Human Milk for the At-Risk Infant

Heidi E. Karpen, M.D.
Assistant Professor of Pediatrics
Division of Neonatology
Emory University

Disclosures

- Research grant support from Prolacta Bioscience
- Research support from the Chatham Valley Foundation, Inc.
- I will be discussing products using trade names, but this is not an endorsement of any particular product.
Objectives

- Define “The At-Risk Infant”
- Outline the biology of human milk and its benefits for the “At-Risk” infant
- Expand on the role of donor human milk and donor human milk-based fortifier
- Contrast the key differences between pasteurized donor milk and sterilized donor milk products
- Discuss recent and ongoing research studies on Human Milk and the “At-Risk” infant

The “At-Risk Infant”

- Preterm infants (GA<28 weeks, BW<1500g)
  - High risk of feeding intolerance, necrotizing enterocolitis (NEC), infections and death
- Infants with congenital gastrointestinal disorders
  - Delayed feeding causes absence of trophic factors
  - Abnormal colonization due to antibiotics/NICU environment
  - Disorganized motility
  - Poor barrier function
- Infants with high disease acuity
  - Congenital diaphragmatic hernia, congenital heart disease
BW is most predictive for risk of NEC and NEC mortality

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of NEC (%)</th>
<th>Died</th>
<th>Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1</td>
<td>500-750g (34%)</td>
<td>42%</td>
<td>58%</td>
</tr>
<tr>
<td>Category 2</td>
<td>750-1000g (10.7%)</td>
<td>29.4%</td>
<td>70.6%</td>
</tr>
<tr>
<td>Category 3</td>
<td>1000-1250g (4.1%)</td>
<td>21.3%</td>
<td>78.7%</td>
</tr>
<tr>
<td>Category 4</td>
<td>1250-1500g (2.6%)</td>
<td>15.9%</td>
<td>84.1%</td>
</tr>
</tbody>
</table>

N=71,808  P<0.001

Risk of NEC (%)

Causes of Intestinal Failure

- NEC (35%)
- Gastroschisis (18%)
- Hirschsprung’s (2%)
- Midgut volvulus (14%)
- Intestinal Atresias (25%)

J Ped Surg (44):6, June 2009, p1072-1076
Clin Perinatol 40 (2013) 53-68
NEC and Congenital Heart Disease

NEC has been associated with all of the following CHD lesions:

- Hypoplastic left heart syndrome (HLHS)***
- Coarctation of the aorta
- Total anomalous pulmonary venous return (TAPVR)
- Truncus arteriosus
- Tetralogy of Fallot (TOF)
- Patent ductus arteriosus (PDA)
- Secundum atrial septal defects (S-ASD)


NEC in the Preterm with Congenital Heart Disease

![Graph showing the incidence of NEC in preterm infants with CHD](image)

NEC Mortality in the Preterm with Congenital Heart Disease


The Neonatal Intestine

- The neonatal intestine is a work in progress:
  - Slowly proliferating epithelium
  - Immature barrier function
  - Poor pathogen defense system
  - Excessive, uncontrolled inflammatory response
  - Lack of protective, commensal bacteria
  - Exposure to broad spectrum antibiotics

- These are all exaggerated in the preterm infant

Breast Milk Provides Protective Nutrients

Breast milk contains nutrients and specific factors that protect the infant and promote gut maturation/immunity

- **Growth factors** (EGF, GH, glutamine), **Anti-inflammatory molecules** (IL-10, TGF-β2)

- **Lactoferrin** – A multifunctional protein that facilitates iron absorption and inhibits bacterial growth; present in quantities 100x greater than found in bovine milk.

- **Lysozyme** – An antibacterial protein that kills gram positive and gram negative bacteria; present in quantities 3000x greater than found in bovine milk.

- **Secretory IgA** – An antibody custom to pathogens in the maternal environment; present in quantities 4000x greater than found in bovine milk.

- **Human Milk Oligosaccharides (HMOs)** – Indigestible, short chain sugars that serve many functions in the intestinal tract, including pathogen binding and promotion of microbiome development; third most abundant factor in human milk compared to trace amounts found in bovine milk.

- **Preterm milk contains high levels of protective factors**

Breast Milk Constituents

- **Lactose:** carbohydrate source in human milk
  - Ideal choice for infants who are preterm or who are “at-risk”.
  - In the absence of human milk, it is often recommended to start enteral feeding with glucose polymers as those contained in eHPF and AABF.

- **Proteins:** HM- whey proteins; limited bovine protein exposure

- **Fats:** MCTs and LC-PUFAs

- **Probiotics:** HM comes ready made!
Colostrum - the Super Milk!

- **Colostrum is more trophic than mature milk**
- The protein content is very high (B11% v/v)
- Whey proteins in HM include $\alpha$-lactalbumin, $\beta$-lactoglobulin, serum albumin, immunoglobulins, lactoferrin and peptide hormones such as growth hormone and insulin-like growth factors, epidermal growth factor, $\beta$–cellulin, TGF-$\beta$ and platelet-derived growth factor.
- If available, colostrum and breast milk may offer some advantages. In the animal model, colostrum and colostrum protein concentrate have been shown to stimulate mucosal growth.


Benefits of Human Milk

**Decreased risk of:**
- Respiratory tract infections and otitis media
- Sudden infant death syndrome
- GI infections such as Rotavirus
- IBD and Celiac disease
- Asthma, atopic dermatitis and eczema
- Obesity and Type I and II diabetes

**Positive effect on:**
- Neurodevelopmental outcomes
- Severity of Retinopathy of Prematurity (ROP)

Maternal breast milk and preterm infants

- Reduction in sepsis and mortality for VLBW/ELBW infants (Fraser Askin 2005, Hylander 1998)
- Decreased rates of necrotizing enterocolitis (NEC) (Walker 2010, Lucas 1990)
- Infants with gastroschisis are also at risk for necrotizing enterocolitis
  - Exclusive breastfeeding (MBM) or partial breastfeeding associated with a decreased rate of NEC (Jayanthi 1998)
- Reduction in bronchopulmonary dysplasia
  - Proportionate increase based on percentage of MBM (Patel 2011)
- Increase in IQ points at 18 month neurodevelopmental follow up (Vohr 2006)
  - Estimated an increase by 0.53 in IQ for every 10mL/kg increase in breast milk in the diet of ELBW infants

HM and weaning from PN in SBS

- The ideal enteral nutrition formulation for neonates with intestinal failure remains controversial. It has been shown that both breast milk and commercially available elemental formulas are associated with a reduction in the time of PN dependence in neonates with severe SBS (Andorsky 2001)
- It has been shown that as little as four per cent of calories from enteral nutrition may help stimulate bowel adaptation (Pediatr Ann 1985;14(53):57-60)
Breastfeeding and the Use of Human Milk: AAP Statement 2012

- 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 (PDHM), 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.


Human Milk in Neonates with CHD

- Despite overwhelming evidence supporting the benefits of human milk, there have been no studies on the benefits of a human milk diet on outcomes in infants with CHD.
- Barriers to providing human milk to these infants include:
  - separation of mother and infant after delivery
  - stress of having a critically ill infant
  - lack of lactation support
  - clinician opinion
Mother’s Own Milk (MOM)

- The majority of mothers of NICU and CICU infants do not have adequate milk supply
- Preterm birth and recent betamethasone exposure shown to significantly decrease milk supply (Henderson 2008)
- Only 27% able to provide sufficient milk for PT infants (Schanler 2005)
- Study from CHOP: rates of pumping initiation of pumping was higher among mothers whose babies were inborn (96%) versus mothers who were separated from their infant after birth because of transport to a tertiary care center (67%) (Torowicz DL, Breastfeed Med 2015)
- Breastfeeding rates at discharge are also low (Pineda 2011)
Is this the answer?

Milk Banks

This will be the greatest breast sucking facility the world has ever seen
The Origins of Milk Banking

- Studies conducted by Theodor Escherich, Chair of Pediatrics at the University of Vienna from 1902 to 1911, demonstrated that the intestinal bacteria of breastfed neonates were significantly different than that of infants fed by other means.

- His efforts resulted in eventual construction of the Imperial Institute for Maternal and Infant Care and in the opening of the first human milk bank in Vienna in 1909.

- First milk bank in U.S. established in 1910 in Boston.

- AAP published recommendations for milk banking in 1945.

- HUMBANA is established in 1985.

HMBANA Milk Banks

- Non-profit association, established 1985.
- New sites under development in Salt Lake, Nashville, Rogers, MN and Saint-Laurent, QC.
- Largest supplier: over 1 million ounces distributed per year.
- Donor moms are screened for medication use, travel and medical history, and for infectious illness.
- Milk is pooled, Holder pasteurized, and sampled for bacterial contamination then frozen and shipped.

https://www.hmbana.org
Prolacta Bioscience

- For profit company
- High level of safety checks for milk: maternal health questionnaires, DNA fingerprinting of milk to donor, alteration/dilution, tissue donation level of security
- Offers PDHM, cream product to increase fat calories
- Currently only source of *human milk based* fortifier
- Maintain hospital based donor programs
- Now have a paid portal for mothers to donate
- Donors must have permission forms from their doctor as well as baby’s pediatrician to donate

Holder Pasteurization

- Holder pasteurization is the most common processing technique used globally by milk banks to eliminate bacteria and viruses.
- A low-heat method of processing: milk is warmed to 62.5 degrees Celsius, held for 30 minutes, rapidly cooled, and then frozen until use.
- Some loss of protective factors found in MOM.
## Pasteurization and Human Milk

**Selected immune components**
- B-cells, T-cells, lymphocytes
- IgA
- IgG
- IgM
- Lactoferrin*
- IL-10*
- IFN-γ, IL-1β
- Lysozyme

**Effect of pasteurization**
- Abolished
- 0-48% reduction
- 34% reduction
- Abolished
- 57-80% reduction
- Marked reduction
- Reduction
- 24-60% reduction

Ewaschuk 2011

## Pasteurization and Breastmilk

**Growth and nutrition components**
- Vitamin A
- Erythropoietin
- Iron
- Electrolytes
- Total Fats
  - Free fatty acids
- Oligosaccharides*
- IGF-1, IGF-2
- EGF, TGF-β

**Effect of pasteurization**
- No change
- Marked reduction
- 15% reduction
- No change
- No change
  - Increase (80%)
- No effect
- 7-39% reduction
- No effect

Ewaschuk 2011
Shelf-stable donor human milk

- **Medolac**: public benefit life sciences company
- Mothers Milk Co-Op
- Makes a sterilized donor milk product that has a long shelf life (2 years) and does not need to be refrigerated or frozen

- **Ni-Q**: For profit company
- Paid donations
- Makes a sterilized donor milk product that has a long shelf life (12 months) and does not need to be refrigerated or frozen

- Sterilized by heating to 121°C for 5 min, with added pressure of 15 pounds per square inch above atmospheric pressure
- Provides mothers a safe way to supplement rather than “milk sharing”
- Milk can be ordered by hospitals and by families for post discharge donor milk supply.
- Extensive screening, including DNA fingerprinting

http://www.medolac.com
Sterilization vs. Pasteurization


Retort vs VAT vs Holder

Table 3. Comparison of Mean and Relative Standard Deviations (%) of Immune Protective Proteins of Human Milk Among the Different Banked Milk Groups.

<table>
<thead>
<tr>
<th></th>
<th>Retort (n = 3)</th>
<th>VAT (n = 3)</th>
<th>Holder (n = 3)</th>
<th>Human milk reference (n = 1)</th>
<th>Retort (n = 3)</th>
<th>VAT (n = 3)</th>
<th>Holder (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lgA (concentrations as g/L)</td>
<td>0.19 (0.03)</td>
<td>0.38 (0.02)</td>
<td>0.52 (0.15)</td>
<td>0.32</td>
<td>15.1</td>
<td>4.1</td>
<td>47.6</td>
</tr>
<tr>
<td>lgH (concentrations as g/L)</td>
<td>[0.16-0.22]</td>
<td>[0.35-0.39]</td>
<td>[0.18-0.49]</td>
<td>0.02</td>
<td>9.1</td>
<td>10.5</td>
<td>17.0</td>
</tr>
<tr>
<td>lgG (concentrations as g/L)</td>
<td>[0.01-0.001]</td>
<td>[0.02-0.002]</td>
<td>[0.03-0.003]</td>
<td>0.03</td>
<td>1.7</td>
<td>0.7</td>
<td>21.1</td>
</tr>
<tr>
<td>Lysozyme (concentrations as g/L)</td>
<td>[0.05-0.06]</td>
<td>[0.08-0.09]</td>
<td>[0.02-0.04]</td>
<td>0.05</td>
<td>2.6</td>
<td>1.7</td>
<td>8.3</td>
</tr>
<tr>
<td>Lactoferrin (concentrations as g/L)</td>
<td>0.5 (0.10)</td>
<td>1.12 (0.14)</td>
<td>1.45 (0.12)</td>
<td>1.15</td>
<td>20.3</td>
<td>12.5</td>
<td>8.1</td>
</tr>
<tr>
<td>α-lactalbumin (concentrations as g/L)</td>
<td>1.95 (0.06)</td>
<td>3.70 (0.58)</td>
<td>4.44 (0.25)</td>
<td>3.90</td>
<td>6.8</td>
<td>15.6</td>
<td>2.2</td>
</tr>
<tr>
<td>α-antitrypsin (concentrations as g/L)</td>
<td>0.06 (0.01)</td>
<td>0.03 (0.01)</td>
<td>0.03 (0.003)</td>
<td>0.04</td>
<td>9.7</td>
<td>5.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Cystatin (abundances as 1 x 10^4)</td>
<td>[0.07-0.09]</td>
<td>[0.08-0.09]</td>
<td>[1.21-1.30]</td>
<td>1.15-2.57</td>
<td>3.3</td>
<td>5.2</td>
<td>9.8</td>
</tr>
<tr>
<td>α-casein (abundances as 1 x 10^4)</td>
<td>0.93 (0.22)</td>
<td>1.9 (0.14)</td>
<td>2.7 (0.05)</td>
<td>2.0</td>
<td>24.1</td>
<td>7.5</td>
<td>31.1</td>
</tr>
<tr>
<td>β-casein (abundances as 1 x 10^4)</td>
<td>[0.71-1.13]</td>
<td>[1.21-1.98]</td>
<td>[2.08-3.87]</td>
<td>3.7</td>
<td>6.4</td>
<td>3.6</td>
<td>9.8</td>
</tr>
<tr>
<td>κ-casein (abundances as 1 x 10^4)</td>
<td>3.9 (0.44)</td>
<td>6.7 (0.20)</td>
<td>10.0 (0.32)</td>
<td>4.8</td>
<td>11.7</td>
<td>3.3</td>
<td>5.3</td>
</tr>
</tbody>
</table>

Note: Different letters superscripts represent statistically significant differences among groups. p < 0.05.

Journal of Human Lactation2018, Vol. 34(1) 120–129
Pasteurization and breast milk

- Silvestre 2008 J Human Lactation
- Compared bactericidal capacity of raw mature milk with two mechanisms of pasteurization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean</th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated milk</td>
<td>70.10 ± 8.14</td>
<td>83.81</td>
<td>56.85</td>
</tr>
<tr>
<td>Low pasteurization</td>
<td>52.27 ± 16.95</td>
<td>74.21</td>
<td>30.33</td>
</tr>
<tr>
<td>High pasteurization</td>
<td>36.39 ± 14.98</td>
<td>54.45</td>
<td>8.26</td>
</tr>
</tbody>
</table>

Values are reported as mean ± standard deviation. Different letters mean significant differences (P < .05). Low pasteurization, 63°C/50 minutes. High pasteurization, 75°C/15 seconds.

Pasteurized human milk

- 226 <2500g infants randomized to four groups, followed infection rates
  - Raw human milk 10.5%
  - Pasteurized human milk 14.3%
  - R-HM + Formula 16.1%
  - P-HM + Formula 33.3%

- Concluded that human milk had a protective effect, which was reduced by pasteurization
On the Horizon...

- **Higher-temperature short-time pasteurization (HTST)** may be more effective at retaining milk properties.
  - The most frequently evaluated HTST using a temperature of 72°C for 15 seconds,
  - Has never been tested in HMB conditions, as there is not yet a marketed device

- **High Pressure Processing (HPP)** has been used to inactivate pathogenic microorganisms in solid and liquid foods.
  - This technology applies high hydrostatic high pressure (usually 400–800 MPa) for a short time.
  - Different levels of pressure (200–900 MPa), during different times (1–120 minutes)

- **UV irradiation, specifically UV-C**, destroys microorganisms, such as bacteria, viruses, and yeasts
  - Penetration capacity is low, which limits its use to liquid foods and flat surfaces
  - Data are mostly experimental, but it has never been used in HMB to pasteurize large amounts of milk

- **Ultrasound processing or sonication** is one of the alternative technologies that have been proposed for food processing with a reduced impact on nutritional content and overall food quality
  - Sonication alone is not very effective in killing bacteria in food and has been coupled with mild heating (**thermo-ultrasonication**).
  - A 2- to 8-minute treatment at 50°C of artificially contaminated HM inactivates bacteria such as *E.coli* and *Staphylococcus epidermidis*, with a retention of secretory IgA, lysozyme, lactoferrin, and BSS: of 91%, 80%, 77%, and 45%, respectively.

Milk Sharing

- Rules governing wet nursing are described in the Babylonian Code of Hammurabi (roughly 1800 BC)
  - Selection criteria described in Greco-Roman texts; children were thought to inherit the physical, mental, and emotional traits of their wet nurse through breast milk, so selection of the nurse was considered very important.

- By the 11th century, the aristocracy and royalty of Europe almost exclusively used we nurses. Breastfeeding was considered to be indecent and ridiculous; this ideology persisted through the 1800s.

- In 1740, the infant mortality rate in Paris was 38%, with the majority (>95%) of infants breastfed by wet nurses. During this time, European women were making more money as wet nurses than any other occupation open to women.

- The popularity of feeding by wet nurses began to decline in the 19th century as shock and concern about depravity among wet nurses reached an all-time high and alternative milk sources (e.g., animals) and formula was first conceived.
Community HM Sharing

- Donor milk sharing
  - The “wet nurse”
  - “Cross nursing”
  - “Eats on Feets”
  - Craigslist, eBay sales

Policy on Informal Milk Sharing for the Healthy Term Infant

**Table 1. Guidelines for Medical Screening of Potential Milk Donors**

1. Mother-to-mother screening process through face-to-face and/or telephone interview/conversation. Donor mothers should be:
   - In good health
   - Only on medications or herbal preparations that are compatible with breastfeeding. It is recommended that LactMed\(^\text{11}\) and “Medications and Mother’s Milk” by Dr. Thomas Hale\(^\text{12}\) be used for decisions on whether medications are compatible with breastfeeding.

2. Review the donor mother’s prenatal and (if performed) regular postnatal infectious screening tests. The donor mother should be negative for:
   - HIV
   - Hepatitis B virus
   - HTLV-1 (in high prevalence areas)

3. Social practices. A woman is not a suitable breast milk donor if she
   - uses illegal drugs or marijuana,
   - smokes or uses tobacco products, including nicotine gum, patch, e-cigarettes,
   - consumes >1.5 ounces (44 mL) of hard liquor/spirits, 12 ounces (355 mL) of beer, 5 ounces (148 mL) of wine, or 10 ounces (296 mL) of wine coolers (beverage of wine and fruit juice with lower alcohol content than wine) daily, and
   - is at risk for HIV or had a sexual partner within past 12 months who is at risk for HIV.

- Internet-based breast milk sharing, and especially the purchase of milk over the internet, is strongly discouraged since (1) the donors are unknown to the recipient and/or cannot be medically screened and (2) the milk is often not suitable for consumption upon arrival.
- Strongly consider home pasteurization of milk

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*BREASTFEEDING MEDICINE Volume 13, Number 1, 2018*
Donor breast milk and preterm infants

- **Cochrane Review** (Quigley 2014)
  - 9 trials comparing formula with donor human breast milk (1976-2013) as supplement to MBM
    - Majority using unfortified breast milk*
  - Better short term growth in formula fed group
  - No difference in long term growth
  - No difference in neurodevelopmental outcomes at 18 months (2 studies)
  - Meta-analysis of five trials showed a statistically significant increased risk of necrotizing enterocolitis in formula fed group
    - Number needed to harm = 25
    - Rate of feeding intolerance was also increased in formulaf ed groups
    - Effect was present even when MOM/PDHM was fortified with HMF

Exclusive Human Milk-Based Diet in Preterm Infants

- Development of concentrated human milk for fortification has provided a potentially safer alternative
- Currently only available from a single, for profit company (Prolacta)

- **Sullivan 2010**
  - 207 infants <1250g at 12 NICUs
  - Randomized to three groups when maternal milk supply was inadequate: HM 100, HM 40, and BOV
  - Mother own milk constituted a large proportion of feedings (70-83%)
  - No difference in length of stay, late onset sepsis, or growth*
Exclusive HM Diet and NEC in Preterm Neonates

- Reduction in NEC of 50% in exclusively human milk fed infants (p =0.05). Reduction in surgical NEC of almost 90% (p=0.02)
- Estimated NNT = 10 to prevent 1 case of NEC; NNT=8 for surgical NEC
- Decreased days on TPN


Beyond NEC- EHMD Trial

- 1,587 infants from 4 centers: TX, CA, IL, FL
- Retrospective cohort of the 3 years preceding the introduction of an EHMD feeding protocol
- Primary outcomes were necrotizing enterocolitis (NEC) and mortality.
- Secondary outcomes included late-onset sepsis, retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD).
NEC and Mortality Significantly Reduced with EHMD

![Graph showing NEC cases vs gestational age]

Significant Caloric Variation in Donor Human Milk

- Study of 415 sequential samples from 273 unique donors
- Analyzed for fat, protein, carbohydrate
- Mean energy content of milk was 19 kcal/oz
  - 25% of the samples were < 17 kcal/oz
  - 65% were < 20 kcal/oz
- Fat content was the most variable
  - 3.2 g/dL

What about the term sick infant?

- Surgical intestinal disorders
  - NEC, gastroschisis, atresias, SBS
- Cardiac lesions- HLHS, coarctation
- CDH
- Almost all late-preterm to term
- Greater than 1,250g so do not qualify for typical donor human milk protocols
- Increased caloric needs not met by human milk alone
- Preterm fortifiers not appropriate for these babies
HM for CGD Study-Retrospective Cohort

- This retrospective study assessed enteral feeding outcomes of neonates with surgical GI disorders admitted within the first seven days of life to a single center between January 1, 2012 and August 10, 2015.

- Outcomes were assessed according to diet from the point of first enteral intake through seven days of full enteral feeds. Diets were classified as 100%BM, ≥50%BM, or <50%BM.

### Study Population

<table>
<thead>
<tr>
<th></th>
<th>BM only diet (N=54)</th>
<th>Mostly BM (&gt;50%) (N=65)</th>
<th>Partly or no BM (&lt;50%) (N=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34 (63.0%)</td>
<td>33 (51.0%)</td>
<td>22 (50.0%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Female</td>
<td>20 (37.0%)</td>
<td>32 (49.0%)</td>
<td>22 (50.0%)</td>
<td></td>
</tr>
<tr>
<td><strong>Gestational Age in Weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Birth weight in Grams</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (+/- std)</td>
<td>2560.3 (+/- 706.2)</td>
<td>2562.3 (+/- 737.4)</td>
<td>2497.0 (+/- 564.6)</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Age at Admission in Days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (+/- std)</td>
<td>1.0 (+/- 1.6)</td>
<td>0.8 (+/- 1.4)</td>
<td>0.8 (+/- 1.5)</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>30 (56.4%)</td>
<td>28 (44.4%)</td>
<td>18 (40.9%)</td>
<td>0.42</td>
</tr>
<tr>
<td>AA</td>
<td>14 (26.4%)</td>
<td>17 (26.2%)</td>
<td>17 (38.6%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (3.8%)</td>
<td>2 (3.2%)</td>
<td>4 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (13.2%)</td>
<td>6 (9.5%)</td>
<td>5 (11.4%)</td>
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<tr>
<td><strong>Primary Diagnosis</strong></td>
<td></td>
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</tr>
<tr>
<td>Gastroschisis</td>
<td>15 (27.8%)</td>
<td>30 (46.2%)</td>
<td>23 (52.3%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Small Bowel Atresia</td>
<td>24 (44.4%)</td>
<td>20 (30.8%)</td>
<td>9 (20.5%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>15 (27.8%)</td>
<td>15 (23.1%)</td>
<td>12 (27.3%)</td>
<td></td>
</tr>
<tr>
<td>Median (25th – 75th percentiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Presence of a Stoma</strong></td>
<td>8 (14.8%)</td>
<td>17 (26.2%)</td>
<td>14 (31.8%)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Days to bowel continuity</strong></td>
<td>10 [4 – 42]</td>
<td>7 [4 – 38]</td>
<td>5 [3 – 35]</td>
<td>0.58</td>
</tr>
<tr>
<td>Median (25th – 75th percentiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Surgical Diagnoses

- **Gastroschisis** (N=69)
- **Intestinal Atresia** (N=54)
- **Omphalocele** (N=23)
- **Necrotizing Enterocolitis** (N=8)
- **Spontaneous Intestinal Perforation** (N=6)

### Exclusive Human Milk Diet Improves Outcomes in Surgical Neonates

<table>
<thead>
<tr>
<th></th>
<th>100%BM (N=54)</th>
<th>≥50%BM (N=65)</th>
<th>&lt;50%BM (N=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Initial Enteral Feeds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [25th – 75th percentiles]</td>
<td>8.0 [6.0 – 12.0]</td>
<td>11.0 [6.0 – 21.0]</td>
<td>10.7 [8.0 – 18.5]</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Time to Full Enteral Feeds</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [25th – 75th percentiles]</td>
<td>21.0 [15.0 – 30.0]</td>
<td>29.5 [18.5 – 42.5]</td>
<td>32.0 [21.0 – 61.5]</td>
<td>*0.013</td>
</tr>
<tr>
<td><strong>Number of Culture-proven Sepsis Episodes</strong></td>
<td>1 (1.85%)</td>
<td>1 (1.54%)</td>
<td>3 (6.8%)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Total days on PN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [25th – 75th percentiles]</td>
<td>21.0 [15.0 – 29.0]</td>
<td>28.5 [18.0 – 41.0]</td>
<td>30.0 [18.0 – 55.0]</td>
<td>*0.025</td>
</tr>
<tr>
<td><strong>Hospital LOS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median [25th – 75th percentiles]</td>
<td>27.5 [19.0 – 43.0]</td>
<td>40.0 [29.0 – 72.0]</td>
<td>51.0 [26.0 – 89.0]</td>
<td>*0.006</td>
</tr>
<tr>
<td><strong>Biopsy-Supported Diagnosis of TPN Cholestasis</strong></td>
<td>14 (25.9%)</td>
<td>19 (29.2%)</td>
<td>18 (40.9%)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Survival</strong></td>
<td>54 (100%)</td>
<td>65 (100%)</td>
<td>44 (100%)</td>
<td>1</td>
</tr>
</tbody>
</table>
HM for CGD-Prospective Cohort

**Hypothesis**
- The use of an exclusive human milk diet (EHMD), when compared to formula or HM fortified with cow-milk based fortifier, will **decrease the amount of time neonates with CGD and AGD are on PN**.

**Specific Aims**
- To compare the time to full enteral feeds and days on PN in neonates with CGD and AGD who receive an EHMD, compared with those receiving partial and non-human milk diets, while hospitalized in the NICU.
- To compare peak conjugated bilirubin levels, episodes of sepsis, feeding tolerance, feeding interruptions, episodes of NEC, LOS, and death between CGD neonates who receive EHMD versus partial and formula feeding, while hospitalized in the NICU.

Prospective Cohort

- A minimum of 150 patients with CGD or AGD admitted to participating NICUs with a qualifying CGD diagnosis (gastroschisis, omphalocele, intestinal atresia), <7 days of age, >1,250g and/or >32 weeks’ GA

- These patients will be fed an EHMD comprised of mother’s own milk (MOM) or pasteurized donor human milk (PDHM-Prolacta Bioscience, Inc).

- Fortification will be provided with human milk-based fortifier (HMBF): Prolact+ H2MF® for infants born at less than 37 weeks or PBCLN-002, formulated for infants >37 weeks and/or >2,200g (Prolacta Bioscience, Inc.).

- All management decisions, laboratory and radiologic studies will be at the discretion of the treating physicians and dietician caring for the patient.

- Primary outcomes are days to full enteral feedings and days on PN

- Secondary outcomes: peak conjugated bilirubin levels, episodes of sepsis, episodes of feeding intolerance, feeding interruptions, episodes of NEC, LOS, and death between neonates with CGD who receive EHMD, versus partial HM and formula diets, while hospitalized in the NICU
Cardiac Study

- Randomized, single blinded, controlled trial to evaluate growth velocity and clinical outcomes in term infants (>37 weeks GA) with single ventricle physiology fed an EHMD prior to, and throughout the post-operative period following, surgical repair.

- The study hypothesis is that infants fed an exclusive human milk diet will have short and long term benefits, with improved wound healing, growth, and neurodevelopmental outcomes while reducing episodes of feeding intolerance and necrotizing enterocolitis (NEC).

- Experimental: Exclusive Human Milk All infants randomized to this arm will receive exclusive human milk diet with addition of human milk derived fortifier from birth to 30 days post initiation of feedings after initial palliative cardiac surgery

- Active Comparator: Human/Bovine Milk All infants randomized to this arm will receive exclusive human milk diet prior to randomization and will use either human and/or bovine milk and fortifier per the institution's standard practice 30 days post initiation of feedings after initial palliative cardiac surgery

- Primary Outcome: Weight velocity

- Secondary Outcomes: Linear and HC growth, feeding intolerance, NEC, LOS, sepsis, wound infections, wound dehiscence, days of PN

For which population do you use PDHM?

![Chart showing distribution of PDHM use across different populations](image)
Reasons PDHM Not Used

So what is the cost?

http://www.verticalbandingastroplasty.org/
Costs of Doing Business with Babies

- Maternal Milk: equipment for pumping and storing, time
- Bovine human milk fortifier (HMF): $1.30/packet
  - 1 packet: 25mL= 24cal/oz
- Formula: Enfamil premature 24cal/oz $1.00/oz
  - Most hospitals receive free formula
- Pasteurized Donor Human Milk: HMBANA banks $3-5/ounce; Prolacta~$10-15/oz
- Sterilized HM: $6-9/oz
- Concentrated human milk based fortifier: $6.25/mL
  - 10mL HHMF + 40mL HM = 50mL 24cal/oz

Breastfeeding Medicine 2012

- Used California state data for 2007 for extremely premature (<28wks GA) hospital costs and NEC incidence
  - 2560 EP infants, 259 NEC cases (10%), 82 surgical NEC cases (3.2%)

- Estimated decreased incidence of medical NEC and surgical NEC with completely human milk based feeds using data from Sullivan 2010 paper
NEC is Expensive!

- Mortality significantly increased in NEC groups as were hospital costs
  - Surgical NEC $198,040
  - Medical NEC $74,000
  - Late onset sepsis $10,055
  - BPD $31,565
  - ROP requiring surgery $35,749
  - PDA $49,457

- Lower estimated LOS (4.5 NICU days) and cost for infants feed exclusively human milk ($15,700 per day)

- Cost savings of TPN estimated at up to $1,436 per day

- Result was as estimated an average cost savings of $8,167/infant.

- By these estimates, it could be possible to avoid ~3000 cases/year of NEC. This would provide an estimated total healthcare savings of >$200 million.


Save for a rainy NEC day...

Bottom line...

- Human milk is the ideal source of nutrition for most at-risk infants
- Human milk contains nutritional elements, immune modulators and growth factors essential for intestinal growth, adaptation and rehabilitation
- Pasteurization and storage do partially attenuate the beneficial effects of breast milk
  - Still the closest alternative to maternal milk
- Use of PDHM holds promise especially in high risk infants
  - Appears to be cost-effective even with added cost of HMBF
- As use increases, availability and supply may lead to difficult ethical questions
Take home points for EHMD

• **Encourage mother’s own milk**
  - Pumps at every bedside
  - Education families about benefits of mother’s own milk
  - Lactation Support!!!

• **Use of Pasteurized Donor Human Milk**
  - Milk Bank-HMBANA, hospital based program vs. private company
  - Availability- guaranteed supply vs. possible shortages
  - Drop off site for donated human milk
  - Potential variability in energy density of donor human milk depending on milk bank
  - **Third party payer/Medicaid reimbursement**

• **Expanded access for other “at-risk” groups such as CHD and CGD patients**

Questions??

www.medelabreastfeedingus.com

http://www.thenewbornbaby.com/