Compelling Evidence for Nursing Advocates for an Exclusive Human Milk Diet (EHMD) in the NICU

NANN Annual Education Conference
Terry S. Johnson, APN, NNP-BC, CLEC, ASPPS, MN, CE

Immunological benefits of human milk - The role of human milk in neonatal immune system development
Olivia Mayer, RD, CSP, IBCLC

Preterm nutrition - Recommendations for optimal human milk-based human milk fortification
Sergio G. Golombek, MD, MPH, FAAP

Clinical and economic outcomes for the use of an EHMD for ≤1250g birthweight infants
Emily Million, RN

Dual perspective on the importance of human milk nutrition in the NICU and the importance of parent advocacy and empowerment

Panel

Terry Johnson
Olivia Mayer
Sergio Golombek
Emily Million

11/21/2016


- **“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”


- **“Milk as Medicine”**
  - “The major components of human milk are not primarily for nutrition, but for host defense”

Hanson, LA Immunobiology of human milk (2004).
Compelling Evidence: EHMD in NICU

**Evolutionary Biology**

- "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".


*For the purpose of my discussion today, either is OK... I just mean for as long as we have been having babies...*
• Evolutionary Biology
  • For millennia woman have delivered and babies have been born –
    – At term
    – With labor after/with ROM
    – Vaginally delivered
    – Remained with their mother
    – Exclusively breastfed

We Have Changed a LOT of That!

• “Evolutionary Discordance”
  – Changing clinical practices
    • Preterm, near term delivery
    • ↑ Elective/Non-Elective C/S
    • Labor with/without ROM
    • Hyper-hygienic measures
    • ↑ Maternal/infant antibiotics
    • Limited mother/infant contact
    • ↓ Exposure to colostrum and breast milk feeding

• Neonatal Microbiome
  – Delivery Mode: Colostrum Microbiome

Compelling Evidence: EHMD in NICU
Neonatal Microbiome

Delivery Mode: Milk Microbiome

Compelling Evidence:
EHMD in NICU

“Lack of breast milk may be the commonest immunodeficiency of infancy.”

Adjunctive Immunologic Interventions in Neonatal Sepsis

Listed with major clinical strategies, immunologic & pharmacologic therapies

Compelling Evidence:
EHMD in NICU

Dose-Response Benefits of Breastfeeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Lower Risk</th>
<th>Comments</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>77</td>
<td>NICU Stay</td>
<td>0.23</td>
<td>0.51-0.94</td>
</tr>
<tr>
<td>RDS</td>
<td>36</td>
<td>Any &gt; 1 mo</td>
<td>0.64</td>
<td>0.37-0.91</td>
</tr>
<tr>
<td>RSV Bronchiolitis</td>
<td>74</td>
<td>&gt;4 mo</td>
<td>0.26</td>
<td>0.07-0.91</td>
</tr>
<tr>
<td>Otitis media</td>
<td>23</td>
<td>Any</td>
<td>0.77</td>
<td>0.44-0.96</td>
</tr>
<tr>
<td>Otitis media</td>
<td>50</td>
<td>≥3 or 6 mo</td>
<td>0.50</td>
<td>0.35-0.70</td>
</tr>
</tbody>
</table>

### Compelling Evidence: EHMD in NICU

#### Dose-Response Benefits of Breastfeeding

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<thead>
<tr>
<th>Condition</th>
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<th>Breastfeeding</th>
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<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent OM</td>
<td>77</td>
<td>Exclusively BF ≥6 mo²</td>
<td>Compared with BF to &lt;6 mo²</td>
<td>1.95</td>
<td>1.06-3.59</td>
</tr>
<tr>
<td>LRTI</td>
<td>63</td>
<td>&lt;6 mo</td>
<td>Exclusive BF</td>
<td>0.80</td>
<td>0.58-1.14</td>
</tr>
<tr>
<td>LRTI</td>
<td>72</td>
<td>≥6 mo</td>
<td>Exclusive BF</td>
<td>0.28</td>
<td>0.16-0.54</td>
</tr>
<tr>
<td>LRTI</td>
<td>75</td>
<td>Exclusive BF ≥6 mo</td>
<td>Compared with BF &lt;6 mo</td>
<td>4.27</td>
<td>1.27-14.29</td>
</tr>
</tbody>
</table>

**Notes:**
- All data are from pediatric literature. BF, breastfeeding; EBM, evidence-based medicine; EHMD, early human milk diet; NICU, neonatal intensive care unit.
- Pooled data.
- % lower risk refers to lower risk while BF compared with feeding commercial infant formula or referent group specified.
- OR expressed as increased risk for commercial infant feeding.
- Referent group is exclusive BF ≥6 months.


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<tr>
<td>Asthma</td>
<td>40</td>
<td>&lt;3 mo</td>
<td>Atopic family history</td>
<td>0.60</td>
<td>0.40-0.92</td>
</tr>
<tr>
<td>Asthma</td>
<td>26</td>
<td>&lt;3 mo</td>
<td>No atopic family history</td>
<td>0.7</td>
<td>0.60-0.92</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>27</td>
<td>&lt;3 mo</td>
<td>Exclusive BF; (+) family history</td>
<td>0.84</td>
<td>0.59-1.25</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>42</td>
<td>&gt;3 mo</td>
<td>Exclusive BF; (+) family history</td>
<td>0.58</td>
<td>0.40-0.92</td>
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**Notes:**
- ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; BF, breastfeeding; EBM, evidence-based medicine; EHMD, early human milk diet; NICU, neonatal intensive care unit.
- Pooled data.
- % lower risk refers to lower risk while BF compared with feeding commercial infant formula or referent group specified.
- OR expressed as increased risk for commercial infant feeding.
- Referent group is exclusive BF ≥6 months.

Compelling Evidence: EHMD in NICU

**Dose-Response Benefits of Breastfeeding**

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</thead>
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<tr>
<td>Type 1 diabetes</td>
<td>30</td>
<td>≥6 mo</td>
<td>Exclusive BF</td>
<td>0.73</td>
<td>0.54-0.97</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>40</td>
<td>Any</td>
<td>-</td>
<td>0.80</td>
<td>0.65-0.99</td>
</tr>
<tr>
<td>Leukemia (ALL)</td>
<td>20</td>
<td>≥6 mo</td>
<td>-</td>
<td>0.80</td>
<td>0.71-0.91</td>
</tr>
<tr>
<td>Leukemia (AML)</td>
<td>15</td>
<td>≥6 mo</td>
<td>-</td>
<td>0.80</td>
<td>0.71-0.91</td>
</tr>
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</table>

American Academy of Pediatrics (Breastfeeding and the use of human milk: Section on Breastfeeding Pediatrics originally published online February 27, 2012; DOI: 10.1542/peds.2011-3552

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**Compelling Evidence: EHMD in NICU**

**Immunonutrition**

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

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

**Evolutionary Immunobiology**

Supports OFALT and GALT tissue maturation

Provides barrier function against pathogens

Stimulates proliferation of intraepithelial lymphocytes

Lowers intraluminal pH

~70% of the immune system is located in the gut
Mucosal Immunologic System (MIS)
- Provides a complex mechanical barrier and an inherent defense against pathogens that constantly threaten the human body

Compelling Evidence: EHMD in NICU

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Mucosal Immunologic System (MIS)
- Evidence suggests that these systems do not work independently, but an integrated network of tissue, cells, and signaling molecules

Compelling Evidence: EHMD in NICU

Compelling Evidence: EHMD in NICU

Mucosal Immunologic System (MIS)
- The lining of the GI tract provides the largest interface with the external environment and is critical to host defense.
• Mucosal Immunologic System (MIS)
  — At no time in life is this function more important than shortly after birth.


Compelling Evidence: EHMD in NICU

• Evolutionary Immunobiology


Compelling Evidence: EHMD in NICU

• EHMD: Multicenter Retrospective Cohort Study
  — Method
  • Conducted at four geographically disparate hospitals: Texas, California, Illinois, and Florida.
  • Each of the four hospitals reviewed charts from an equal period before and after implementing an exclusive human milk-based protocol
Compelling Evidence: EHMD in NICU

• EHMD and Extrauterine Growth Failure

Texas Children's Hospital
- <1250 g BW to 34 weeks PMA
  - Prolect+ fortification initiated at 60 mL/kg/day with Prolact+4 H2MF®
  - If weight gain was <15 g/kg/day, fortification increased to Prolact+6 H2MF®

Good Samaritan San Jose
- <1250 g BW to 34 weeks PMA until 120 days of age
  - Prolect+ fortification initiated at 60 mL/kg/day with Prolact+4 H2MF®
  - At 100 mL/kg/day fortification increased to Prolact+6 H2MF®, Prolact+8 H2MF® as needed

Northwestern
- <1250 g BW to 34 weeks PMA or 1500 g, then transitioned off
  - Prolect+ fortification initiated at 100-120 mL/kg/day with Prolact+4 H2MF®
  - If weight gain was <15 g/kg/day, fortification increased to Prolact+6 H2MF®

Winnie Palmer Hospital
- <1250 g BW and 120-160 weeks PMA
  - Prolect+ fortification initiated at 100-120 mL/kg/day with Prolact+4 H2MF®
  - If weight gain was deemed suboptimal by the attending doctor based on growth curve velocity, an additional 2-4 cal/oz of fortification was added to the feeds for a total of 6-8 kcals/oz

Compelling Evidence: EHMD in NICU

The EHMD group had significantly lower incidence of:

<table>
<thead>
<tr>
<th>CMD</th>
<th>EHMD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIC</td>
<td>16.7%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Mortality</td>
<td>17.2%</td>
<td>13.6%</td>
</tr>
<tr>
<td>BPD</td>
<td>56.3%</td>
<td>47.7%</td>
</tr>
<tr>
<td>ROP</td>
<td>9.0%</td>
<td>5.3%</td>
</tr>
<tr>
<td>PDA</td>
<td>64.7%</td>
<td>55.1%</td>
</tr>
<tr>
<td>Late-Onset Sepsis</td>
<td>30.3%</td>
<td>19.0%</td>
</tr>
</tbody>
</table>

The results are consistent in both academic and “real world” nonacademic settings over a long period of time and in a large study population.

AAP Policy:

• Breastfeeding & Use of Human Milk 2012
  - The potent benefits of human milk are such that all preterm infants should receive human milk
  - Mother’s own milk, fresh or frozen, should be the primary diet
  - If mother’s own milk is unavailable despite significant lactation support, pasteurized milk should be used
  - Supports the use of banked human milk as the “first alternative” to own mother’s milk

Endorsement of Human Milk Feeding

Professional

A.A.P.
A.C.O.G.
A.O.B.M.N.
A.H.M.
A.A.P.
A.A.O.H.M.
A.O.N.D.

Government

C.C.C.
W.H.O.
U.S.S.O.
U.S.S.C.

Advocacy

N.O.D.
N.P.H.I.
N.I.C.H.A.N.

Fiscal

EHMD in NICU

Practice, Policy, and Programs Endorsing Human Milk Diets for all Newborns Infants

Thompson, (2015)

Preterm Nutrition - Recommendations for optimal human milk-based human milk fortification

Olivia Mayer RD, CSP, IBCLC
Palo Alto, CA
Disclosure

• I am a member of the Nutrition Advisory Committee (sponsored by Prolacta Bioscience)
• My contribution to this symposium is as a paid consultant and is not part of my duties and responsibility of Stanford University
• I have received an honorarium for this presentation.

Learning Objectives

• Review factors that impact energy expenditure and protein needs in very low birth weight infants (VLBW).
• Review how micronutrients impact growth in VLBW.
• Discuss recommendations to meet the nutritional needs of VLBW.

Energy Stores in the Newborn

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Weight (g)</th>
<th>Energy (kcal)</th>
<th>Water (%)</th>
<th>Protein (%)</th>
<th>Lipid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>690</td>
<td>13.5</td>
<td>86.6</td>
<td>9.6</td>
<td>0.1</td>
</tr>
<tr>
<td>26</td>
<td>880</td>
<td>123.6</td>
<td>86.8</td>
<td>9.2</td>
<td>1.5</td>
</tr>
<tr>
<td>28</td>
<td>1160</td>
<td>326.2</td>
<td>84.6</td>
<td>9.6</td>
<td>5</td>
</tr>
<tr>
<td>40</td>
<td>3450</td>
<td>152.4</td>
<td>74</td>
<td>12</td>
<td>15.3</td>
</tr>
</tbody>
</table>
Estimates of Energy Requirement

<table>
<thead>
<tr>
<th></th>
<th>AAP (kcal/kg/day)</th>
<th>ESPGHAN Average (kcal/kg/day)</th>
<th>ESPGHAN Range (kcal/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Expenditure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Resting Metabolic Rate</td>
<td>50</td>
<td>52.5</td>
<td>45-60</td>
</tr>
<tr>
<td>- Activity</td>
<td>15</td>
<td>7.5</td>
<td>5-10</td>
</tr>
<tr>
<td>- Cold Stress</td>
<td>10</td>
<td>7.5</td>
<td>5-10</td>
</tr>
<tr>
<td>- Synthesis/thermic effect of food</td>
<td>8</td>
<td>17.5</td>
<td>10-25</td>
</tr>
<tr>
<td>Energy Stored</td>
<td>25</td>
<td>25</td>
<td>20-30</td>
</tr>
<tr>
<td>Energy Excreted</td>
<td>12</td>
<td>20</td>
<td>10-30</td>
</tr>
<tr>
<td>Estimated Energy Requirement</td>
<td>120</td>
<td>120</td>
<td>95-165</td>
</tr>
</tbody>
</table>

Calorie and Protein

Expert Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Agostoni et al.</th>
<th>Koletzko et al.</th>
<th>Tsang et al.</th>
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<tbody>
<tr>
<td>Energy (kcal/kg/day)</td>
<td>110-135</td>
<td>110-130</td>
<td>ELBW: 130-150</td>
</tr>
<tr>
<td>VLBW: 110-130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amino Acids (g/kg/day)</td>
<td>3.5-4.5</td>
<td>3.5-4.5</td>
<td>ELBW: 3.8-4.4</td>
</tr>
<tr>
<td>VLBW: 3.2-4.2</td>
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</table>
What about micronutrients?

Micronutrients are essential for growth and development.

There is risk for both deficiency and toxicity.

Micronutrients

Important for weight and length growth in infants:
- Folic Acid, Iodine, Zinc, Sodium, Chloride, Calcium, Magnesium, Vitamin A, Phosphorus, Manganese, and Pyridoxine

Important for brain development and brain growth, which, in turn, are related to head growth:
- Iron, Zinc, Copper, Iodine, Selenium, Chloride, Folate, and Vitamin A

Essential for bone mineralization:
- Calcium, Phosphorus, and Vitamin D

Calories are in human milk

Boyce, C, et. al.
24 studies
GA 23-37 weeks
Range: 15-26 cal/oz
Still using 20 cal/oz
As ‘standard’
What About Protein?
Personal Investigation

19 Articles from 2009-2015 and Medical Director of HMBANA Milk Bank of San Jose, CA
• Protein Avg 1.42 g/dL
• Protein Range 0.2-4.1 g/dL (Difference 3.9 gm)

PEDIRD Listserve Replies on 10/20/2015
• Protein Avg 1.09 g/dL
• Protein Range 0.8-1.4 g/dL (Difference 0.6 gm)

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Amount in Human Milk</th>
<th>ASPEN &amp; AAP Guidelines</th>
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How do we ‘bridge the gap’?

Calorie and Protein
Expert Recommendations

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Human Milk-Based, Human Milk Fortification

Macronutrients

<table>
<thead>
<tr>
<th>Feeds of 160 mL/kg/day</th>
<th>+4</th>
<th>+6</th>
<th>+8</th>
<th>+10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calories</strong></td>
<td>131</td>
<td>142</td>
<td>155.2</td>
<td>166.4</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>3.7</td>
<td>4.5</td>
<td>5.12</td>
<td>5.92</td>
</tr>
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Human Milk-Based, Human Milk Fortification
Micronutrients

Proterm Human Milk + Human Milk-Based Fortifier @ 160 mL/kg/day
Infant Multivitamin (without Fe) - 1 mL/day

<table>
<thead>
<tr>
<th>Meet Guidelines</th>
<th>Do Not Meet Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A, D, E, C, B1, B2, B6, Niacin</td>
<td>Iron* “supplementation routinely given</td>
</tr>
<tr>
<td>Calcium, Phosphorous, Magnesium</td>
<td>Folic Acid (Folic Acid content of fortified feeds is increased 3-7x more than breast milk alone)</td>
</tr>
<tr>
<td>Zinc, Copper, Sodium, Potassium</td>
<td>Vitamin K</td>
</tr>
</tbody>
</table>

Summary

1. VLBW infants have very high macro and micronutrient needs to promote growth
2. It IS possible to meet those high needs with an exclusive human milk diet

Clinical and economic outcomes for the use of an EHMD for ≤1250g birthweight infants

Sergio G. Golombek, MD, MPH, FAAP
Professor of Pediatrics & Clinical Public Health – NY Medical College
Attending Neonatologist
Maria Fareri Children’s Hospital - Westchester Medical Center
Valhalla, New York
President - SIBEN
Disclosure

- Paid speaker on behalf of Prolacta Bioscience.
- Received speaker honorarium for this presentation.

Better neurodevelopmental and growth outcomes for the ELBW when:

Weight gain > 18g/kg/d
HC > 0.9 cm/week

If those rates falter, the infant’s diet should be reviewed and modified to achieve the target growth parameters.

Ehrenkranz et al Peds April 2006

Long Term Benefits of HM Dose Response Relationships

- Long term follow up of 300 preterm infants at 7.5 to 8 years of age by Lucas et al who received HM demonstrated a significantly higher IQ with an 8.3 point advantage after adjustments over infants who received no maternal HM.1

- The NICHD Glutamine trial revealed a dose-response relationship between the amount of HM feedings over the entire NICU stay and neurodevelopment outcomes at 18 mo of age.1

1 Patel AL, Mear JJ, Engstrom JL. The Evidence for Use of Human Milk in Very Low-birthweight Preterm Infants. NeoReviews2007;e10-w106.DOI 10.1542/nr.8-11-w106
Impact on NEC Rates in 1990

<table>
<thead>
<tr>
<th>Feeding</th>
<th>100% Formula</th>
<th>Formula + EBM*</th>
<th>100% EBM*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of NEC</td>
<td>7.2%</td>
<td>2.5%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

83% decrease in NEC

52% decrease in NEC

*EBM (Expressed Breast Milk): combination of mom's milk and donor milk

Source: Lancet, 1990

---

HM Dose Response Relationship with Severity of ROP in 2001


---

Data Supporting an Exclusive Human Milk Diet

Randomized Control Trial:

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

- **Endpoints**
  - Days on Total Parenteral Nutrition (TPN)
  - Necrotizing Enterocolitis (NEC)


---

### The Exclusive Human Milk Diet

**Enrolled (n = 207)**

<table>
<thead>
<tr>
<th>Group</th>
<th>HUM (n = 128)</th>
<th>CMB (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>When MOM is available in sufficient quantity</td>
<td>Human Milk-based Fortifier was used</td>
<td>Cow Milk-based Fortifier was used</td>
</tr>
<tr>
<td>When MOM is not available in sufficient quantity</td>
<td>Cow Milk-based Preterm Formula was used</td>
<td>Human Milk-based Fortifier was used with Donor Milk used</td>
</tr>
</tbody>
</table>

---

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hum (n = 138)</th>
<th>CMB (n = 69)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Parenteral Nutrition - Number of Days</td>
<td>20</td>
<td>22</td>
<td>0.79</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC)</td>
<td>8</td>
<td>11</td>
<td>0.045</td>
</tr>
<tr>
<td>NEC - Surgery</td>
<td>2</td>
<td>7</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

1 in 10
The estimated number of infants needed to feed with human milk fortified with Prolact+ HMF® 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+ HMF 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+ HFMF 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

Mother’s Own Milk Not Available
BW ≤1,250g
(n = 53)

DM and Human-Milk Based Fortifier used

HUM
(n = 29)

CMB
(n = 24)

Cow milk-based preterm formula

The Exclusive Human Milk Diet

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hum (n=29)</th>
<th>CMB (n=24)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Parenteral Nutrition – Number of Days</td>
<td>27</td>
<td>36</td>
<td>0.04</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC)</td>
<td>1</td>
<td>5</td>
<td>0.08</td>
</tr>
<tr>
<td>NEC - Surgery</td>
<td>0</td>
<td>4</td>
<td>0.033</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Hum (n=167)</th>
<th>CMB (n=93)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Parenteral Nutrition – Number of Days</td>
<td>9</td>
<td>16</td>
<td>0.002</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis (NEC)</td>
<td>2</td>
<td>11</td>
<td>0.0003</td>
</tr>
<tr>
<td>NEC - Surgery</td>
<td>3</td>
<td>7</td>
<td>0.04</td>
</tr>
</tbody>
</table>

For every 10% increase in the intake of other than an exclusive human milk diet, there is a 17.9% increase in risk of sepsis.

For every 10% increase in the intake of other than an exclusive human milk diet, there is a 11.8% increase in risk of NEC.

For every 10% increase in the intake of other than an exclusive human milk diet, there is a 21% increase in risk of Surgical NEC.


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.


The Exclusive Human Milk Diet

Human Milk Cream Study

Results for Cream vs. Control Groups

**The Exclusive Human Milk Diet**

**Human Milk Cream Study**

**Comparison of Length Velocity**

<table>
<thead>
<tr>
<th></th>
<th>Cream Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>1.03</td>
<td>0.83</td>
</tr>
</tbody>
</table>

The Cream Group had superior length velocity (1.03 ± 0.33 vs. 0.83 ± 0.41, p = 0.05)

**Comparison of Weight Velocity**

<table>
<thead>
<tr>
<th></th>
<th>Cream Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>14.0</td>
<td>12.4</td>
</tr>
</tbody>
</table>

The Cream Group had superior weight velocity (14.0 ± 3.8 vs. 12.4 ± 3.8, p = 0.05)

---

Results for Cream vs. Control Groups

**The Exclusive Human Milk Diet**

**Human Milk Cream Study**

**Decreased PMA at Discharge by 1.7 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>Cream Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMA</td>
<td>38.2</td>
<td>39.9</td>
</tr>
</tbody>
</table>

The Cream Group had a decreased PMA at discharge (38.2 ± 2.7 vs. 39.9 ± 2.3, p<0.05)

**Decreased LOS by 12 Days**

<table>
<thead>
<tr>
<th></th>
<th>Cream Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td>74.0</td>
<td>86.0</td>
</tr>
</tbody>
</table>

The Cream Group tended toward a decreased LOS (74.0 ± 2.7 vs. 86.0 ± 2.7, p<0.05)

---

Results for Cream vs. Control Groups for Infants with BPD

**The Exclusive Human Milk Diet**

**Human Milk Cream Study**

**Decreased PMA at Discharge by 2.9 Weeks**

<table>
<thead>
<tr>
<th></th>
<th>Cream Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMA</td>
<td>41.3</td>
<td>64.2</td>
</tr>
</tbody>
</table>

For 21 infants with BPD, the values trended toward significance for PMA at discharge (41.3 ± 2.7 vs. 64.2 ± 4.1, p=0.08)

**Decreased LOS by 17 Days**

<table>
<thead>
<tr>
<th></th>
<th>Cream Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td>104.0</td>
<td>121.0</td>
</tr>
</tbody>
</table>

For 21 infants with BPD, the values trended toward significance for LOS (104.0 ± 2.2 vs. 121.0 ± 4.9, p=0.08)

---
Conclusions
Premature infants who received a human milk-derived cream supplement had improved weight and length velocity compared with the Control Group. Human milk-derived cream should be considered an adjunctive supplement to an exclusive human milk-based diet to improve growth rates in premature infants.


Data Supporting an Exclusive Human Milk Diet
More Data...

Independent Hospital-Conducted Clinical Studies Corroborate the Medical Benefit of Prolacta Products

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Size of Study</th>
<th>Summary of Findings</th>
</tr>
</thead>
</table>
| Hospital 1 | 708 | • Medical NEC rate for bovine-based diet — 14.3%  
• Medical NEC rate for 100% human milk diet — 2.3% |
| Hospital 2 | 156 | • With aggressive feeding, weight growth averaged 25 g/kg/day |
| Hospital 3 | 260 | • Overall NEC rate for histologic NEC rate of 17.5% to 9.6%  
• Surgical NEC reduced from 7.3% to 2.3% |
| Hospital 4 | 177 | • Overall NEC rate for bovine-based nutrition — 6.2%  
• Overall NEC rate for 100% human milk diet — 0% |
| Hospital 5 | 361 | • Overall NEC rate for — exclusive human milk 2.3%; human milk / HMF 4.0%; formula diet 8.6%  
• Mortality rate for — exclusive human milk 2.2%; human milk / HMF 2.2%; formula diet 4.3% |

### Independent Hospital- Conducted Clinical Studies Corroborate the Medical Benefit of Prolacta Products

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Size of Study</th>
<th>Summary of Findings</th>
</tr>
</thead>
</table>
| Carle    | n/a           | - Overall NEC rate down from 12% in 2008 to 4% in 2012 in babies weighing < 1,500g  
                        - Late onset sepsis similarly reduced  
|          | 149           | - NEC rate was from 6% in 2006-2009 to 4% in 2010 – present in babies weighing < 1,000g |
|          | n/a           | - Decrease in TPN days, central line days and infection rate in NICU lines |
|          | 605           | - NEC rate after Day 7 of life was reduced from 4.4% to <1% |
|          | 228           | - 80% decrease in the incidence of NEC since starting an EHMD  
                        - Decrease in feeding intolerance |

1. Data presented by Jose Perez, MD in a public forum
2. Data presented by Jose Perez, MD in a public forum
4. Hermann, K et al: An Exclusively Human Milk Diet Reduces Necrotizing Enterocolitis, Breastfeeding Medicine; Vol.9 No.4; May 2014.

### Independent Hospital - Pharmacoeconomic Studies Corroborate Cost Savings Associated with use of EHMD

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Size of Study</th>
<th>Summary of Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>660</td>
<td>- Net savings in medical costs $12,048 per infant</td>
</tr>
<tr>
<td></td>
<td>177</td>
<td>- Net savings of additional healthcare costs associated with medical NEC $499,000</td>
</tr>
</tbody>
</table>
|          | 228           | - Total hospitalization costs for bovine fed group $27,000 - $107,000 higher  
                        - Indirect costs for bovine and mixed group $14,490 - $25,765 higher |

1. Hamilton Spence, EC et al. Cost Effectiveness of an Exclusively Human Diet (EHD) To Reduce Necrotizing Enterocolitis (NEC) in Infants <1250 Grams; Presented at the Pediatric Academic Societies Annual Meeting, May 2013, Washington, DC.
2. Tuttle, DJ et al. Reduction in NEC Associated with Human Milk Based Fortifier as a Value Added Strategy; Abstract 3838. Presented at the Pediatric Academic Societies Annual Meeting, May 2013, Washington, DC.

---

**Data Supporting an Exclusive Human Milk Diet**

**Multicenter Retrospective Cohort Study**
To compare clinical outcomes in 1,587 Extremely Premature infants (birth weight <1250 g) before and after an institutional change to the use of an exclusive human milk–based diet (EHMD) from a diet that included cow milk-based (CMD) products.

Conducted at four geographically disparate hospitals: Texas, California, Illinois, and Florida.

The Exclusive Human Milk Diet
Multicenter Retrospective Cohort Study

**Purpose**
- To compare clinical outcomes in 1,587 Extremely Premature infants (birth weight <1250 g) before and after an institutional change to the use of an exclusive human milk–based diet (EHMD) from a diet that included cow milk-based (CMD) products.
- Conducted at four geographically disparate hospitals: Texas, California, Illinois, and Florida.

**The EHMD group had significantly lower incidence of:**

<table>
<thead>
<tr>
<th></th>
<th>CMD (%)</th>
<th>EHMD (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>16.7%</td>
<td>6.1%</td>
<td>p &lt; 0.00001</td>
</tr>
<tr>
<td>Mortality</td>
<td>17.2%</td>
<td>13.6%</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>BPD</td>
<td>16.3%</td>
<td>47.2%</td>
<td>p = 0.0015</td>
</tr>
<tr>
<td>ROP</td>
<td>9.0%</td>
<td>5.2%</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>PDA</td>
<td>64.7%</td>
<td>55.1%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Late-Onset Sepsis</td>
<td>30.3%</td>
<td>19.0%</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

The results are consistent in both academic and “real world” nonacademic settings over a long period of time and in a large study population.

**The Exclusive Human Milk Diet Multicenter Retrospective Cohort Study**

**Hospital Protocols**

**Texas Children’s Hospital**
- <1250g BW or 34 weeks PMA
  - Prolact+ fortification initiated or no feed with Prolectin+10®
  - If weight gain was <15 g/kg/day, fortification increased to Prolactin+10® and then Prolactin+15®

**Good Samaritan San Jose**
- <1000 g BW protocol continued until 60 days of age
  - Prolact+ fortification initiated at 100-120 mL/kg/day with Prolact+4 H2®
  - At 150 mL/kg/day fortification increased to Prolact+6 H2®
  - Prolact+8 H2® as needed

**Northwestern**
- <1000 g BW or 34 weeks PMA or 750 g, then transitioned off
  - Prolact+ fortification initiated or no feed with Prolactin+10®
  - If weight gain was <15 g/kg/day, fortification increased to Prolactin+15®
  - Increased to Prolactin+15® if low weight gain continued

**Winnie Palmer Hospital**
- <1250g BW and <36 weeks gestational age or <32 weeks PMA
  - Prolact+ fortification initiated or no feed with Prolactin+10®
  - If weight gain was deemed suboptimal by the attending pediatrician or growth curve velocity, an additional 2-4 kcal/oz added to the feeds for a total of 6-8 kcal/oz

This study demonstrates that an EHMD, no matter the protocol, provides important benefits beyond NEC.
Data Supporting an Exclusive Human Milk Diet
Herman and Walter Samuelson Children’s Hospital at Sinai Study

Objective
To examine the effects of an EHMD on:

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Length of stay</td>
<td>• Incidence of NEC</td>
</tr>
<tr>
<td>• Incidence of feeding intolerance</td>
<td>• Cost effectiveness of an EHMD</td>
</tr>
<tr>
<td>• Time to full feeds in VLBW infants</td>
<td></td>
</tr>
<tr>
<td>in a community level III NICU</td>
<td></td>
</tr>
</tbody>
</table>

Method
• Included 293 preterm infants ≤ 28 weeks gestational age and/or ≤ 1500 g (VLBW) from March 2009 until March 2014
• Four different feeding groups:

<table>
<thead>
<tr>
<th>H</th>
<th>B</th>
<th>M</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entirely human milk (Prolact+ H2M®)</td>
<td>Bovine fortifier and maternal milk</td>
<td>Mixed combination of maternal milk, bovine fortifier and formula</td>
<td>Formula fed infants 10%</td>
</tr>
<tr>
<td>N=87</td>
<td>N=127</td>
<td>N=49</td>
<td>N=30</td>
</tr>
</tbody>
</table>

Study Limitation
• Retrospective study design
• Small (87) EHM group

“Feeding intolerance was significantly worse in all groups compared with the human milk group.”


**The Exclusive Human Milk Diet**
Herman and Walter Samuelson Children’s Hospital at Sinai Study

"Number of Times Feeds Held"

Using Fisher's exact test (P<0.001) for all groups, N = 293.

Formula group excluded from analysis (statistically inder group), medica NEC represents 1% of bovine and mixed group, all others were surgical.

"Incidence of NEC"

Using Fisher's exact test (P<0.01) for all groups, N = 293.

Additional Days of Hospitalization

Analysis using linear regression adjusted for gestational age, R² = 0.35, P < 0.04, N = 293.

**The Exclusive Human Milk Diet**

Herman and Walter Samuelson Children’s Hospital at Sinai Study

"An EHMD is cost-effective, even when factoring in the added costs of donor human milk and human milk-derived fortifiers. This study confirms previous studies showing decreased morbidities (e.g., BPD, ROP) associated with an EHMD."

Cost-effectiveness: a misunderstood term

- Cost-effective does not mean cost-neutral or cost-saving
- Cost-effectiveness is used to compare the costs of therapeutic alternatives to achieve a specific health benefit

Doublet P: Use and misuse of the term “cost-effective” in medicine. NEJM 1986;314:253-6

Linear regression analysis adjusted for gestational age P<0.001, between human and mixed group, R² = 0.33, N = 293.
Cost-effectiveness: a misunderstood term

Many medical choices are based on factors that can't be given a monetary value
✓ Pain relief
✓ Sonograms during pregnancy for reassurance
✓ Negative test results for reassurance

Double P: Use and misuse of the term "cost-effective" in medicine. NEJM 1986;314:253-6

Randomized clinical trials show the clinical and economic benefit of an exclusive human diet
Multiple field studies support the same findings
The evidence is overwhelming

Exclusive Human Milk Diet
Advantages

Randomized clinical trials show the clinical and economic benefit of an exclusive human diet
Multiple field studies support the same findings
The evidence is overwhelming

Thank you!
Emily Million, RN
Dual perspective on the importance of human milk nutrition in the NICU and the importance of parent advocacy and empowerment