QI: Exclusive Human Milk Diet for Preterm Infants

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• I receive speaker honoraria from Prolacta Bioscience®
Overview

• Human milk use in preterm infants

• Necrotizing enterocolitis and Human Milk

• Fortification of Human Milk

• Exclusive human milk-based diet

• Postnatal Growth Failure

• Implementation
AAP Statement 2012
“Breastfeeding and the Use of Human Milk”

“All preterm infants should receive human milk.”

- Human milk should be fortified, with protein, minerals, and vitamins to ensure optimal nutrient intake for infants weighing <1500 grams at birth

- Pasteurized donor human milk (DHM), appropriately fortified, should be used if mother’s own milk is unavailable or its use is contraindicated

- Significant short and long-term beneficial effects of feeding preterm infants human milk

AAP Statement 2012
“Breastfeeding and the Use of Human Milk”

Significant short and long-term beneficial effects of feeding preterm infants human milk

- Lower rates of sepsis and necrotizing enterocolitis
- Reduction in incidence of NEC include not only lower mortality rates but also lower long-term growth failure and neurodevelopmental disabilities
- Improved feeding tolerance
- Fewer hospital readmissions for illness in the year after NICU discharge
- Improved neurodevelopment

Benefits of Human Milk

- ↓ respiratory tract infections and otitis media
- ↓ sudden infant death syndrome and mortality
- ↓ GI infections
- ↓ risk of celiac disease and IBD
- ↓ asthma, atopic dermatitis and eczema
- ↓ incidence of NEC

- Associated with a decrease in obesity and diabetes
- Beneficial influence on neurodevelopmental outcomes
- Possible reduction in severity of retinopathy of prematurity

Necrotizing Enterocolitis

• NEC is a devastating illness that affects 5.4 to 7.4% of VLBW infants/year (Vermont Oxford Network)

• Despite years of ongoing research, the exact pathophysiology of necrotizing enterocolitis is still not known
  - Multifactorial
  - Mucosal injury leading to an exaggerated immune response, which then results in bacterial translocation, systemic infection, and inflammation
Necrotizing Enterocolitis

# Human Milk and NEC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Infants</th>
<th>Characteristics</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucas et al, 1990</td>
<td>926 infants</td>
<td>Multicenter</td>
<td>- 6-10 times more NEC in formula fed vs. HM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>study</td>
<td>- No difference in type of HM</td>
</tr>
<tr>
<td>Schanler et al, 1999</td>
<td>62 (FHM)</td>
<td>FHM vs. formula</td>
<td>- ↓ NEC in FHM 1 (1.6%) vs. formula 6 (13%)</td>
</tr>
<tr>
<td></td>
<td>46 formula</td>
<td></td>
<td>- ↓ late onset sepsis</td>
</tr>
<tr>
<td>Sisk et al, 2007</td>
<td>222 infants</td>
<td>FHM vs. formula</td>
<td>- Associated with a 6 fold decrease in NEC with an intake of just 50% HM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in 1st 14 days</td>
<td></td>
</tr>
<tr>
<td>Henderson et al, 2007</td>
<td>10 neonatal</td>
<td>Look at practices</td>
<td>- Human milk was associated with lower risk of NEC</td>
</tr>
<tr>
<td></td>
<td>centers -53</td>
<td>associated with</td>
<td></td>
</tr>
<tr>
<td></td>
<td>infants</td>
<td>NEC</td>
<td></td>
</tr>
</tbody>
</table>

FHM=Fortified human milk

*Pediatrics*
‘Survival’ Curves for NEC or death* by amount of human milk (ml/kg/d)

*For NEC or Death after 14 days, adjusted for birth weight, race, PDA treatment, ventilation, and site.

Pasteurized Donor Human Milk

• Human Milk Banking Association of North America

• Medolac / Mothers Milk Cooperative

• Prolacta Bioscience

• Hospital Based Milk Banks
Donor Human Milk

• Human Milk Banking Association of North America
  - 20 Milk Banks

• Medolac- Mother’s Milk Cooperative
  - Mother’s are paid

• Prolacta DHM
  - Extensive screening process
  - Donors have the option to be paid or donate $ to charity
  - DNA fingerprinting, Drug Screens, tests for bacterial contamination
Donor Qualification Requirements

POTENTIAL DONORS:
- Are screened via an online survey and are assigned a number
- Must obtain approval from physician and pediatrician
- Stored milk must be frozen and cold enough to donate

DONOR EBM SCREENING PROCESS:
- A blood test are conducted for presence of HIV 1&2, HTLV I&II, HBV, HCV, and syphilis.
- Full microbiological panel is obtained including Aerobic count, B. cereus, Escherichia coli, Salmonella, Pseudomonas, coliforms, Staphylococcus aureus, yeast and mold.
- Bovine protein
- Will screen for drugs of abuse
## Pasteurization

### Effect of Pasteurization Conditions on Human Milk Constituents:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Untreated Human Milk</th>
<th>Pasteurized Human Milk</th>
<th>% Remaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin A (mg/mL)</td>
<td>315</td>
<td>230</td>
<td>73</td>
</tr>
<tr>
<td>Secretary IgA</td>
<td>462</td>
<td>379</td>
<td>83</td>
</tr>
<tr>
<td>Lysozyme (IU/mL)</td>
<td>39,000</td>
<td>22,000</td>
<td>57</td>
</tr>
<tr>
<td>Lactoferrin (g/100 mL)</td>
<td>0.24</td>
<td>0.033</td>
<td>14</td>
</tr>
<tr>
<td>Vitamin B6 (µg/100 mL) (g/100 mL)</td>
<td>8.8</td>
<td>7.8</td>
<td>89</td>
</tr>
</tbody>
</table>
## Meta-Analysis: Donor Milk vs. Formula

<table>
<thead>
<tr>
<th>Studies</th>
<th>Donor Milk</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1983</td>
<td>1/42 (2%)</td>
<td>3/29 (10%)</td>
</tr>
<tr>
<td>Cooper 1984</td>
<td>1/24 (4%)</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Lucas 1990</td>
<td>1/87 (1%)</td>
<td>4/80 (5%)</td>
</tr>
<tr>
<td>Schanler 2005</td>
<td>5/78 (6%)</td>
<td>10/88 (11%)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>8/231 (3%)</td>
<td>20/212 (9%)</td>
</tr>
</tbody>
</table>

Risk of NEC is reduced significantly with pasteurized donor milk: 0.35 (0.15; 0.81)

Donor Human Milk

- Formula fed infants had a higher incidence of NEC
  - 8 studies included (RCT with preterm or LBW infants)
    - 5 trials (812 infants) showed a statistically significant increased incidence of NEC in formula group vs. donor human milk group
    - Risk ratio 2.5 (CI 1.2, 5.1)

Human Milk Fortification

A response to the need to provide additional nutrients, especially minerals, for premature infants

• Protein
• Calcium
• Phosphorus
• Zinc
Human Milk Fortification

• Liquid HMF (LHMF)-Bovine
  - Each packet/vial of LHMF is 5 mL
  - 1 packet/vial of LHMF + 25mL EBM = 30 mL of 24 kcal/ounce

• Powder HMF-Bovine
  - Each packet/sachet of HMF, when added to 100 mL EBM increases calories by 1 kcal/oz
  - 4 packets/sachets of HMF per 100 mL EBM = 24 kcal/oz

• Donor human milk-derived fortifier
  - 24 kcal/oz: 80 mL EBM+20 mL +4 (4:1)
  - 26 kcal/oz: 70 mL EBM+30 mL +6 (7:3)
  - 28 kcal/oz: 60 mL EBM+40 mL +8 (3:2)
  - 30 kcal/oz: 50 mL EBM+50 mL +10 (1:1)
Human Milk Fortification: Pros & Cons

• Bovine human milk fortifier- *Liquid*
  - Sterile, DHA
  - Displaces more human milk than powder

• Bovine human milk fortifier- *Powder*
  - Displaces less human milk than liquid
  - Not sterile, lower protein

• Donor human milk-based fortifier
  - Early fortification, provides an exclusive human milk protein diet
  - Need to supplement vitamins and iron, $
<table>
<thead>
<tr>
<th>Nutrients per kg/day</th>
<th>AAP¹ 2014</th>
<th>ESPGHAN² 2010</th>
<th>EBM + 4 Similac Powder HMF per 100 mL</th>
<th>EBM + 4 MJ Liquid HMF per 100 mL</th>
<th>EBM + 4 Similac Liquid HMF per 100 mL</th>
<th>EBM + Prolacta+6 per 100 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td>--</td>
<td>--</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Energy (kcal)</td>
<td>105-130</td>
<td>110-135</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>135</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>3.5-4</td>
<td>3.5-4</td>
<td>2.9</td>
<td>3.9</td>
<td>3.6</td>
<td>3.6</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>100-220</td>
<td>120-140</td>
<td>202</td>
<td>174</td>
<td>179</td>
<td>183</td>
</tr>
<tr>
<td>Phosphorus (mg)</td>
<td>60-140</td>
<td>60-90</td>
<td>120</td>
<td>96</td>
<td>102</td>
<td>96</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>2-4</td>
<td>2-3</td>
<td>0.6</td>
<td>2.3</td>
<td>0.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Exclusive Human Milk-Based Diet

- The use of an exclusive human milk-based diet in infants ≤ 1250 grams birth weight is associated with a lower rate of necrotizing enterocolitis (NEC)\(^1,2\) and decreased parenteral nutrition days\(^2\).

- An exclusive human milk diet is associated with lower mortality and morbidity compared to a cow milk based protein diet\(^3\).

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An Exclusive Human Milk-Based Diet and NEC¹

### NEC Surgery

<table>
<thead>
<tr>
<th></th>
<th>Bovine</th>
<th>HM 40</th>
<th>HM 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>

A baby receiving bovine products has 8 times higher odds of requiring surgery for NEC.

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Exclusive Human Milk-Based Diet

• Sullivan et al\textsuperscript{1} showed that there is no difference in growth between infants fed an exclusively human milk-based diet and infants fed human milk plus bovine milk-based products.

• However, concerns remain related to risks of slow growth in these infants.

Growth and Donor Human Milk

• Small descriptive studies suggest that the nutrient content of DHM is lower in fat, calories, protein, sodium, and calcium as compared to formula
  - Premature infants have increased nutritional requirements
  - All infants with a birth weight \( \leq 1250g \) are at risk for poor growth and metabolic abnormalities

• One meta-analysis showed that DHM is associated with slower growth in the early postnatal period

Postnatal Growth Restriction/Failure

NICHD Neonatal Research Network reported outcomes of VLBW infants cared for at 14 participating centers

4,438 infants 501-1500 gram BW

-22% of infants were < 10\textsuperscript{th} percentile at birth
  -97% of the VLBW population had growth failure at 36 weeks corrected age

-Infants weighing 501-1000 grams BW
  -17% of infants were < 10\textsuperscript{th} percentile at birth
  -99% had growth failure at 36 weeks corrected age

Postnatal Growth Failure

Clark et al: Database review of growth data

• 24,371 premature infants 23-34 weeks gestation

• 28% of infants had postnatal growth failure

• The incidence of growth failure increased with decreasing gestational age and birth weight

Why is this important?

• Infants 501-1000 grams BW were divided into quartiles of in-hospital growth velocity rates
  – 495 infants were evaluated at 18-22 months CGA
  – As the rate of weight gain increased from 12.0 to 21.2 g/kg/day (quartile 1 to 4) and head circumference increased from 0.77 to 1.07 cm/wk
• the incidence decreased significantly for:
  • Cerebral palsy, Bayley II MDI 70 and PDI 70, abnormal neurologic exam, neurodevelopmental impairment and need for re-hospitalization

Human Milk Feeding Supports Adequate Growth

- Exclusive Human Milk-Based Diet
- Early and rapid advancement of fortification\(^1\)
  - 104 infants, consecutively followed, BW ≤ 1250 g, received diet until 34 weeks PMA
  - Weight gain 24.8 ± 5.4 g/kg/day, length 0.99 ± 0.23 cm/week, HC 0.72 ± 0.14 cm/week
  - Compared to human milk-fed cohorts (Sullivan et al\(^2\))
    - Infants had greater growth in weight and length
  - 43% of infants had postnatal growth failure

<table>
<thead>
<tr>
<th></th>
<th>Hair et al Study(^1)</th>
<th>Sullivan et al. <em>J Pediatrics</em>. 2010(^2)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Human Milk + HMF 60 (n=104)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to full feeds(^*)</td>
<td>18.2 ± 10.6</td>
<td>24.4 ± 12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TPN days(^†)</td>
<td>13 (10,19)</td>
<td>20 (11,33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Feeds initiated (DOL)(^*)</td>
<td>3.3 ± 2.9</td>
<td>5.6 ± 6.6</td>
<td>0.56</td>
</tr>
<tr>
<td>Fortification of feeds (DOL)(^*)</td>
<td>13.0 ± 8.3</td>
<td>14.1 ± 9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Human Milk + HMF 40 (n=71)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to full feeds(^*)</td>
<td>24.4 ± 12.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN days(^†)</td>
<td>20 (11,33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeds initiated (DOL)(^*)</td>
<td>5.6 ± 6.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortification of feeds (DOL)(^*)</td>
<td>14.1 ± 9.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Human Milk + HMF 100 (n=67)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to full feeds(^*)</td>
<td>26.5 ± 18.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN days(^†)</td>
<td>20 (13,34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeds initiated (DOL)(^*)</td>
<td>4.3 ± 3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortification of feeds (DOL)(^*)</td>
<td>21.0 ± 14.9</td>
<td></td>
<td></td>
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<tr>
<td><strong>Bovine (n=69)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Days to full feeds(^*)</td>
<td>25.0 ± 13.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN days(^†)</td>
<td>22 (13,34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeds initiated (DOL)(^*)</td>
<td>4.7 ± 4.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortification of feeds (DOL)(^*)</td>
<td>18.4 ± 9.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Mean ± SD, \(^†\)Median (25\(^{th}\), 75\(^{th}\) percentile).  DOL = day of life; TPN = total parenteral nutrition.

Costs- Exclusive HM Diet

• Costs of NEC and cost-effectiveness of exclusively human milk-based diet compared to bovine based diet in extremely premature infants

• NEC $74,004 and NEC requiring surgery $198,040
  - Costs over the hospitalization for a preterm infant

• 100% human milk diet infants had decreased length of stay = cost savings of $8,167

Implementation

• Increase maternal milk supply for premature infants
  - Pumps at the bedside
  - Education about benefits of mother’s own milk
  - Lactation Support

• Use of Pasteurized Donor Human Milk
  - Milk Bank
  - Availability
  - Drop off site for donated human milk
  - Potential variability in energy density of donor human milk depending on milk bank
Implementation Plan

• Evaluate your highest risk population for NEC and feeding intolerance

• Gather data regarding NEC rates, TPN days, and feeding intolerance so you have a baseline

• Implement Donor Human Milk and DHM Fortifier
  - Evaluate your results using balancing measures
  - If cost is an issue consider collecting data including length of stay as a surrogate marker
Positive Outcomes to Follow

- Rates of Necrotizing Enterocolitis
- Central line days, Parenteral Nutrition Days
  - CLABSI infection
- Growth- weight, length, head circumference
- Postnatal growth failure
- Feeding tolerance- number of times feeds are stopped and restarted
- Costs $$, Decreased Length of Stay
- Number of infants not transferred to higher level of care
Balancing Measures

• Extra Costs
  - Administrative
  - Staffing
    • Milk Bank Techs, Nurses, Preparing Milk
  - Donor Milk and DHM Fortifier Storage (Freezer)

• Implementation
  - Education of Staff
  - Implement Consent / Assent of Parents
  - Risk of Milk Errors

• Possible Delay of Enteral Feeding
  - Awaiting Mother’s own milk or Donor Human Milk Consent
Advocacy to Prevent NEC

www.NECsociety.org
Thank You!

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