provide fresh blood to neonates
• At least one study documents similar 2,3 DPG levels in infants post-Tx of either fresh or stored blood, proving that infants are capable of 2,3 DPG regeneration
Who requires HbS neg RBC?

- Recipients of intrauterine or neonatal exchange transfusions
- Infants undergoing cardiac bypass or extracorporeal membrane oxygenation
- Preterm infants given repeated transfusions from the same unit
- Patients who have sickle hemoglobin disorders and are undergoing erythrocytapheresis or simple or exchange transfusions.

• Ref: Table 34 Pediatric Transfusions. AABB 2003
Cold Storage

• RBC are stored at 2-6°C.
• Rapid transfusion results in hypothermia, hypocalcemia
• Rapid transfusion requires use of a blood warmer-Use only FDA cleared with alarm. Microwave ovens (not intended for blood warming) have been associated with fatal hemolysis.
Limiting Donors to Neonates

• Iowa program assigns a specific unit <7 days old to a neonate or group of neonates.
  – BW<1kg = 1/2 unit
  – BW1-1.3kg = 1/4-1/2 unit
  – BW>1.3kg as needed

• May use dedicated directed donor.

• Continues same unit until d42. Only irradiate aliquots, not directed donor unit
Erythropoietin vs. Transfusions for Neonates

• > 20 controlled trials of Epo Rx of neonates
  – No convincing evidence that Epo Rx substantially reduces transfusion requirements in NICU patients at greatest risk for the most transfusions, i.e. the profoundly premature.
  – Currently <50% of infants with BW >1.0kg require RBC Tx
  – Nearly all infants <1.0 kg require Tx within first 3-4 weeks.
BUT, Epo (E), Darbo (D) and Neurological outcome!

• 3 arm trial 80/102 infants returned for long term follow-up.

• Significantly higher cognitive scores and object permanence among D, E arms compared to placebo

• No D/E recipients had CP compared to 5 in placebo arm

Ohls et al “Cognitive outcomes of preterm infants randomized to Darbepoietin, Erythropoietin or Placebo” Ped (2014) 133 (6) 1023-1030
Immediate vs. delayed clamping

- Strauss Transfusion 48:658
  - Randomized neonates 30-36 weeks to immediate vs. delayed (>1 min) clamping
    - Yielded increased hct, RBC mass but did NOT lead to fewer transfusions.
    - Delayed group got more phototherapy but extent and initial bilirubin levels did not differ
  - Group <30 weeks randomized to delayed clamping were not evaluable due to resuscitation requirements
Delayed clamping associated with improvement in fine motor skills and social domains

• No difference in full scale IQ but better fine motor and social skills at age 4, with greater difference observed in males.

• Swedish study 141 delayed (>3 min) vs 122 early (<10 sec)

• Other studies show better Fe status at 4 months following delayed clamping

Neonatal Transfusion: X match

• AABB Standard 5.15.5.1: ABO, Rh test either neonate or mother for Ab
• 5.15.5.1.1 Repeat ABO, Rh may be omitted rest of admission
• 5.15.5.1.2 If Ab Sc (-), no X-match is required for initial or subsequent transfusions.
Neonatal Transfusion: Xmatch II

- If AbSc+, give RBC negative for that antigen, OR X-match compatible UNTIL Ab no longer detectable (since antibodies are invariably maternal, i.e. passive)
- If non group-O neonate is to receive non-group O cells, test neonate for anti-A, and anti-B, including by antiglobulin phase
Intrauterine Transfusion

• By definition premature, Initial ABO, Rh type unknown
• Generally receive: Irradiated, CMV- (Ab or leukoreduced), group O cells, AB plasma.
• Follow-up of HDN patients who received IUT required as they may have prolonged erythroblastopenia, due to large unadsorbed load of maternal allo-RBC antibody
Ordering Blood Products

• What product?
• How much?
• When needed?
• Give indication for transfusion!
• Special requirements (irradiation, leukoreduction)
• Sample must have 2 identifiers, date, time and phlebotomist initials
Neonatal Summary

- Many premies Transf.
- Relatively large amounts transfused
- Passive Transfer of Ab
- Lack of Isohemagglutinin
- Long life expectancy
- Immature immune system-Risk of TAGVHD

- Limited donor program
- Citrate, K+, vol., Temp: special requirements
- Test maternal serum
- Lack back-type, no X-match required
- Limit donors, boutique components
- Irradiate for extreme premies, exchange Tx.
Dilutional Hemostatic Dysfunction

- Occurs following massive RBC transfusion.
- Neonatal levels of vitamin K dependant factors normally lower.
- Thrombocytopenia may precipitate bleeding.
- Consider whole blood or plasma component prime of large extracorporeal volume circuits like Cardiac Bypass or ECMO.
Neonatal Bleeding: Platelets

- Normal range: Similar to adults
- Clinical ramification of thrombocytopenia (TCP) (<100K)
  - ICH 78% in TCP <1.5kg, vs 48% in non-TCP
  - Extent and prognosis worse in TCP
- BUT, a randomized trial showed no benefit of platelet Tx with a 150K trigger vs. 50K trigger for Premies.
Neonatal Platelet Rx

• Role for prophylactic platelet transfusions unproven
• Nonetheless, general consensus support platelet Tx for neonates with plt<50K either with clinical bleeding or pre-procedure.
• Asymptomatic infants generally transfused to >20K.
Neonatal Platelet Rx: How much?

• Goal = > 100K
• Generally easily achieved by 5-10ml/kg of platelet rich plasma from a unit of whole blood. No additional concentration is required unless no concentrate with compatible plasma is available (e.g. AB infant may require plasma depletion of non-AB component) Andrew J Ped (1993) 123:285
• Like RBC may require irradiation
Guidelines for Platelet transfusion*

- Platelets < 100,000/ul and bleeding or clinically unstable (inc. IVH)
- Platelets < 50,000/ul and invasive procedure
- Platelets < 20,000/ul and no bleeding and clinically stable

* from Strauss, Chap 20 Neonatal Transfusion in Anderson, Ness Scientific Basis of Transfusion Medicine
Pediatric plasma transfusion

- Most infants have low levels of vitamin K dependant factors, hence, all infants receive vitamin K at birth.
- IM vitamin K is more effective than PO.
- Many infants, especially premature normally have prolonged INR, hence prolongation of INR, in absence of clinical bleeding or significant risk of bleeding is NOT an indication for plasma transfusion. Rx is vitamin K.
- Plasma 10-15cc/kg is usual dose
- Cryoprecipitate may be required if treating fibrinogen level <100.
## Normal Coags (pre Vit K)

<table>
<thead>
<tr>
<th>Test</th>
<th>30-38 wk</th>
<th>Newborn</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>3.0 (1.5-5)</td>
<td>1.7 (0.9-2.7)</td>
<td>1.1 (0.8-1.2)</td>
</tr>
<tr>
<td>aPTT</td>
<td>105 (76-128)</td>
<td>44 (35-52)</td>
<td>33 (25-39)</td>
</tr>
<tr>
<td>F IX</td>
<td>12.3 (5-24)</td>
<td>32 (15-50)</td>
<td>105 (70-142)</td>
</tr>
</tbody>
</table>
References

• Andrew J Ped (1993) 123:285
• Bell Pediatrics 2005 Jun;115(6):1685-91
• Strauss et al Transfusion (2008) 48:658
• Strauss How I transfuse Transfusion 48:209
• Immunohematology (2008) 24(1) 4-26
• ARIPI study (Ferguson): JAMA. 2012;308(14):1443-1451
• Stricker et al (Craniofacial) Ped Crit Care Med (2012) 13 e 357-362