Outline of Presentation

- Common causes of anemia in the preterm
- Strategies to reduce the severity of anemia
  - Placental transfusion
  - Reduce phlebotomy blood loss
  - Support erythropoiesis
- Transfusion guidelines
  - Any guidelines reduce transfusion frequency
  - What guidelines should we use?
  - What hemoglobin range is safest and most beneficial?
- Transfusion of Prematures (TOP) Trial
Physiological Anemia

- The hemoglobin level is high at birth and declines in all newborn infants.
- Fetal polycythemia is needed to assure adequate tissue oxygen delivery in the presence of hypoxemia.
- Red cells die faster than they are replaced by erythropoiesis during the first months of life.
Anemia in the Preterm Baby

- Other factors, superimposed on physiological anemia, result in “anemia of prematurity”

- Early cord clamping even more likely in preterm baby – urgency to start resuscitation

- Phlebotomy losses (“hemorrhage into the laboratory”)

Physiological anemia
  + early cord clamping
  + phlebotomy losses

= anemia of prematurity
Phlebotomy Blood Loss in VLBW Babies

Freise KJ and Widness JA, *J Pharmacol Exp Ther* 2010
Phlebotomy Blood Loss in VLBW Babies

- Cumulative phlebotomy losses typically reach 40 to 80 ml/kg and, in many babies, exceed the baby’s blood volume

**DIAGNOSTIC EXSANGUINATION**

- This is the single most important contributor to anemia of the preterm, and it is the factor that is most easily corrected
Transfusions for Preterm Babies

- Very preterm babies are one of the most heavily transfused patient groups.
- More than 90% of ELBW babies are transfused, most multiple times.
  - The mean number of transfusions per baby ranges from 3 to 10 in published reports.
- Transfusion risks are very low, but adverse effects occur nonetheless.
Transfusion Risks

- Infection
  - Hepatitis
  - HIV
  - Others, including unknown pathogens

- Necrotizing enterocolitis?

- Lung injury?
Strategies for Avoiding Transfusion

- Increase initial blood volume
- Decrease phlebotomy blood loss
- Support production of new RBCs
- Use standardized transfusion guidelines
Ways to increase placental transfusion

- Delay umbilical cord clamping
- Milk the cord
- Collect and store placental blood for later transfusion to baby
Delayed Umbilical Cord Clamping

- Delaying cord clamping for 30-120 seconds
  - Increases blood volume
  - Raises hemoglobin and blood pressure
  - Reduces need for transfusion
  - Improves cerebral oxygenation
  - Provides an extra endowment of progenitor cells
  - In preterm infants, reduces IVH, NEC, and late-onset sepsis

## Intraventricular Hemorrhage

McDonald et al. *Cochrane* 2013

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>More placental trans n/N</th>
<th>Less placental trans n/N</th>
<th>Risk Ratio M-H</th>
<th>Fixed,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strauss 2008</td>
<td>1/45</td>
<td>1/60</td>
<td></td>
<td>1.33 [0.09, 20.75]</td>
<td>1.5%</td>
</tr>
<tr>
<td>McDonnell 1997</td>
<td>0/15</td>
<td>1/16</td>
<td></td>
<td>0.35 [0.02, 8.08]</td>
<td>2.5%</td>
</tr>
<tr>
<td>Oh 2002</td>
<td>4/16</td>
<td>3/17</td>
<td>1.42 [0.37, 5.37]</td>
<td>5.0%</td>
<td></td>
</tr>
<tr>
<td>Rabe 2000</td>
<td>1/19</td>
<td>3/20</td>
<td>0.35 [0.04, 3.09]</td>
<td>5.1%</td>
<td></td>
</tr>
<tr>
<td>Kugelman 2007</td>
<td>2/30</td>
<td>4/35</td>
<td></td>
<td>0.58 [0.11, 2.96]</td>
<td>6.4%</td>
</tr>
<tr>
<td>Mercer 2003</td>
<td>3/16</td>
<td>5/16</td>
<td>0.60 [0.17, 2.10]</td>
<td>8.6%</td>
<td></td>
</tr>
<tr>
<td>Hosono 2008</td>
<td>3/20</td>
<td>5/20</td>
<td>0.60 [0.17, 2.18]</td>
<td>8.6%</td>
<td></td>
</tr>
<tr>
<td>Hofmeyr 1993</td>
<td>8/40</td>
<td>11/46</td>
<td>0.84 [0.37, 1.87]</td>
<td>17.7%</td>
<td></td>
</tr>
<tr>
<td>Hofmeyr 1988</td>
<td>8/23</td>
<td>10/13</td>
<td>0.45 [0.24, 0.85]</td>
<td>22.1%</td>
<td></td>
</tr>
<tr>
<td>Mercer 2006</td>
<td>5/36</td>
<td>13/36</td>
<td>0.38 [0.15, 0.97]</td>
<td>22.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>260</strong></td>
<td><strong>279</strong></td>
<td><strong>0.59 [0.41, 0.85]</strong></td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 35 (More placental trans), 56 (Less placental trans)
Heterogeneity: Chi² = 4.55, df = 9 (P = 0.87); I² = 0.0%
Test for overall effect: Z = 2.82 (P = 0.0048)
Test for subgroup differences: Not applicable

McDonald et al. *Cochrane* 2013
Cord Clamping vs Milking

- **Delayed clamping** of the umbilical cord has been shown to have significant benefits for preterm infants.

- However, delayed cord clamping has not gained wide acceptance in obstetrical practice, in part because of the preterm infant’s frequent need for resuscitation.

- Many obstetricians and neonatologists are unwilling to delay the resuscitation until the cord is clamped and cut 1 to 2 minutes after delivery.

- **Cord milking** offers an alternative to delayed cord clamping that may provide the same benefits without the need to delay resuscitation.
Umbilical Cord Milking

  - 40 infants 24-28 weeks gestation
  - Randomized to early cord clamping or cord milking
  - Milking reduced need for transfusion
  - No need to delay resuscitation
  - No adverse effects

  - 58 infants <33 weeks
  - Milking vs delayed clamping
  - No differences
Collection and Storage of Placental Blood for Later Transfusion

- Not practically feasible
- Limited blood volume can be collected from preterm placenta
- Sterility, anticoagulation, and avoiding hemolysis have proved challenging
- Does not allow taking advantage of the cardiorespiratory and neuroprotective effects of early placental transfusion
Cautions Regarding Delayed Cord Clamping or Cord Milking

- Impact on long-term neurodevelopmental outcome unknown
- Data are sparse for extremely preterm babies, those who stand to gain the most
- There may be groups of patients for whom risks are greater, for example babies with poor cardiac function – volume loading may be harmful
Reducing Phlebotomy Blood Loss

- Shown to be feasible – How?

- Use methods and instruments that require less blood

- Avoid overdraw
  - “We wanted to be sure we had enough in case we had to repeat the analysis. We didn’t want to have to stick the baby again.”

- Order only the laboratory studies that are necessary; trainees tend to order too many
Supporting Erythropoiesis

- Erythropoietin
  - Reduces need for transfusions but by only a small amount (<1 transfusion per baby)
  - Most transfusions occur during the first week, when erythropoietin is less effective
  - Not recommended for routine use
  - There may be a subgroup for whom benefit outweighs risk, but this has not yet been defined

  - Reduced transfusions with weekly dosing
Supporting Erythropoiesis

**Nutrition**

Optimal erythropoiesis requires adequate intakes of

- Iron
- Folate
- Vitamin B₁₂
- Vitamin E
- Protein
Limiting Donor Exposures

- Transfusions cannot be avoided completely.
- Single donor transfusion programs can reduce donor exposures to 1 or at most 2 donors for anemic preterm babies.
- Modern storage media allow blood to be stored for up to 42 days with acceptable quality; a unit or part of a unit can be set aside to meet the transfusion needs of a single preterm baby.
Transfusion Guidelines

- Introduction of standardized transfusion guidelines has been shown in several studies to reduce transfusions
- But what should these guidelines be?
- Can more restrictive guidelines reduce transfusions?
- If so, are there any harmful consequences of restrictive guidelines?
Transfusion Guidelines

What do we know from existing clinical trials?

Two most recent and largest trials:

1. Iowa Trial

2. PINT Trial
# Comparison of Iowa and PINT Trials

## Experimental Design

<table>
<thead>
<tr>
<th>Participating centers</th>
<th>Iowa Trial</th>
<th>PINT Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restrictive</td>
<td>Liberal</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Treatment allocation</td>
<td>Randomized</td>
<td>Randomized</td>
</tr>
<tr>
<td>Stratification</td>
<td>Birth weight</td>
<td>Birth weight, center</td>
</tr>
<tr>
<td>Mean BW (g)</td>
<td>954</td>
<td>958</td>
</tr>
<tr>
<td>Mean GA (wk)</td>
<td>28</td>
<td>28</td>
</tr>
</tbody>
</table>
## Comparison of Iowa and PINT Trials

### Transfusion Thresholds & Hemoglobin Separation

<table>
<thead>
<tr>
<th></th>
<th>Iowa Trial</th>
<th>PINT Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restrictive</td>
<td>Liberal</td>
</tr>
<tr>
<td><strong>Transfusion thresholds</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Hemoglobin, g/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>11.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Lowest</td>
<td>7.3</td>
<td>10.0</td>
</tr>
<tr>
<td>Mean hemoglobin</td>
<td>8.3</td>
<td>11.0</td>
</tr>
<tr>
<td><strong>Mean hemoglobin difference</strong></td>
<td><strong>2.7</strong></td>
<td><strong>1.1</strong></td>
</tr>
</tbody>
</table>
Transfusion Thresholds
Iowa Trial vs PINT Trial

![Graph showing transfusion thresholds for Iowa Liberal, Iowa Restrictive, PINT Liberal, and PINT Restrictive trials. The graph illustrates hematocrit levels across different levels of respiratory support: Intubated, CPAP or Oxygen, and No Support. The graph indicates that the Iowa Liberal and PINT Liberal trials have higher hematocrit thresholds compared to the Restrictive trials (both Iowa and PINT).]
Comparison of Iowa and PINT Trials

## Results

<table>
<thead>
<tr>
<th></th>
<th>Iowa Trial</th>
<th>PINT Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Restrictive</td>
<td>Liberal</td>
</tr>
<tr>
<td>No. of transfusions</td>
<td>3.3</td>
<td>5.2*</td>
</tr>
<tr>
<td>No. of donors</td>
<td>2.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Never transfused</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Apnea</td>
<td>More frequent in restrictive</td>
<td>55%</td>
</tr>
<tr>
<td>Died</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Brain injury (HUS)</td>
<td>12%</td>
<td>0%*</td>
</tr>
<tr>
<td>Death or brain injury</td>
<td>16%</td>
<td>2%*</td>
</tr>
</tbody>
</table>

* $P < 0.05$
Iowa Trial: Severe IVH and Cystic PVL

<table>
<thead>
<tr>
<th></th>
<th>Liberal</th>
<th>Restrictive</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade-4 IVH</td>
<td>0</td>
<td>4</td>
<td>0.054</td>
</tr>
<tr>
<td>Cystic PVL</td>
<td>0</td>
<td>4</td>
<td>0.115</td>
</tr>
<tr>
<td>Grade-4 IVH or cystic PVL</td>
<td>0</td>
<td>6</td>
<td>0.012</td>
</tr>
</tbody>
</table>

Caution: Composite outcome combining grade-4 IVH and PVL was not planned; small numbers
### PINTOS Outcomes: Odds Ratios

**Restrictive vs Liberal**

<table>
<thead>
<tr>
<th>Primary Outcome and Components</th>
<th>Odds Ratios with 95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td>1.50</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>1.18</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Cerebral Palsy</strong></td>
<td>1.32</td>
<td>0.55</td>
</tr>
<tr>
<td><strong>MDI &lt;70</strong></td>
<td>1.74</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Blindness</strong></td>
<td>2.16</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Deafness</strong></td>
<td>1.45</td>
<td>0.63</td>
</tr>
</tbody>
</table>

PINTOS Outcomes: Odds Ratios
Restrictive vs Liberal

Primary Outcome and Components
Odds Ratios with 95% CI

<table>
<thead>
<tr>
<th>Component</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>1.71</td>
<td>1.12, 2.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Death</td>
<td>1.18</td>
<td>0.72, 1.93</td>
<td>0.52</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>1.32</td>
<td>0.53, 3.27</td>
<td>0.55</td>
</tr>
<tr>
<td>MDI &lt;85</td>
<td>1.81</td>
<td>1.12, 2.93</td>
<td>0.02</td>
</tr>
<tr>
<td>Blindness</td>
<td>2.16</td>
<td>0.19, 24.1</td>
<td>0.53</td>
</tr>
<tr>
<td>Deafness</td>
<td>1.45</td>
<td>0.32, 6.58</td>
<td>0.63</td>
</tr>
</tbody>
</table>

There are Possible Protective Effects of Higher Hemoglobin Against Brain Injury, but...

- **Iowa Trial**
  - Composite analysis of grade-4 IVH or PVL was not planned but was done *post hoc*
  - Small numbers, 0 vs 6

- **PINT Trial**
  - Using preplanned MDI threshold 70 (mean – 2 SD), there were nonsignificant trends toward benefit with liberal transfusion in cognitive outcome (MDI) and composite
  - Using MDI threshold 85 (mean – 1 SD), these effects were significant
Potential Mechanisms for Neuroprotection by Higher Hemoglobin

- Higher cerebral oxygen delivery
  - Higher arterial oxygen content
  - Higher blood volume after transfusion with increased cerebral perfusion pressure

- Less frequent apnea, eliminating episodic hypoxia-ischemia and subsequent reperfusion
The story continues...

- School age assessment of Iowa Transfusion Study subjects
- 54 children examined at school age (mean 12 y)
- 54% of original cohort (56% of survivors)
- Evaluated with extensive neuropsychological testing and brain MRI
School Age Assessment of Iowa Transfusion Study Subjects

- Children in the liberally transfused group, compared to the restrictive group, performed more poorly on measures of
  - Associative verbal fluency
  - Visual memory
  - Reading
- And they had lower white matter volume by MRI
- Girls were more affected than boys!

Impact of Hematocrit on Systemic Oxygen Transport

Anemic hypoxia

Hyperviscosity

Hematocrit

Flow

Oxygen content

Oxygen transport
Impact of Hematocrit on Systemic Oxygen Transport

- Anemic hypoxia
- Hyperviscosity
- "Sweet spot"

Flow

Oxygen content

Oxygen transport

Hematocrit
## Potential CNS Risks and Benefits of High and Low Hematocrit

<table>
<thead>
<tr>
<th>Risks</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperviscosity</td>
<td>High cerebral O₂ delivery and perfusion pressure</td>
<td>Anemic hypoxia and lactic acidosis</td>
</tr>
<tr>
<td>Iron excess (oxidation and free radical injury)</td>
<td>Increased cardiac work</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More frequent apnea</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Benefits</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher cerebral O₂ delivery and perfusion pressure</td>
<td>Increased erythropoietin production</td>
<td></td>
</tr>
<tr>
<td>Less apnea (less ischemia-reperfusion injury)</td>
<td>Lower viscosity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoid risk of iron excess</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less free radical injury</td>
<td></td>
</tr>
</tbody>
</table>
What Have We Learned from the Iowa and PINT Trials?

- Restrictive transfusion criteria may reduce RBC transfusions
- With a single-donor system, donor exposures are not reduced
- Higher transfusion thresholds may reduce apnea frequency and severity
What Have We Learned from the Iowa and PINT Trials?

- Neurological implications are unclear
- Higher transfusion thresholds may be protective in the short term but harmful in the long term
- Or, it may be a matter of degree
  - High thresholds (Iowa liberal) may be harmful long term
  - Intermediate thresholds (PINT liberal) may be better
How Can We Resolve This?

- Evidence to date suggests that transfusion threshold or hemoglobin level affects the developing brain, but the evidence is not strong enough to warrant treatment recommendations.

- The most important outcome is survival without neurodevelopmental impairment.

- The Iowa trial was underpowered to look at neurodevelopmental outcomes, and the PINT trial may have been, too.

- More research is needed!
Aim of Transfusion of Prematures (TOP) Trial

- To test, in an adequately powered RCT, the hypothesis that the use of higher hemoglobin transfusion thresholds (similar to PINT high thresholds but with bigger high-low separation) will confer neuroprotection in extremely low birth weight (ELBW) infants compared to low transfusion thresholds.
**Transfusion of Prematures (TOP) Trial**

<table>
<thead>
<tr>
<th>Population</th>
<th>BW $\leq 1000$ g, GA 22-28 weeks, postnatal age $&lt;48$ h, $n=1824$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention:</strong></td>
<td>Liberal RBC transfusion strategy</td>
</tr>
<tr>
<td><strong>Comparison:</strong></td>
<td>Restrictive transfusion strategy</td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
<td>Survival without impairment</td>
</tr>
<tr>
<td><strong>Assessment age:</strong></td>
<td>22-26 months corrected age</td>
</tr>
</tbody>
</table>
## Transfusion of Prematures (TOP) Trial

<table>
<thead>
<tr>
<th></th>
<th>High Threshold</th>
<th></th>
<th>Low Threshold</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory support</td>
<td>No support</td>
<td>Respiratory support</td>
<td>No support</td>
</tr>
<tr>
<td>Week 1</td>
<td>13.0</td>
<td>12.0</td>
<td>11.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Week 2</td>
<td>12.5</td>
<td>11.0</td>
<td>10.0</td>
<td>8.5</td>
</tr>
<tr>
<td>Week 3+</td>
<td>11.0</td>
<td>10.0</td>
<td>8.5</td>
<td>7.0</td>
</tr>
</tbody>
</table>