The Power of The Human Touch

Prolacta Bioscience
Advancing the Science of Human Milk
100% Human Milk Diet: Meeting the Challenge of Infant Nutrition in the NICU

Terry S. Johnson, APN, NNP-BC, CLEC, MN
The First 1000 Days of Life

What is the Challenge?

Brain Development

- Neurons generated at 250,000 per minute
- 1.8 million new synapses form every second
- Lower CNS functions mature the earliest & cerebral cortex is last to develop increasing 5-fold from 35-41 weeks
- **70% of every calorie is used for brain growth**
Infants in the NICU

- Premature and/or LBW infants
- Exposure to maternal-fetal complications
  - Compromised placentation, maternal nutrition
  - History of diminished placental perfusion
  - PIH, preterm labor, PPROM, emergent delivery
- At risk for morbidities of prematurity
  - Infection, sepsis, antibiotic exposure
  - NEC, IVH, PVLM, ROP, CLD, osteopenia
  - Extra-uterine growth restriction
**Estimates of Fetal Growth**

<table>
<thead>
<tr>
<th>GA</th>
<th>Wt gain in g/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 wks</td>
<td>23.3</td>
</tr>
<tr>
<td>26 wks</td>
<td>21.1</td>
</tr>
<tr>
<td>28 wks</td>
<td>18.3</td>
</tr>
<tr>
<td>30 wks</td>
<td>17.2</td>
</tr>
<tr>
<td>32 wks</td>
<td>16.2</td>
</tr>
<tr>
<td>34 wks</td>
<td>14.8</td>
</tr>
<tr>
<td>36 wks</td>
<td>11.8</td>
</tr>
<tr>
<td>38 wks</td>
<td>8.6</td>
</tr>
<tr>
<td>40 wks</td>
<td>7.4</td>
</tr>
</tbody>
</table>

What is the Challenge?


“Preterm infants less than 30 weeks gestation accumulate an ENERGY deficit of 812 kcal/kg and a develop a PROTEIN deficit of 23 g/kg in the first 5 weeks of life.”
What is the Challenge?

Infants in the NICU

- Premature and/or LBW infants
- Born at period of maximal growth (brain & body)
  - Altered height, length, body composition
  - Deep, pervasive growth deficits
  - Impact on CNS development
  - Cognitive performance issues
  - Chronic health problems
  - Adult health risks
“The potent benefits of human milk are such that all preterm infants should receive human milk”

“Milk as Medicine”

- A substance or preparation of treating disease; something that effects well-being
- The science and art of dealing with the maintenance of health and the prevention, alleviation or cure of disease
- Professionals referencing human milk as a “medicine” that “only a mother can provide”
AAP Policy Breastfeeding & Use of Human Milk 2012

- Mother’s own milk, fresh or frozen, should be the primary diet
- If mother’s own milk is unavailable despite significant lactation support, pasteurized donor milk should be used
- It should be fortified appropriately for the infant born weighing less than 1.5 kg
Human Milk: Protein and Fat Levels

“Milk as Medicine”

- “Human milk is an evolutionary wonder whereby the lactating mother produces a species-specific nutritional and biologically active product that confers the best health to the human offspring”.

- “Major components of human milk are not primarily for nutrition, but for host defense”

“Immunonutrition”

- The modulation of the immune and inflammatory responses in critically ill patients with the use of enteral feedings enriched with immune-enhancing ingredients.

Lack of breastmilk may be the most common immunodeficiency of infancy.

Neu J & Bernstein, H Update on host defense and immunonutrients Clinics in Perinatology 29(1); 2002.
What is the Challenge?

Necrotizing Enterocolitis

- Most common severe neonatal GI emergency
- Multifactorial etiology
- Mortality ranges from 20% to 30%
- 1 in 7 NEC hospitalizations end in death
- 20-40% of affected infants require surgery
- Mortality for surgical NEC is ~ 50%
- Recurrent NEC incidence 4% to 6%
- Long term morbidities

Data Supporting an
Exclusive Human Milk Diet
Randomized Control Trial: Arm 1
Randomized Control Trial: Arm 1

- Purpose
  - To compare current standards of nutritional care with a completely human milk-based diet.

Randomized Control Trial: Arm 1

- Entry Criteria
  - Birth weight 500-1250 g
  - Mother has committed to providing breast milk
  - PN initiated within 48 hours of birth
  - Enteral feeding initiated by DOL 21
  - No major congenital anomalies
  - Expected survival of at least 90 days

The Exclusive Human Milk Diet

n=207 Preterm Infants  BW ≤ 1250 g

Mothers Own Milk

Donor Milk
When MOM is not available in sufficient quantity

- Human HMF @ 100 mL/kg/d  H100 n=67
- Human HMF @ 40 mL/kg/d  H40 n=71

Cow Milk-Based Preterm Formula
When MOM is not available in sufficient quantity

- Cow Milk-Based HMF @100 mL/kg/d  C100 n=69

Randomized Control Trial: Arm 1

- Endpoints
  - Days on Total Parenteral Nutrition
    - Quantifiable surrogate marker for feeding tolerance
  - Necrotizing Enterocolitis
    - Study conditionally powered for this endpoint

The Exclusive Human Milk Diet: Total Parenteral Nutrition
Randomized Control Trial: Arm 1

○ Primary Outcomes – Total Parenteral Nutrition

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hum 100 (n=67)</th>
<th>Hum 40 (n =71)</th>
<th>CMB (n=69)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral Nutrition - Days¹</td>
<td>20</td>
<td>20</td>
<td>22</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Could the absence of findings be related to the high breast milk intake in the control group?

Amount of Breast Milk in Randomized Control Trial: Arm 1

<table>
<thead>
<tr>
<th>Study Group</th>
<th>% of total volume of Mother’s Own Milk¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (CMB)</td>
<td>81.6%</td>
</tr>
<tr>
<td>Hum 40</td>
<td>69.9%</td>
</tr>
<tr>
<td>Hum 100</td>
<td>73.2%</td>
</tr>
</tbody>
</table>

Re-Analysis of TPN Data Randomized Clinical Trial:

Arm 1

- Re-evaluates these data from a different statistical perspective that considers the probability or likelihood of needing TPN on any given day rather than the number of days on TPN (through DOL 91)
- Accounts for stop/start interruptions in TPN therapy
- HUM 40 and HUM 100 groups
  - 11-14% reduction \((p<0.001)\) of likelihood of needing TPN on any given day²

The Exclusive Human Milk Diet: Necrotizing Enterocolitis
## Necrotizing Enterocolitis

<table>
<thead>
<tr>
<th></th>
<th>CMB</th>
<th>Hum 40</th>
<th>Hum 100</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>15.9%</td>
<td>7.0%</td>
<td>4.5%</td>
<td>5.8%</td>
</tr>
<tr>
<td>P value</td>
<td>0.09</td>
<td>0.05</td>
<td>0.045</td>
<td></td>
</tr>
</tbody>
</table>

### Necrotizing Enterocolitis-Surgery

<table>
<thead>
<tr>
<th></th>
<th>CMB</th>
<th>Hum 40</th>
<th>Hum 100</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical NEC</td>
<td>8/69</td>
<td>1/71</td>
<td>1/67</td>
<td>2/138</td>
</tr>
<tr>
<td>Rate</td>
<td>11.6%</td>
<td>1.4%</td>
<td>1.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>P value</td>
<td>0.017</td>
<td>0.03</td>
<td>0.0027</td>
<td></td>
</tr>
</tbody>
</table>

## Analysis of NEC Cases

### CMB

<table>
<thead>
<tr>
<th>Exposure to:</th>
<th>NEC</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cow Milk-Based</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Cow Milk–Based Formula Only</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cow Milk-Based Fortifier Only</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Cow Milk-Based Formula &amp; HMF</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Every surgical case was exposed to cow milk-based nutrition.

### Analysis of NEC Cases

#### HUM 40

<table>
<thead>
<tr>
<th>Exposure to:</th>
<th>NEC</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cow Milk-Based</td>
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<td>0</td>
</tr>
<tr>
<td>Cow Milk–Based Formula Only</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cow milk-based Fortifier Only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cow Milk-Based Formula &amp; HMF</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### HUM 100

<table>
<thead>
<tr>
<th>Exposure to:</th>
<th>NEC</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Cow Milk-Based</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Cow Milk-Based Formula Only</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cow Milk-Based Fortifier Only</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cow Milk-Based Formula &amp; HMF</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

1 in 10

The estimated number of infants needed to feed with human milk fortified with Prolact+ H²MF to prevent 1 case of NEC would be 10.

1 in 8

The estimated number of infants needed to feed with human milk fortified with Prolact+ H²MF to prevent 1 case of surgical NEC or death would be 8.

77%

Reduction in the odds of developing NEC
In premature infants weighing ≤ 1250g at birth while receiving an exclusively human milk diet, including Prolact+ H²MF when compared with infants receiving cow milk-based fortifier, or when mother’s own milk was unavailable, preterm formula.

Data Supporting an Exclusive Human Milk Diet Randomized Control Trial: Arm 2
Randomized Control Trial: Arm 2

- Purpose
  - To compare an Exclusive Human Milk Diet versus a Cow Milk-Based Preterm Formula Diet

The Exclusive Human Milk Diet

N=53 Preterm Infants  BW ≤ 1250 g

Mothers Own Milk Not available

EHM
DM and Human HMF used
EHM  n=29

CMB
Cow Milk-Based Preterm Formula
CMB  n=24

### Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control</th>
<th>Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPN Days</td>
<td>36</td>
<td>27</td>
<td>0.04</td>
</tr>
<tr>
<td>NEC</td>
<td>5</td>
<td>1</td>
<td>0.08</td>
</tr>
<tr>
<td>NEC Surgery</td>
<td>4</td>
<td>0</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Data Supporting an Exclusive Human Milk Diet: Combined Clinical Trial Data Analysis
Combined Clinical Trial Data Analysis

Purpose

- To combine Randomized Control Trial-Arm 1 and Randomized Control Trial-Arm 2 data to provide a comprehensive evaluation of the risk associated with the exposure of extremely preterm infants to cow milk protein.

Combined Clinical Trial Data Analysis

- Criteria
  - Birth weight 500g to 1250g
  - Arm 1 and Arm 2 conducted similar protocols
  - 260 patients in combined clinical data (Arm 1 and Arm 2)
  - 167 patients fed with 100% human milk diet
    - If MOM was not available then DM used
    - Human milk-based fortification at 40mL/kg/day or 100mL/kg/day
  - 93 patients fed with cow milk-based products
    - Mom with cow milk-based fortification or cow milk-based preterm formula

Combined Clinical Trial Data Analysis
Arm 1 and Arm 2
n=260 Preterm Infants  BW ≤ 1250 g

Arm 1 n=207

MOM

DM
When MOM is not available in sufficient quantity

Human HMF @ 100 mL/kg/d
H100 n=67

Human HMF @ 40 mL/kg/d
H40 n=71

Preterm Formula
When MOM is not available in sufficient quantity

Cow Milk-Based HMF @100 mL/kg/d
C100 n=69

Arm 2 n=53

EHM

EHM n=24

Cow Milk-Based Preterm Formula

CMB n=29

The Exclusive Human Milk Diet

Combined Clinical Trial Data Analysis-Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CMB N=93</th>
<th>EHM N=167</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>16/93 (17%)</td>
<td>9/167 (5%)</td>
<td>0.002</td>
</tr>
<tr>
<td>NEC Surgery</td>
<td>11/93 (12%)</td>
<td>2/167 (1%)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Mortality</td>
<td>7/93 (8%)</td>
<td>3/167 (2%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**The Exclusive Human Milk Diet**

**Combined Clinical Trial Data Analysis-Results**

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Incidence of NEC</th>
<th>Incidence of Surgical NEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% Human Milk</td>
<td>5%, p=0.002</td>
<td>12%</td>
</tr>
<tr>
<td>Any Cow Milk-Based Nutrition</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>100% Human Milk</td>
<td>1%, p=0.0003</td>
<td></td>
</tr>
<tr>
<td>Any Cow Milk-Based Nutrition</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>

"An exclusive human milk diet, devoid of cow milk containing products, was associated with lower mortality and morbidity in extremely preterm infants without compromising growth and should be considered as an approach to nutritional care of these infants."

Combined Clinical Trial Data Analysis

- Sepsis Outcomes

Probability of Remaining Sepsis Free vs. Cow Milk-Based Diet

Combined Clinical Trial Data Analysis

- NEC Outcomes

**Probability of Remaining NEC Free vs. Cow Milk-Based Diet**

Combined Clinical Trial Data Analysis

- NEC Surgery Outcomes

**Probability of Remaining NEC Surgery Free vs. Cow Milk-Based Diet**

Data Supporting an Exclusive Human Milk Diet: Human Milk Cream Study
Human Milk Cream Study

○ Purpose

○ To evaluate whether premature infants who received an exclusive human milk-based diet and a human derived cream supplement would have weight gain at least as good as infants receiving a standard feeding regimen.

Human Milk Cream Study

- Two center, prospective randomized study, preterm infants with a birth weight (BW) 750-1250 grams were randomly assigned to a Control or a Cream intervention group:

  - **Control Group**
    - Mother’s own milk or donor HM with donor HM-derived fortifier-Prolact+H²MF® (Prolacta Bioscience®, Industry, CA)

  - **Cream Group**
    - Additionally received HM-derived cream supplement-Prolact-CR™ (Prolacta Bioscience, Industry, CA) after fortification was initiated, if the HM tested < 20 kcal/oz. by infrared HM analyzer

Human Milk Cream Study

- **Design**
  - Infants were followed from first enteral feeding until 36 weeks postmenstrual age or weaned off fortifier.
  - Primary outcomes included growth velocities.
  - The incidence of NEC, sepsis or death were recorded.
  - The analysis was based on intent-to-treat and employed the two sample t-test, chi square test, and Fishers exact test.
  - The hypothesis of non-inferiority was established if the lower bound of the 95% confidence interval for the difference in weight velocities exceeded -3 g/kg/day.

## Human Milk Cream Study

### Growth Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=39)</th>
<th>Cream group (n=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight velocity (g/kg/day)</strong></td>
<td>12.4 ± 3.9*</td>
<td>14.0 ± 2.5</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Length velocity (cm/week)</strong></td>
<td>0.83 ± 0.41</td>
<td>1.03 ± 0.33</td>
<td>0.02</td>
</tr>
<tr>
<td>Head circumference (cm/week)</td>
<td>0.84 ± 0.22</td>
<td>0.90 ± 0.19</td>
<td>0.21</td>
</tr>
<tr>
<td>Weight velocity from time infant regained BW (g/day)</td>
<td>18.6 ± 6.4</td>
<td>21.8 ± 5.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Weight velocity from time infant regained BW (g/kg/day)</td>
<td>13.7 ± 4.0</td>
<td>15.7 ± 2.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Hair A, et al. / Pediatrics 2014; DOI: 10.1016/j.peds.2014.07.005*
• Human Milk Cream Study

  o Growth Outcomes

  o This study met its primary goal, and in fact showed superior growth in the cream group.

  o Lower bound of 95% confidence interval for difference in weight velocity (cream – control)

    o =0.38 g/kg/d

    o This value is greater than -3, which was set as the lower bound defining non inferiority

**Human Milk Cream Study**

○ Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Control group (n=39)</th>
<th>Cream group (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing enterocolitis (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sepsis (%)</td>
<td>7.7*</td>
<td>10.3</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Culture proven

## Human Milk Cream Study

- Discrepancy in human milk nutritional content

<table>
<thead>
<tr>
<th></th>
<th>Texas Children's Hospital</th>
<th>UTHSC-San Antonio</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOM</td>
<td>20.0 ± 1.5 Cal/Oz</td>
<td>17.6 ± 5.6 Cal/Oz</td>
</tr>
<tr>
<td>Donor milk</td>
<td>20.6 ± 1.5 Cal/Oz</td>
<td>19.0 ± 2.1 Cal/Oz</td>
</tr>
</tbody>
</table>

As measured by near IR spectroscopes calibrated specifically for human milk

Human Milk Cream Study

○ Conclusion

○ Premature infants who received HM-derived cream supplement to fortified HM had improved weight and length velocity compared to the Control group.

○ HM-derived cream supplement can be considered in infants receiving an exclusive HM-based diet with slow growth or evidence that the human milk that they are receiving is low in fat content.

“This is an exciting time in neonatal nutrition as the focus has shifted from survival and growth, which are still important goals, to effects of each micro/macronutrient on development, prevention of disease states, the effects of neonatal nutrition on future health as an adult, and opportunities to improve long-term neurodevelopmental outcomes by optimal early nutrition.”

Poindexter B & Karpen  H Clinics in Perinatology, Volume 41, Issue 2, xix 2014;
“The aim of the Guideline is to help clinicians apply research-based knowledge to the promotion, protection, and support of breastfeeding as the ideal and normative method for feeding infants, including the provision of human milk for preterm and other vulnerable newborns.”