Transfusion NEC: How Could This Be Real? Insights Into the Physiology

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Objectives

• What is Storage Lesion and could this be a reason for transfusion gut injury?

• Can PRBC transfusion lead to “Necrotizing Enterocolitis” in some preterm infants?

• What are the physiological potential risk factors that may lead from PRBC transfusion to neonatal gut injury?
Storage Lesion

• Over the last 25 years understanding of RBC transfusions has improved

• Issues with infection and immunosuppression were well known

• More recently issues with proinflammatory responses are better understood

• Lately its understood that stored red blood cells undergo time-dependent metabolic, biochemical, and molecular changes called storage lesion
### Storage Effects on Red Cells

<table>
<thead>
<tr>
<th>Red blood cell storage lesion</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Storage effects</td>
<td></td>
</tr>
<tr>
<td>Decreased 2,3-diphosphoglycerate</td>
<td>Increased oxygen affinity and decreased oxygen unloading by hemoglobin</td>
</tr>
<tr>
<td>ATP depletion</td>
<td>Erythrocyte shape changes</td>
</tr>
<tr>
<td></td>
<td>Increased osmotic fragility</td>
</tr>
<tr>
<td></td>
<td>Decreased deformability</td>
</tr>
<tr>
<td>Microvesiculation and loss of lipid membrane</td>
<td>Decreased erythrocyte viability</td>
</tr>
<tr>
<td>Lipid peroxidation</td>
<td>Cellular injury and death</td>
</tr>
<tr>
<td>Bioactive substance generation: histamine, cytokines, lipids</td>
<td>Febrile transfusion reactions</td>
</tr>
<tr>
<td></td>
<td>Neutrophil priming/endothelial activation</td>
</tr>
<tr>
<td></td>
<td>Cellular injury</td>
</tr>
<tr>
<td></td>
<td>Transfusion-related acute lung injury</td>
</tr>
<tr>
<td></td>
<td>Multiple organ failure (?)</td>
</tr>
</tbody>
</table>
RBC Aging Markers are Accelerated During the Storage Process

• RBC senescence assumed accelerated, but neither RBC protein profile, or impact of additives are well studied.¹
• Protein aggregation, degradation, oxidation, and topology were worsened during storage¹
• That buffers CPD and SAGM were less detrimental than CPDA¹
• Kriebardis et al found greater deterioration in stored RBC after day 14²

Effects on RBC membrane stored in CPDA Buffer

Rate of ATP Decline

D'Almeida, Jagger, Duggan, White, Ellis & Chin-Lee, 2000
Rate of 2,3-DPG Decline

D'Almeida, Jagger, Duggan, White, Ellis & Chin-Lee, 2000
RBC Storage and how it Relates to Oxidative Injury and Aging Profile

Antonelou et al. Transfusion Feb 2010
Summary Storage Lesion

1) Cells Change Shape - Potential Micro-sludging
2) Increased Apoptosis - Cell death/rupture and release of free Hgb
3) Decreased 2,3 DPG - Decreased O2 delivery
4) Decreased ATP - Cell Shape Changes, more fragile
5) Potentially Pro-Inflammatory
Conclusion

So Red Cells Change Over the Amount of Time Stored.

They “Age” Differently in storage than when they are in the body.

They “Age” differently depending on which buffer is used.

Is That a Bad Thing?
Concern in The Literature

• The adult literature understanding of: Transfusion Associated Lung Injury (TRALI) with different blood components. (for recent review see Triulzi D. Anesth Analg. 2009 Mar;108(3):770-6)
Fatality due to TRALI by Blood Component

![Bar graph showing fatality rates per 10^6 components for different blood components: FFP, SDP, RBC, RDP, Cryo. FFP has the highest fatality rate, followed by SDP. RBC, RDP, and Cryo have significantly lower fatality rates.](image-url)
More From Adult Literature

- Splanchnic Ischemia was noted in Adults who were being transfused with “older blood products”

Marik et al. JAMA 269 (23) 1993
More From Adult Literature

• In the NEJM in 2008, Cleveland Clinic Reported that mortality and morbidity increased by more than 2 fold after cardiac surgery when “Old Blood” was used. (Defined as >20 days of storage)
<table>
<thead>
<tr>
<th>Study: first author, year</th>
<th>Population</th>
<th>Design</th>
<th>Number</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciesla, 2005¹¹³</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>1,344</td>
<td>Increased multiorgan failure</td>
</tr>
<tr>
<td>Gong, 2005⁰⁶</td>
<td>ICU patients</td>
<td>Prospective cohort</td>
<td>688</td>
<td>Increased risk of ARDS*</td>
</tr>
<tr>
<td>Lebron, 2005¹⁰⁰</td>
<td>Liver transplant</td>
<td>Retrospective cohort</td>
<td>241</td>
<td>Increased early postoperative renal failure</td>
</tr>
<tr>
<td>Shorr, 2005¹⁰⁷</td>
<td>ICU patients</td>
<td>Prospective cohort</td>
<td>3,502</td>
<td>Increased ICU acquired bacteremia</td>
</tr>
<tr>
<td>Silverboard, 2005¹¹²</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>102</td>
<td>Increased risk of ARDS</td>
</tr>
<tr>
<td>Smith, 2004¹⁰⁸</td>
<td>Subarachnoid hemorrhage</td>
<td>Prospective cohort</td>
<td>441</td>
<td>Worse outcome with intraoperative transfusions</td>
</tr>
<tr>
<td>Vincent, 2004⁴</td>
<td>ICU patients</td>
<td>Prospective cohort</td>
<td>1,136</td>
<td>Increased ICU, hospital and 28-day mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased organ dysfunction</td>
</tr>
<tr>
<td>Leal-Noval, 2003¹⁰⁴</td>
<td>Cardiac surgery</td>
<td>Prospective cohort</td>
<td>103</td>
<td>Increased ICU LOS, mechanical ventilation, and pneumonia</td>
</tr>
<tr>
<td>Malone, 2003⁹⁶</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>15,534</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Chelemner, 2002¹⁰⁰</td>
<td>CABG</td>
<td>Prospective cohort</td>
<td>533</td>
<td>Increased bacterial infections</td>
</tr>
<tr>
<td>Claridge, 2002¹¹⁰</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>1,593</td>
<td>Increased infection</td>
</tr>
<tr>
<td>Convin, 2002⁴</td>
<td>ICU</td>
<td>Prospective cohort</td>
<td>4,892</td>
<td>Increased ICU and hospital LOS, mechanical ventilation, and pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased complications</td>
</tr>
<tr>
<td>Taylor, 2002⁹⁵</td>
<td>ICU</td>
<td>Retrospective cohort</td>
<td>1,717</td>
<td>Increased nosocomial infections, ICU LOS, and mortality</td>
</tr>
<tr>
<td>Vamvakas, 2002¹¹¹</td>
<td>Cardiac surgery</td>
<td>Retrospective cohort</td>
<td>416</td>
<td>Increased postoperative ventilation associated with volume of RBC supernatant</td>
</tr>
<tr>
<td>Leal-Noval, 2001⁹⁶</td>
<td>Cardiac surgery</td>
<td>Prospective cohort</td>
<td>738</td>
<td>Increased ICU LOS, mechanical ventilation, and pneumonia</td>
</tr>
<tr>
<td>Chang, 2000⁹⁷</td>
<td>Colorectal surgery</td>
<td>Retrospective cohort</td>
<td>282</td>
<td>Increased postoperative infection</td>
</tr>
<tr>
<td>Carson, 1999¹⁰¹</td>
<td>Hip fracture</td>
<td>Retrospective cohort</td>
<td>9,598</td>
<td>Increased risk of serious bacterial infection and pneumonia</td>
</tr>
<tr>
<td>Offner, 1999¹⁰⁶</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>61</td>
<td>Increased infection</td>
</tr>
<tr>
<td>Vamvakas, 1999¹⁰³</td>
<td>Cardiac surgery</td>
<td>Retrospective cohort</td>
<td>416</td>
<td>Increased postoperative infection (5% /unit)</td>
</tr>
<tr>
<td>Carson, 1998¹⁰⁴</td>
<td>Hip fracture</td>
<td>Retrospective cohort</td>
<td>416</td>
<td>No change in mortality or morbidity</td>
</tr>
<tr>
<td>Moore, 1997¹⁰²</td>
<td>Trauma</td>
<td>Prospective cohort</td>
<td>513</td>
<td>Increased multiorgan failure</td>
</tr>
<tr>
<td>Martin, 1994³⁰⁰</td>
<td>ICU</td>
<td>Retrospective cohort</td>
<td>698</td>
<td>Increased mortality</td>
</tr>
</tbody>
</table>

* ARDS = acute respiratory distress syndrome.
So What About Our Babies?

• There has been debate about the existence of Transfusion Associated NEC
• Is there a small proportion of our babies that are at risk for Transfusion associated NEC
• This has been coupled with concerns about Feedings during transfusions, timing, and how much to give; but the evidence has been only recently recognized.
A Nugget We in Neonatology May Have Originally Overlooked

- 1987: McGrady et al. Reports an outbreak of NEC (20 cases) during a 4 month period.
- Prevalence was 30% in VLBW babies
- In a Case control study, in matched patients, The Only Association Found was PRBC Transfusion (OR 15.1; CI 2.6 - 92.5)

Why That Likely Didn’t Ring Alarm Bells

- Could be due to tainted or contaminated Blood
- Could be attributed to Infectious Agent in the Blood (viral or other)
- May have been a Unit Issue
- Etc.
Growing Data Behind PRBC Transfusion and NEC in Preterm Infants

In a Study looking at transfusion Practices in 6 Boston NICU’s as part of the SNAP II Study Group, An interesting finding was noted.

In Units that Transfused the lowest amount of blood product, multivariate assessment showed that NEC was statistically lower than units that transfused higher overall amounts of blood (2% vs 7% incidence)

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>NICU transfusion practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High (NICUs A, B)</td>
</tr>
<tr>
<td>NEC</td>
<td>15/232 (7%)</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>1.1 (0.5-2.2)</td>
</tr>
<tr>
<td></td>
<td>Medium (NICUs C, D)</td>
</tr>
<tr>
<td>NEC</td>
<td>19/305 (6%)</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>Reference</td>
</tr>
<tr>
<td></td>
<td>Low (NICUs E, F)</td>
</tr>
<tr>
<td>NEC</td>
<td>5/280 (2%)</td>
</tr>
<tr>
<td>Adjusted OR</td>
<td>0.3 (0.1-8.8)</td>
</tr>
</tbody>
</table>

Bednarek et al J. Pediatr 133(5) 1998
More Concerning Data For PRBC Transfusion and NEC

• In 2006, Mally at NYU conducted a chart review to look at Elective PRBC transfusions and NEC

• A total of 908 (inborn) neonatal admissions had received 751 PRBC transfusions

• 17 patients (1.8%) had developed NEC

• 6/17 cases of NEC (35%); were associated with a previous transfusion within 48 hours of NEC

Mally et al. Am J Perinatol. 23 (8) 2006
More Concerning Data For PRBC Transfusion and NEC

### Table 5: Indications for Blood Transfusions

<table>
<thead>
<tr>
<th>Indication</th>
<th>Transfusion-Associated NEC (n = 6)</th>
<th>Non-Transfusion-Associated NEC (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct 48 h prior to onset of NEC</td>
<td>Mean ± SEM 24 ± 3</td>
<td>Mean ± SEM 37 ± 7*</td>
</tr>
<tr>
<td></td>
<td>Median (range) 24 (20–28)</td>
<td>Median (range) 37 (25–48)</td>
</tr>
<tr>
<td>Apnea/d* (48 h prior to NEC)</td>
<td>Mean ± SEM 6 ± 5</td>
<td>Mean ± SEM 3 ± 5</td>
</tr>
<tr>
<td></td>
<td>Median (range) 4 (4–14)</td>
<td>Median (range) 0 (0–16)</td>
</tr>
<tr>
<td>Ventilator use 48 h prior to onset of NEC</td>
<td>0% (0/6)</td>
<td>45% (5/11)*</td>
</tr>
</tbody>
</table>

*p < 0.05.

### Table 6: Transfusion History

<table>
<thead>
<tr>
<th>Transfusion History</th>
<th>Transfusion-Associated NEC (n = 6)</th>
<th>Non-Transfusion-Associated NEC (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hours to presenting signs of NEC after the last PRBC transfusion</td>
<td>Mean ± SEM 22 ± 5</td>
<td>Mean ± SEM 185 ± 91</td>
</tr>
<tr>
<td></td>
<td>Median (range) 19 (12–38)</td>
<td>Median (range) 180 (96–312)</td>
</tr>
<tr>
<td>Age of blood (d)</td>
<td>Mean ± SEM 12 ± 10</td>
<td>Mean ± SEM 6 ± 4</td>
</tr>
<tr>
<td></td>
<td>Median (range) 5 (5–27)</td>
<td>Median (range) 8 (0–10)</td>
</tr>
</tbody>
</table>

Mally et al. Am J Perinatol. 23 (8) 2006
Christensen et al.: Antecedents of Bells Stage III NEC

- 7 year review (2001-07) of every case of Bells Stage III NEC

- Reviewed preceding 48 hours

- Showed a transfusion was given in 39% of the patients with an average of 19 hours prior to onset of NEC

Christensen et al. J Perinatol. (30) 2010
Transfusion Associated NEC

• Case Control Study Surgical NEC (1:4 match)

• Neonates that developed NEC were more likely to have had an antecedent transfusion: OR 11.8; Confidence Interval 4.6 to 30.4

• In relation to feeding, the group that had been feeding larger volumes and got transfusion were more likely to develop NEC (p=0.04)

• They were also more likely to have been fed a cow’s milk formula (p=0.03)

Christensen et al. Transfusion May 2010
# RBC transfusion and NEC Studies

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Study Design/Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGrady</td>
<td>1987</td>
<td><strong>Retrospective</strong>: case-control, no time interval recorded, 61% had onset of NEC following PRBC transfusion N=33 NEC and N=40 controls; (OR=15.5, 95%CI=2.59-92.51)</td>
</tr>
<tr>
<td>Bednarek</td>
<td>1998</td>
<td><strong>Prospective</strong>: NICUs with lower transfusion rates had lower NEC incidence, studied at level of NICU not the patient No time interval recorded</td>
</tr>
<tr>
<td>Mally</td>
<td>2006</td>
<td><strong>Retrospective</strong>: study of a small sample size (n=17) 6 tx-associated NEC &lt;48 hrs and 11 non-tx associated. Subset of stable, growing, premature neonates who developed a fulminant form of NEC after RBC transfusion for symptomatic anemia</td>
</tr>
<tr>
<td>Krimmel et al.</td>
<td>2008</td>
<td><strong>Prospective</strong>: RCT to feed or not to feed during RBC transfusion; blood flow in SMA did NOT increase in infants when feeding after receiving 20 ml/kg RBC transfusion. Speculation: areas of postprandial intestinal hypoperfusion may lead to RBC tx-associated NEC</td>
</tr>
<tr>
<td>Christensen</td>
<td>2009</td>
<td><strong>Retrospective</strong>: 38% of infants had a blood transfusion (18 ± 12 h) preceding NEC development (Surgical NEC) <strong>Retrospective</strong>: N=40 infants developed NEC post RBC transfusion, and 70 developed NEC unrelated to transfusion RBCs not older than 14 days, but infants developed NEC, and were fed large volumes of cows milk 24 hrs before and during transfusion</td>
</tr>
<tr>
<td>Christensen</td>
<td>2010</td>
<td></td>
</tr>
</tbody>
</table>
### RBC Transfusion and NEC Studies

<table>
<thead>
<tr>
<th>Investigator/Journal</th>
<th>Year</th>
<th>Study Design/ Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blau et al. <em>J Pediatrics</em></td>
<td>2010</td>
<td>Retrospective: 9/36 NEC cases in 18 months were associated with RBC prior to NEC. Infants with lower BW, older post-natal age, lower hct (anemia). Coined Transfusion-Related Acute Gut Injury (TRAGI)</td>
</tr>
<tr>
<td>Josephson et al. <em>J Pediatrics</em></td>
<td>2010</td>
<td>Retrospective: case-control: 93 cases studied. Infants with late-onset NEC (&gt; 4 weeks of age) were more frequently associated with hx of RBC tx than early-onset NEC (OR, 6.7;95% CI :1.5-31.2, P=0.02). Tx related NEC babies had lower GA, BW, sicker. 38% of pts had a RBC tx 48-hrs before NEC onset</td>
</tr>
<tr>
<td>El-Dib et al. <em>J Perinatology</em></td>
<td>2011</td>
<td>Retrospective: case-control: 25 NEC cases studied. NEC cases associated with RBC transfusion in the preceding 48 and 72h; and withholding feeds during transfusion associated with lower incidence of NEC</td>
</tr>
<tr>
<td>Singh et al. <em>J Perinatology</em></td>
<td>2011</td>
<td>Retrospective: case control: Infants with NEC had lower Hct and were more likely to be transfused within 24 hrs (OR 7.6, p=0.001), 48 hrs (OR 5.55, p=0.001) of NEC onset than controls</td>
</tr>
<tr>
<td>Paul et al. <em>Pediatrics</em></td>
<td>2011</td>
<td>Retrospective: &lt; 1500 gram infants; 33/122 (27%) NEC cases post-RBC transfusion, (OR 2.3 95% CI: 1.2-4.2) Rate of NEC 1.4% after transfusion Mean age RBCs – 5 days, 83% from male donors</td>
</tr>
</tbody>
</table>
• So Transfusion NEC appears to be real in a small subset of our babies, but why?
Potential Reasons

- AGE OF BLOOD/ BLOOD BANKING ISSUES
- STRESS/INFLAMATION
- Vascular Issues
- Reperfusion Injury
Does RBC Storage Time Matter?

• Paper by Josephson C.D. et al from Emory and UAB: did chart review looking for Transfusion associated NEC.

• Did not show statistically significant difference, unless you looked at Age of Blood, blood older than 7 days there was a strong statistical significance
Background for Examining Perfusion Changes during Transfusions

- Post transfusion NEC
  - May result from perfusion changes associated with red cell transfusions

- Storage lesion
  - Red cells undergo changes
  - Produces microsludging
  - Loss of blood constituents
  - May impair blood flow increasing risk for ischemia

(McGrady, 1987; Mally, 2006; Tinmouth, 2001; Yoshida, 2007; Ho, 2003; Christensen, 2009)
Hypothesis

- Transfusion of older PRBCs is associated with decreased somatic tissue perfusion and greater severity of perfusion changes
Study Design

• Commercial piglets weighing 1.5 - 2.5 kg (n=12) 6-9 days old

• Cerebral, splanchnic and renal NIRS monitoring before, during and following PRBC transfusion.

• PRBC's were stored for 5-7, 10-14, and 20-23 days

• Piglets were anesthetized prior to transfusion, continuous vital signs, sats were monitored with labs including gases q30 minutes

• At autopsy, tissue histology and gross exam were performed
21 Day Old Blood

Transfusion

Time

rSO2

Head
Leg
Kidney
Gut
# Average Percent Decline from Baseline

<table>
<thead>
<tr>
<th></th>
<th>Cerebral</th>
<th>Gut</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No Transfusion</strong></td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td><strong>CPDA-1 and NS</strong></td>
<td>12%</td>
<td>13%</td>
<td>16%</td>
</tr>
<tr>
<td><strong>5 day Old Blood</strong></td>
<td>11%</td>
<td>23%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>14 day old Blood</strong></td>
<td>16%</td>
<td>32%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>14 day old Blood</strong></td>
<td>12%</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>7.5cc/kg</strong></td>
<td>12%</td>
<td>21%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>21 day old Blood</strong></td>
<td>17%</td>
<td>40%</td>
<td>65%</td>
</tr>
</tbody>
</table>
Perforation with Coagulation Necrosis
Conclusions of Our Piglet Study

- Transfusion of older stored blood decreased gut and renal tissue oxygenation at least transiently.

- Spontaneous intestinal perforations occurred in two out of eight piglets receiving \( \geq 10 \) day old blood.

- All animals receiving blood \( > 10 \) days of storage demonstrated gross and microscopic ischemic changes in the intestine.
Should Feeds Make a Difference

• Two reports (Krimmel and El-Dib), showed stopping feeds around the time of RBC transfusion reduced the rate of Transfusion Associated NEC in individual units.

• BUT WHY would that be likely?
Figure 2: Peak systolic mesenteric blood flow velocity (asterisk; MBFV; \( p = 0.02 \)) and mean MBFV (dagger; \( p = 0.01 \)) increased in response to feeding in the anemic but not the posttransfusion state.

Krimmel et al. Am. J. Perinatol. 26(2) 2009
Storage of RBC Reduces iNO

Gladwin et al. Curr Opin Hematology (16) 2009
Our Preterm Infant Study Design

• Observational, prospective
• Observe tissue oxygenation patterns using near-infrared spectroscopy in preterm infants before, during and 48 hours following transfusions
• Evaluate tissue oxygenation in different body regions
  – Cerebral, splanchnic, renal
• Compare findings using relational analysis
Inclusion/Exclusion Criteria

- cGA < 36 weeks
- No current or previous NEC
- Not on any type of inotrope
- Receiving transfusion
- May be on ventilator or oxygen therapy
- No major anomalies
Study Protocol

• PI notified of transfusion order
• Parental consent obtained
• NIRS monitor applied
• Data collected/recorded
• No changes in regular/routine care
• Transfusion practice is Neonatologist dependent and variable
  – Hold feeds v. continue (how long feeds held)
  – Volume of transfusion (divided v. full)
Data collected

- Demographics/birth history
- Pertinent diagnoses
- NIRS tracings and rSO₂ values
- Transfusion information
- Labs
- Feedings
- Physiologic
- Medications
- Procedures
- Blood sample analysis
Transfusion unit PRBC sample analysis

• From every parent unit of blood transfused:
  – Age of blood (donation date)
  – Date of irradiation
  – Blood group/Rh
  – ATP
  – 2,3-DPG
  – Plasma free Hgb
Instrumentation

- Near-infrared Spectroscopy (NIRS)
- Simultaneously measures tissue oxygenation of different regions of body
- Allows direct, real-time monitoring of differential oxygenation reflecting perfusion
Splanchnic Perfusion

Descriptive Statistics

• To date: 22 babies enrolled
• Transfusion events: 36
• Current Gestational age
  – Range: 24-30 weeks
  – Mean: 27 weeks
• Current weight
  – Range: 696-1996g
  – Mean: 1250g
• Gender
  – 13 Males; 9 females
• Ethnicity
  – 17 Black; 5 caucasian
Gut rSO2
Baseline

CW03 Day1 (NEC baby)

Transfusion start
Transfusion end

rSO2

Fdg
Cerebral
Gut
Renal

Fdg
Fdg
Fdg
Fdg
SO

- Feeds MAY be an issue, HOWEVER, the affect of feeds on tissue oxygenation actually persists much longer than all previous studies have held feeds
- Not ALL babies drop their tissue oxygen index
- Is there other risk factors that may “Set UP” the patient for increased risk??????
Hct 23.1

Hct = 19.5

Tx start

Tx end

NIRS Gut Readings Compared
Babies that developed NEC after PRBC Transfusion

- We had 4 babies out of 20 that developed NEC on study
- Descriptive statistics of NEC v. nonNEC babies
<table>
<thead>
<tr>
<th></th>
<th># of transfusions</th>
<th>Volume of transfusions</th>
<th>Timing of NEC onset</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby 1</td>
<td>2</td>
<td>7.5cc/kg x 2</td>
<td>30 minutes</td>
<td>Rec’d tx in 12 hour period</td>
</tr>
<tr>
<td>Baby 2</td>
<td>2</td>
<td>20cc/kg &amp; 15cc/kg</td>
<td>38.5 hours (GI perforation)</td>
<td>Rec’d tx in 3 day period</td>
</tr>
</tbody>
</table>
| Baby 3 | 2                 | 15cc/kg & 15cc/kg      | 11.5 hours          | • Rec’d in 24 hour period  
• Rec’d blood from same donor unit as Baby 4   |
| Baby 4 | 2                 | 15cc/kg & 16cc/kg      | During tx? Again 4 days  
Definitive dx 8 days | • Rec’d in 24 hour period  
• Rec’d blood from same donor unit as Baby 3   |
## NEC babies: Feeding data

<table>
<thead>
<tr>
<th></th>
<th>Volume of Feedings</th>
<th>Type</th>
<th>Route/duration</th>
<th>Held for tx?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baby 1</td>
<td>150cc/k/d</td>
<td>PEF 24 cal/oz</td>
<td>OG/30 min</td>
<td>No</td>
</tr>
<tr>
<td>Baby 2</td>
<td>56cc/k/d</td>
<td>BM 20 cal/oz</td>
<td>OG/1 hour</td>
<td>No for 1st tx</td>
</tr>
<tr>
<td>Baby 3</td>
<td>147cc/k/d</td>
<td>PEF 24 cal/oz</td>
<td>OG/1.5 hours</td>
<td>No</td>
</tr>
<tr>
<td>Baby 4</td>
<td>100cc/k/d</td>
<td>PEF 20 cal/oz</td>
<td>OG/bolus</td>
<td>No</td>
</tr>
</tbody>
</table>
### NEC Babies compared to Non-NEC

<table>
<thead>
<tr>
<th></th>
<th>NEC</th>
<th>nonNEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>cGA (mean)</td>
<td>26.5</td>
<td>27</td>
</tr>
<tr>
<td>Current infant age (mean)</td>
<td>18.75</td>
<td>29.24</td>
</tr>
<tr>
<td>Current infant weight (mean)</td>
<td>1081g</td>
<td>1294g</td>
</tr>
<tr>
<td>Received 2\textsuperscript{nd} transfusion</td>
<td>100%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Age of blood (mean)</td>
<td>7.75 days</td>
<td>7.1 days</td>
</tr>
<tr>
<td>Days of irradiation (mean)</td>
<td>4.25 days</td>
<td>3.35 days</td>
</tr>
<tr>
<td>Hct before Tx (mean)</td>
<td>25%</td>
<td>27.24%</td>
</tr>
<tr>
<td>Feeding type</td>
<td>Formula 75% (PEF)</td>
<td>40% formula</td>
</tr>
<tr>
<td>Feeding Volume (mean)</td>
<td>132cc/k/d</td>
<td>97cc/k/d</td>
</tr>
<tr>
<td>Feedings held</td>
<td>1 out of 8 held (transfusions)</td>
<td>11 out of 16 held (transfusions)</td>
</tr>
</tbody>
</table>
Preterm Neonate Study Summary

- This study adds additional information re: transfusions + feeds and NEC from a tissue oxygenation perspective.
- Trending tissue oxygenation patterns v. single “point-in-time” reveals more information about effect of transfusions.
- Babies that developed NEC:
  - had lower starting hematocrits prior to tx
  - fed during transfusions
    - received larger volumes of feeds
    - 3 out of 4 received formula
  - Received 2 transfusions (4 out of 4 got full volume txs)
- Further studies are need regarding the effect of older blood, and the effect of other factors (feedings, medications, etc.)
173 LBWIs (over 20 months) in a related study
13/173 (7.5%) developed NEC
Total transfusions: n=541
Total blood donors: n=243
Median age at initial NEC dx: 34.0 d (17-51d)
Results: Univariate Cox Analysis of Time Dependent Covariates

- Risk of developing NEC increased with each additional RBC transfusion received in a given week.
- Anemia may be a risk factor for NEC (OR=1.6 for a LBWI with anemia relative to a LBWI without anemia in a given week; 95%CI: 0.34-7.71).
- Longer storage of RBCs prior to RBC transfusion and longer irradiation times prior to transfusion were significantly associated with an increased risk of NEC.
Effect of Irradiation

- Free Hb concentrations changes in each group during storage. #: P<0.05 and *: P<0.01 compared with untreated group

Conclusions

• Storage Lesion Exists

• It is clear that most transfusions are safe, but there appears to be a subset of preterm infants at risk for Transfusion Associated NEC

• The exact mechanism leading to Post Transfusion NEC is unclear, but RBC storage time, irradiation time, and feeding issues need further study.
To Be Determined?

• Can we identify the physiologic cause(s) of Transfusion Associated NEC
• Can we develop methods or use technologies to help determine which infants are at risk
• Are we letting Hct’s drop too low?
• Should we feed, stop feeds, and for how long, and how do we tell if its safe to start again?
• Why are some infants susceptible and why are most not?
Pooled data from 6 cohort studies. Pooled mean OR is 7.58 with a 95% CI of 5.97-9.63. However, the study by Paul et al., after multiple regression adjustment, led to an OR of 2.1, similar to the data provided from Christensen (OR of 3.60 [2.50, 5.45]).
Pooled data from 4 case-control studies of Transfusion Associated NEC, of which full values allowed estimates in 3. The pooled mean OR is 2.02 (95% CI 1.40, 2.93).

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Total Events</th>
<th>Total Weight</th>
<th>M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Dib</td>
<td>14</td>
<td>19</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Josephson</td>
<td>47</td>
<td>100</td>
<td>46</td>
<td>84</td>
</tr>
<tr>
<td>McGrady</td>
<td>24</td>
<td>N/A</td>
<td>5</td>
<td>N/A</td>
</tr>
<tr>
<td>Singh R</td>
<td>44</td>
<td>67</td>
<td>67</td>
<td>266</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>186</td>
<td>381</td>
<td>100.0%</td>
<td>2.19 [1.52, 3.17]</td>
</tr>
</tbody>
</table>

Total events: 120  129

Heterogeneity: $\chi^2 = 25.87$, df = 2 ($P < 0.00001$), $I^2 = 92$

Test for overall effect: $Z = 4.17$ ($P < 0.0001$)
Pooled data from 3 randomized controlled trials as analyzed by Whyte and Kirpalani for the Cochrane review. The data here are presented in the form of odds ratio. Where Transfusions are Protective against NEC.
Association of Necrotizing Enterocolitis with Anemia

Future Investigation

- NEC at 48 hours after a blood transfusion may occur less frequently than the overall NEC (likely difficulties doing a RCT).
- The Neonatal Research Network (NICHD) is projecting a study of 2008 infants. The trial will be powered for a primary outcome of death or neurodisability at 18 months,
- the hypothesis is that this cluster outcome will be reduced in the high transfusion group.
- The trial has an 80% power with a 2-tailed alpha of 0.05 to detect differences in NEC rate of up to 3.5% between low or the high threshold groups, based on findings of the ‘Prematures in Need of Transfusion’ (PINT) RCT trial.
• QUESTIONS?