“Feeding During Blood Transfusions: What Does the Evidence Show?”

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Disclosure

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Necrotizing Enterocolitis

• Occurs ~ 7-10% of VLBW infants
• Characterized by intestinal ischemia, infection and bowel necrosis
• Associated with significant mortality/morbidity
• Risk factors: prematurity, enteral feedings, blood transfusions
• Most preterm infants will receive a PRBC transfusion for Anemia of Prematurity
What is Transfusion-Related NEC?

• Current definition:
  When symptoms of NEC appear within 48 hours following a packed red blood cell transfusion

• Controversial among many researchers and medical providers
Transfusion-related NEC

- ~1/3 of VLBW infants who developed NEC were transfused within 48 hours prior
- Unknown pathogenesis
- Common theories:
  - perfusion alteration
  - enteral feedings
  - age of blood
  - severity of anemia

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGrady</td>
<td>1987</td>
<td>(61%) had onset of NEC following PRBC transfusions</td>
</tr>
<tr>
<td>Bednarek</td>
<td>1998</td>
<td>NICUs with lower transfusion rates had lower NEC incidence</td>
</tr>
<tr>
<td>Mally</td>
<td>2006</td>
<td>NEC onset following transfusions received older blood</td>
</tr>
<tr>
<td>Krimmel</td>
<td>2009</td>
<td>blood flow in SMA did NOT increase in infants on feedings in the immediate post-transfusion state</td>
</tr>
<tr>
<td>Christensen</td>
<td>2010</td>
<td>38% of infants had a blood transfusion (18 ± 12 h) preceding NEC development</td>
</tr>
<tr>
<td>Josephson</td>
<td>2010</td>
<td>Transfusions were associated with NEC at a later postnatal age, lower birth weights and had more complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Study Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Dib</td>
<td>2011</td>
<td>NEC 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</td>
<td>2011</td>
<td>Infants with NEC had lower Hct and were more likely to be transfused within 24, 48 and 96 h of NEC onset than controls</td>
</tr>
<tr>
<td>Bailey</td>
<td>2011</td>
<td>Using NIRS, found that mesenteric oxygenation rose after tx and began to decline at 12 hours post (no feeds during tx)</td>
</tr>
<tr>
<td>Paul</td>
<td>2011</td>
<td>Increased OR 2.3 for TR-NEC</td>
</tr>
<tr>
<td>DiRienzo</td>
<td>2014</td>
<td>After implementing a fdg protocol to withhold fdgs, no significant change in TR-NEC incidence</td>
</tr>
<tr>
<td>Wallenstein</td>
<td>2014</td>
<td>PRBC transfusions are not associated with NEC development. N=414 infants &lt; 1500g, p= 0.32 (5.8% developed NEC within 48 hrs of transfusion) *no clear report of feeding practices</td>
</tr>
</tbody>
</table>

Paul et al, *Pediatrics* (2011) 127-4 635-64  
Wallenstein et al, *Journal of Pediatrics* [Epub ahead of print].
Previous Studies: Feeding and Transfusions

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.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Volume of enteral intake 24 hr before the RBC transfusion (mL/kg)</th>
<th>Volume of enteral intake during the RBC transfusion (mL/kg)</th>
<th>Volume of enteral intake 24 hr after the RBC transfusion (mL/kg)</th>
<th>Feeding substance 24 hr before, during, and 24 hr after the RBC transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>38</td>
<td>115 (0-160)</td>
<td>12 (0-73)</td>
<td>0 (0-152)</td>
<td>Human milk only (%) 16, Human milk with bovine fortifier (%) 19, Bovine formula only (%) 35, Mix (%) 11, NPO (%) 19</td>
</tr>
<tr>
<td>Controls</td>
<td>38</td>
<td>16 (0-164)</td>
<td>2 (0-40)</td>
<td>38 (0-164)</td>
<td>51, 13, 15, 3, 18</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>0.04</td>
<td>0.17</td>
<td>0.01</td>
<td>0.03, 0.40, 0.05, 0.17, 0.88</td>
</tr>
</tbody>
</table>

* Matching was on the basis of demographic features and transfusion history. Values are given as median (range) or percent. Mix = mixture of human milk and bovine-based formula; NPO = nil per os (nothing by mouth).
Feedings and TR-NEC

- El-Dib\(^1\) and colleagues found if feedings held during RBC transfusion, the incidence of TR-NEC decreased from 5.3 to 1.3% (p=0.047).
- Wan-Huen\(^2\) and colleagues found that infants who were receiving enteral feedings within a 48 hour period prior to transfusion were 8 times more likely to develop NEC.

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NEAR-INFRARED SPECTROSCOPY (NIRS) STUDIES
NIRS

- Similar technology to pulse-oximetry
- Difference is what is being measured
- Pulse oximetry measures oxygenation in arterial blood as it leaves the heart \(\rightarrow\) depends on pulsatile blood flow
- NIRS measures oxygen extraction at tissue level
Reasons for Decreased NIRS Values

- Decreased blood delivery to tissue bed
- Increased oxygen consumption at tissue level
- Diminished or altered oxygen carrying capacity
- Combination of any of these conditions

Gut oxygenation during feedings

- Dave et al found that in stable growing preterm infants that were receiving bolus feedings, gut oxygenation increased postprandially (~60 minutes)
- This is what we would expect to see

Questions unanswered

• What happens to gut oxygenation during a transfusion when feedings are continued?
• How does this compare to when feedings are held?
• What happens to gut oxygenation in TR-NEC?
Purpose of Marin Studies

- Examine tissue bed perfusion changes using near-infrared spectroscopy (NIRS) before, during and following PRBC administration in preterm infants
- Examine perfusion changes related to enteral feedings given during and following transfusions
- If TR-NEC developed, compare differences if perfusion to those who did not develop disease
Research Design

• Prospective, observational
• Using NIRS, we observed perfusion patterns in mesenteric tissue beds before, during and for up to 48 hours following PRBC transfusion
• Conducted at Emory Midtown University Hospital, Neonatal Intensive Care Unit
Inclusion/Exclusion Criteria

- **Inclusion criteria:**
  - < 37 weeks gestational age
  - Hemodynamically stable as defined by not requiring intravenous vasopressor support

- **Exclusion criteria:**
  - ≥37 weeks gestational age
  - Receiving intravenous vasopressor support
  - Current or previous diagnosis of necrotizing enterocolitis
  - Intraventricular hemorrhage Grade III or greater
  - Congenital anomalies
Methodology: RBC Transfusions

- Volume, rate and decision to administer RBCs made by attending Neonatologist independent of this study
- Decision to hold or continue enteral feed during RBC administration made by attending Neonatologist
Methodology: NIRS

• Near-Infrared Spectroscopy applied to peri-umbilical area
• Measures rSO$_2$ (regional oxygenation) in tissue beds
• rSO$_2$ represents difference between oxygenated and deoxygenated Hgb
• Measures values every 30 seconds in real-time
Statistical Analysis

• Calculated rSO$_2$ mesenteric baselines means for the 30 minute period immediately preceding transfusion event

• Calculated mesenteric means in 30-minute intervals

• Multi-level modeling used due to the nested nature of data with significance set at $p<0.05$
Demographics of Enrolled Subjects

- 33 transfusion events given to 19 subjects
- 12 males, 7 females
- 84% African-American, 16% Caucasian
- Gestational age mean (weeks): 27.7 (±2.1)
- Birthweight (g): 1060.5 (±266.7)
- Postnatal age mean (days): 28 (±17)
- 4 subjects developed TR-NEC*

1st Marin study*: TR-NEC Infants

- 3 of the 4 were fed during transfusion
- All received 2 transfusions in a relatively short amount of time
- 2 developed Medical NEC & 2 developed Surgical NEC

Medical NEC Infants

Surgical NEC infants

Non-NEC infants

Actual NIRS tracings of TR-NEC
Conclusions

• Greater rSO$_2$ variation in TR-NEC infants compared to non-NEC infants
• No changes in physiologic parameters with decreased rSO$_2$ values
• SpO$_2$ values in all TR-NEC infants remained greater than 92% until actual disease onset
• Severe and sudden decreases in mesenteric rSO$_2$ values may increase the risk for TR-NEC onset, especially if prolonged
Further analysis - 2\textsuperscript{nd} Marin study*: Feedings and Transfusion

- We then examined trends across time for all infants Fed during RBC administration to those that were not Fed

- Analysis conducted in 3 phases:
  1: During RBC Transfusion
  2: Elapsed time (end of transfusion but before 1\textsuperscript{st} feeding after transfusion)
  3: During sequential feedings after transfusion

Analysis

- Phases 1 and 2: the average change in slope across time compared using t-tests
- Phase 3: calculated means for each feeding in 10-minute window (5 minutes before feeding started and 5 minutes into feeding event)

Analysis of feeding data
# Sample

<table>
<thead>
<tr>
<th># of Infants</th>
<th># of Transfusions</th>
<th>Tx Sequence 1</th>
<th>Tx Sequence 2</th>
<th>Tx Sequence 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Full dose</td>
<td>Full dose</td>
<td>Divided dose</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Full dose</td>
<td>Full dose</td>
<td>Divided dose</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>Full dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Divided dose</td>
<td>Divided dose</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Full dose</td>
<td>Full dose</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- One infant developed TR-NEC – not included in final sample
- One infant was NPO during entire study – not included in final sample
### Final Sample for Analysis

<table>
<thead>
<tr>
<th>Transfusion dose</th>
<th>Fed</th>
<th>Not Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dose n= 13</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Divided dose n =4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

No statistical differences between Fed v. Not Fed groups except for volume of feedings (p=0.022) Those fed during transfusion were receiving larger volumes than those not fed.
Fed v. Not Fed Groups Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FED (n=9) Mean (SD)</th>
<th>NOT FED (n=8) Mean (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth GA (wks)</td>
<td>27.7 (2.3)</td>
<td>28.0 (2.3)</td>
<td>0.776</td>
</tr>
<tr>
<td>PMA (wks)</td>
<td>32 (3.2)</td>
<td>30.4 (2.9)</td>
<td>0.281</td>
</tr>
<tr>
<td>PNA (days)</td>
<td>30.4 (15.3)</td>
<td>16.8 (12.4)</td>
<td>0.061</td>
</tr>
<tr>
<td>Birthweight (g)</td>
<td>1052.3 (272.7)</td>
<td>1097 (287.6)</td>
<td>0.743</td>
</tr>
<tr>
<td>Current weight (g)</td>
<td>1485 (412.5)</td>
<td>1274.2 (565.8)</td>
<td>0.398</td>
</tr>
<tr>
<td>Feeding Volume (cc/kg/day)</td>
<td>140.5 (37.6)</td>
<td>74.9 (64.7)</td>
<td>0.022</td>
</tr>
<tr>
<td>Age of Blood (days)</td>
<td>7.5 (2.8)</td>
<td>6.7 (3.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.36 (0.26)</td>
<td>0.27 (0.05)</td>
<td>0.743</td>
</tr>
</tbody>
</table>

Feeding Characteristics

• Fed during Transfusion (n = 8)
  – Breastmilk n= 1
  – Formula n=7

• Not Fed during Transfusion (n=9)
  Before and after tx:
  – Breastmilk n=7
  – Formula n= 2
  – All infants were fed prior to and following transfusion

Results

- Phase I: no difference in slopes during transfusion in Fed v. Not Fed groups (p = 0.480)
- Phase II: no difference in slopes during elapsed time between groups (p = 0.173)
- Phase III: Infants fed during RBC transfusion had negative slopes after transfusion completion; infants not fed during RBC transfusion had positive slopes after transfusion completion (p < 0.001).

Slopes by Fed v. Not Fed and separated by PMA

Mesenteric Oxygenation Trends related to Feeding Status during RBC administration

Conclusions

• Feeding during RBC transfusion does not affect gut oxygenation
• Feeding during transfusion may negatively affect gut oxygenation post-transfusion
• This effect may be enhanced in infants with lower PMA
• Pathophysiologically may be related to severity of anemia, GI immaturity or beginning mesenteric oxygenation status

Conclusions cont’

- Negative trends in those fed during transfusion may represent a relative decrease in $O_2$ availability to gut tissues potentially increasing the risk for ischemia.
- Because intestinal circulatory autoregulation in VLBW infants may be impaired—a relative decrease in available oxygen delivery to gut tissues is concerning.

Further Research

- Larger multi-centered studies are needed to fully evaluate the impact of feedings on mesenteric oxygenation during and following PRBC transfusion.
- Need to further analyze if trends are different between those fed breastmilk v. formula.
- Yazji et al\(^1\) found that breastmilk naturally augments NO production – protecting against NEC development.

Acknowledgements

• Cassandra Josephson, MD
• Jim Moore, MD, PhD
• Niki Kosmetatos, MD
• Melinda Higgins, PhD
• Paul Weiss, MPH
Thank you!!

Questions?
Study Limitations

• Small sample size
• Limited generalizability
• Inability to measure all variables related to GI immaturity factors
• Did not capture mesenteric perfusion (NIRS) during enteral feeding event(s) prior to beginning of transfusion event
<table>
<thead>
<tr>
<th></th>
<th>Entire Sample (n=24)</th>
<th>NEC (n=4)</th>
<th>Non-NEC (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± std dev</td>
<td>Mean ± std dev</td>
<td>Mean ± std dev</td>
</tr>
<tr>
<td>Gestational age @ birth (weeks)</td>
<td>27.57 ± 2</td>
<td>26.5 ± 2.1</td>
<td>27.78 ± 1.97</td>
</tr>
<tr>
<td>Postconceptual age (weeks)</td>
<td>31.63 ± 2.84</td>
<td>29.07 ± 3.47</td>
<td>32.14 ± 2.49</td>
</tr>
<tr>
<td>Postnatal Age (days)</td>
<td>28.4 ± 17</td>
<td>18 ± 10.55</td>
<td>30.5 ± 17.5</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1039 ± 243.71</td>
<td>897 ± 173.01</td>
<td>1067.35 ± 249.16</td>
</tr>
<tr>
<td>Current weight (g)</td>
<td>1396 ± 449.8</td>
<td>1084.5 ± 423.63</td>
<td>1458.55 ± 438.21</td>
</tr>
<tr>
<td>Volume of feedings (cc/kg/day)</td>
<td>112.86 ± 55.1</td>
<td>113.25 ± 44.51</td>
<td>112.78 ± 58.25</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>26.24 ± 3.87</td>
<td>24.55 ± 4.56</td>
<td>26.58 ± 3.76</td>
</tr>
<tr>
<td>Volume of 1st transfusion (cc/kg)</td>
<td>13.6 ± 3.64</td>
<td>14.38 ± 5.15</td>
<td>13.45 ± 3.42</td>
</tr>
<tr>
<td>Age of Blood 1st transfusion (days)</td>
<td>6.88 ± 2.38</td>
<td>7.0 ± 0</td>
<td>6.85 ± 2.62</td>
</tr>
<tr>
<td>Irradiation 1st transfusion (days)</td>
<td>3.13 ± 2.19</td>
<td>3.5 ± .577</td>
<td>3.05 ± 2.4</td>
</tr>
<tr>
<td>Volume of 2nd transfusion (cc/kg/day)</td>
<td>9.67 ± 4.89</td>
<td>13.38 ±3.94</td>
<td>6.7 ± 3.37</td>
</tr>
<tr>
<td>Age of Blood 2nd transfusion (days)</td>
<td>8.29 ± 2.75</td>
<td>8.5 ± 2.12</td>
<td>8.2 ± 3.19</td>
</tr>
<tr>
<td>Irradiation 2nd transfusion (days)</td>
<td>4.29 ± 2.75</td>
<td>5.5 ± 2.12</td>
<td>3.8 ± 3.03</td>
</tr>
</tbody>
</table>
Mesenteric Perfusion and Volumes of feedings

- Infants receiving larger volumes of feedings had higher means (p=.007)
- Older infants received greater volumes of feeds and overall had higher means
Reference Ranges

• Cerebral: 60-80%
• Renal: 65-95%
• Gut: 40-60% (32-33 weeks) 25-58% (29-30 weeks)
• Cerebral tracings more stable, gut and renal tracings highly variable
• Established on stable preterm infants in first 21 days of life

Mesenteric Perfusion fluctuation related to feeding episodes-example

Subject ID: CW06

Gut Mean

Time point