State of the Science: Human Milk for Vulnerable Infants

Building Brighter Futures
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Disclosure

I have no conflicts of interest to disclose
Objectives

- List benefits of human milk for preterm infants
- Describe the importance of mother’s own milk for preterm infants
- Describe factors that affect receipt of VLBW mother’s own milk at discharge
- Describe methods to improve mother’s own milk feedings for NICU infants
What Do We Know

• Preterm birth is associated with increased risks of **morbidity** and mortality
• Goal is to improve the rate of morbidity-free survival in this population
• Human Milk enhances preterm infant outcomes – **GOLD STANDARD**
Morbidities Related to Prematurity

- **Impaired Growth**
  - born with nutritional deficits
  - Greater energy requirements
  - Immature GI system

- **Neurologic:**
  - Acute: Intracranial hemorrhage (IVH/PVL)
  - Poor neurodevelopmental outcomes
    - Autism, ADHD, Anxiety and Depression, Social difficulties

**Strong Association between preterm infant growth and neurodevelopment**
Morbidities Related to Prematurity

• Cardiovascular: long term risk of CV disease and metabolic syndrome

• Respiratory:
  – Bronchopulmonary Dysplasia (BPD) - Chronic lung disease
  – Asthma
Morbidities Related to Prematurity

• Gastrointestinal:
  – Necrotizing Enterocolitis - portions of the bowel undergo necrosis (tissue death)
  – Gastroesophageal reflux
  – Feeding intolerance

• Immune System:
  – Infection
  – Allergies

• Visual:
  – Retinopathy of Prematurity
  – Decreased visual acuity
It is well documented that human milk has been shown to improve clinical outcomes and reduce morbidities in the preterm population.
How?
Breast Milk

Nutritional component
- Carbohydrates, proteins, fats, water, lactose, vitamins, minerals, immunoglobulins and enzymes

Cytokines and Growth factors
- VEGF, HGF, IGF, EGF, TGF-β family, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-16, IL-18, G-CSF, IFN-γ, M-CSF, GM-CSF, GRO-α, MCP-1

Cellular components
- Stem/progenitor cells
- Non-Stem cells (Immune and non-immune cells)
  - Luminal Epithelial cells
  - Myoepithelial cells
  - Polymorpho leukocytes
  - Mononuclear lymphocytes

- Mammary stem cells
- Hematopoietic stem cell
- Mesenchymal stem cell
- Pluripotent stem cells
- Side population

- Cell adhesion molecules
- Lactocytes
- Other immune/non-immune cells
Infant Formula  Fresh Human Milk
Gastrointestinal Benefits

• Mechanism:
  – Hormones etc. affect maturation and differentiation of the GI tract
  – Stem cells affect epithelial wall development
  – Decreased intestinal permeability

• Result:
  – Improved feeding tolerance and faster attainment of full enteral feeding (AAP. Pediatrics 2012)
  – Lower rates of long term growth failure (Hintz 2005)

Neurologic Benefits

• Mechanism:
  – Complicated
  – PUFAs, milk globule membrane, lutein, lactoferrin, HMOs

• Results:
  – 2 large randomized controlled trials
    • MOM intake on preterm neurodevelopment
    • Significant positive association with the duration of MOM feeding and neurodevelopment at 12m and 30m corrected age
  – Vohr: Significantly greater scores for mental, motor, and behavior ratings at ages 18 months and 30 months
  – Emotional regulation at 30 months was also significantly associated with maternal milk intake

(O’Connor 2003, Vohr 2007)
Intranasal Mother’s Milk Delivery to Preterm Infants

Passes the blood brain barrier to get components such as stem cells and growth factors directly to the brain.

Lochhead 2012; Scafidi 2014
Immune System

• Mechanism:
  – Adaptive immune function transferred by sIgA (regulates gut microbiota and intestinal gene expression)
  – Nutritional and Immune components (lactoferrin, monoglyecride)
  – Non-nutritional immune components:
    • Anti-inflammatory cytokines
    • Pro-inflammatory cytokine receptor blockers
    • Hormones
    • Human Milk Oligosaccharides

• Results:
  – Decreased risk of sepsis (Meizen-Derr 2004)
  – Lower risk for food allergy, asthma and atopic dermatitis (Van Odijk 2003, Pabst 2012, Dogaru 2014)
• **Respiratory:**
  – Lower incidence of BPD (Schanler 2005, Spiegler 2016)

• **Visual Acuity:**
  – Decreased incidence of ROP (Pammi 2015)

• **Cardiovascular:**
  – Lower rates of metabolic syndrome
  – In adolescents:
    • lower blood pressures and low-density lipoprotein concentrations
    • improved leptin and insulin metabolism (AAP. Pediatrics 2012)
How much is enough?
Clinical Impact of Human Milk for Preterm Infants: Dose Response

- **Objective:** To determine whether VLBW infants continue to show improved developmental outcomes at 18 and 30 months of age

- **Methods:** Neonatal feeding characteristics and morbidities and 30-month interim history, neurodevelopmental outcomes, and growth parameters were analyzed in 773 infants

- **Results:** For every 10 mL/kg per day increase in breast milk:
  - Psychomotor Developmental Index by 0.56 points
  - Mental Development index increased by 0.59 points
  - Total behavior percentile score by 0.99 points
  - Risk of re-hospitalization between discharge and 30 months decreased by 5%

(Vohr 2006, 2007)
Clinical Impact of Human Milk for Preterm Infants: Dose Response

– **Objective:** To prospectively study the impact of MOM received in the NICU on the risk of BPD and associated costs.

– **Methods:** 5-year prospective cohort study of the impact of MOM dose on growth, morbidity and NICU costs in VLBW infants.

– **Results:** Multivariable logistic regression
  - Dose of HM during the first 28 post partum days substantially affected the risk of late-onset sepsis in VLBW infants
  - Each 10 ml/kg/d of HM reduced the risk of sepsis by 19%

(Patel 2017)
Clinical Impact of Human Milk for Preterm Infants: Dose Response

• Objective: To determine the impact on neurodevelopmental outcome of an exact dose of human milk received in the NICU

• Methods: Daily dose of HM for 430 infants was calculated. Dose of human milk and relationship to Bayley III index scores were calculated

• Results: Each 10 ml/kg/d increase in HM was associated with a 0.35 increase in cognitive index score

(Patra 2017)
Human Milk and Dose Dependent Outcomes

Dose Dependent reduction in the risk/incidence/severity of:

– NEC
– Late Onset Sepsis (LOS)
– Bronchopulmonary Dysplasia
– Retinopathy of Prematurity
– Neurodevelopmental problems at 20 months corrected age
– Re-hospitalization after NICU discharge
Language is Important!

Human Milk (Breast Milk)

Mother’s Own Milk
Donor Human Milk
Casual Milk Sharing

- Receiving milk from or through a friend/aquaintance
- Receiving milk via the Internet
- Great infectious risk
- Cohen et al. 2010: San Jose Milk Bank- of 1,091 potential donating mothers 3.3% were positive for an infectious disease including syphilis, Hep B, HTLV and HIV
- Kiem et al. 2013: milk randomly purchased on the Internet had significant bacterial contamination with possibly dangerous organisms in the NICU setting
<table>
<thead>
<tr>
<th>DHM Source</th>
<th>Location</th>
<th>Donors</th>
<th>Laboratory Screening</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMBANA (Professional Association)</td>
<td>18 member banks in 14 states and 3 provinces (10 banks in development) Hmbana.org</td>
<td>Partnership with hospital and community depot Donors unpaid</td>
<td>Pasteurization of donor for HIV Types 1 and 2, HTLV 1 and 2, hepatitis B and C and syphilis Post-pasteurization culture results must be negative for bacteria</td>
<td>Holder Pasteurization Stored Frozen</td>
</tr>
<tr>
<td>Medolac (Private Company)</td>
<td>Headquarters in Lake Oswego, OR Medolac.com</td>
<td>Producer/processor partnership with Mother’s Milk Cooperative Donors Paid</td>
<td>Prepasteurization milk testing for bacteria and viruses: HIV 1 and 2, HTLV 1 and 2, hepatitis A and B, syphilis, West Nile, Trypanosoma cruzi yeast, mold and 7 drugs of abuse</td>
<td>Proprietary biopharmaceutical processing methods Nutritional analysis Stored at room temperature Shelf-life 3 years</td>
</tr>
<tr>
<td>Prolacta (Private Company)</td>
<td>Headquarters in Minerva, CA Prolacta.com</td>
<td>Hospital and community referral donor milk program Donors compensated</td>
<td>Incoming milk DNA matched to donor, tested for bovine protein, prepasteurization testing for HIV 1 and 2, HTLV 1 and 2, hepatitis Band C, syphilis, nicotine, marijuana, cocaine and prescription drugs such as opiates and their metabolites Postpasteurization testing for aerobic count, Bacillus cereus, Escherichia coli and coliforms, salmonella, pseudomonas aeruginosa, Staphylococcus aureus, yeast and mold</td>
<td>Proprietary process for standardization of milk Nutritional analysis Stored frozen</td>
</tr>
<tr>
<td>NiQ</td>
<td>Wilsonville, OR</td>
<td>Donors Paid</td>
<td>Triple screening include DNA</td>
<td>FDA approved process Non-refrigerated, shelf stable</td>
</tr>
</tbody>
</table>
DHM vs Standard or Preterm Formula

• Cochrane Review 2018:
  – Twelve trials with a total of 1879 infants fulfilled the inclusion criteria
  – Formula-fed infants had higher in-hospital rates of weight gain, linear growth and head growth
  – No evidence of an effect on long-term growth or neurodevelopment
  – Formula feeding significantly increased the risk of necrotising enterocolitis

• McGee 2019:
  – Supplemented, nutrient enriched DHM and preterm formula results in comparable growth and body composition in young children born VLBW
Maternal milk has a more significant effect on:

• NEC
• Improved neurodevelopmental scores
• Other morbidities
Why?

• Differences in stage of lactation (term vs preterm milk)
• Great changes in DHM from the point of milk expression to infant feeding
  – Secretory IgA
  – Growth factors
  – CD-114
  – Myoinositol
  – Bioactive hormones
  – Stem cells
  – Lipid loss
  – Microbiome
  – Lactoferrin
Improving Outcomes with DHM

• Cacho 2017. Frontiers in Microbiology: Can DHM be “inoculated” with MOM from mothers of preterm infants to restore the live microbiota?

• Morlacchi 2017 Journal Translational Medicine: Interventional study in which targeted fortification was performed by adding specific quantities of macronutrients to human milk to obtain ratios of fat (4.4g), carbohydrates (8.8g) and protein (3.0g) per 100 ml.

• Retort processing, UV radiation, high pressure-high heat pasteurization
Targeted Fortification

• The process where Mom’s Own Milk (MOM) or Donated Breast Milk (DBM) is analyzed to assess its macronutrient content, and then fortified to meet the macronutrient target for the premature baby.

• MIRIS human milk analyzer (FDA approved)

• “Targeted or adjustable versus standard diet fortification for growth and development in very low birth weight infants receiving human milk” (Fabrizio, Tzaski, Brownell, Esposito, Lainwala, Lussier, Hagadorn)
Review comparing three approaches to human milk fortification for preterm infants:

- **Standard**: assumes that all breast milk has an average caloric content and macronutrient composition and then fortifies with a predetermined amount of fortifier.

- **Adjustable**: addition of fortifying nutrients is individualized using the infant’s metabolic response to enteral protein intake, as measured by blood urea nitrogen (BUN 9-16 mg/dl) adding extra protein if the BUN remains low.

- **Targeted**: individualizes fortification using the results of human milk analysis, specifically adding extra protein, fat, or carbohydrate based on the macronutrient concentration measured.
Recap

- Preterm infants are at risk for a long list of morbidities related to prematurity.
- Human Milk has shown to reduce those morbidities (dose response research).
- Human Milk = MOM and/or DHM.
- DHM decreases incidence and severity of NEC without sacrificing growth.
- Targeted fortification.
THE MORE MOTHER’S OWN MILK THE BETTER!!!
What are the factors that affect the duration of mother’s own milk receipt in the preterm population?
Providing Milk for VLBW Infants: A Challenging Task

• Volume of milk and duration of breastfeeding are decreased in mothers of VLBW infants
  (Chatterton 2000, Hill 2005)

• VLBW Mothers report low milk supply as most common reason for discontinuing milk expression
  (Cockey 2004)

• Stress, infant separation, early return to work and maternal medical complications all contribute to decreased milk expression in this population
Providing Milk for VLBW Infants: A Challenging Task

Preterm infants whose mothers failed to supply at least 75% of daily nutrition as breast milk feedings at day 14 were more likely to be exclusively formula fed 6 weeks after discharge

(Morag 2017)
Purpose: To further understand the relationship between human milk intake in premature newborns and their growth, development and health status

Three umbrella research initiatives:

• A NICU-specific nutrition and clinical database

• A human milk analyzer measuring the macronutrient composition of a mother’s own milk and donor human milk

• A wet lab dedicated to biochemical analysis of human milk
Predictors of mother’s own milk feeding at discharge in VLBW infants in the Connecticut Children’s NICU

Purpose:
To evaluate predictors of Mother’s Own Milk (MOM) receipt in VLBW infants at discharge using a granular data set and rigorous methodology
Methods

• Inclusion criteria:
  – Inborn between August 1, 2010 and July 31, 2015
  – Born at ≤ 32 weeks of gestation or ≤ 1,800 grams (DHM receipt and database criteria)

• Data Collection:
  – Data were abstracted from in-hospital medical records by NICU Lactation Consultants only
  – Outcome measure = MOM receipt at discharge only (no DHM)
Results

• 570 observations available for review
• Excluded deceased infants (n=19) and those transferred to another institution (n=123)
• 428 observations were included in the analyses:
  – 258 (60.3%) received MOM at discharge
  – 170 (39.7%) did not receive MOM at discharge
Data for Analysis

- Maternal Characteristics:
  - Race
  - Hispanic ethnicity
  - Marital Status
  - Partner support
  - Insurance
  - Poly Cystic Ovarian Syndrome
  - Assisted Reproductive Technology
  - Maternal age
  - BF duration goal (yes/no)
  - Feeding intention
  - Pump resource
  - Volume pumped
  - Pump type
  - CV meds
  - Delivery mode
  - Prenatal Care

- Acuity Characteristics:
  - Gestational age
  - NEC Stage 2 or 3
  - Sepsis
  - Total vent days
  - LOS
  - Multiple Gestation

- Diet Characteristics:
  - % MOM intake
  - % DHM intake
## Results: Multivariable Logistic Regression for Breast Milk Receipt at Discharge

<table>
<thead>
<tr>
<th>Infant and Maternal Demographics</th>
<th>B</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Age</td>
<td>1.20</td>
<td>(1.05, 1.38)</td>
<td>0.008</td>
</tr>
<tr>
<td>Maternal Age</td>
<td>1.10</td>
<td>(1.04, 1.17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>0.99</td>
<td>(0.98, 1.00)</td>
<td>0.042</td>
</tr>
<tr>
<td>Proportion of Total Diet MOM 10%↑</td>
<td>1.95</td>
<td>(1.73, 2.19)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Conclusion

• As the proportion of MOM increased by 10%, the odds of receiving MOM at discharge increased by 93%

• The only modifiable factor that is significantly associated with MOM receipt at discharge in the VLBW population is proportion of diet that is MOM throughout the NICU stay
Implications

Strategies to improve the development and maintenance of a strong milk supply are crucial to improving the duration of breast feeding and breast milk feeding in this vulnerable population.
Promoting Human Milk Feedings in Preterm Infants

Initiation:

• Education regarding hormonal contraception and potential impact on milk supply
• Screening for risk factors for delayed or impaired lactation (e.g. hypertension, obesity, Cesarean delivery)
• Do not use exclusive hand expression in the absence of breast pump stimulation (Lussier 2015)
• Initiate pumping within the first hour after birth
• Hospital Grade Breast Pump
• NICU specific lactation support

(Meier 2017)
Promoting Human Milk Feedings in Preterm Infants

Coming to volume:

• Education regarding crucial early time period
• Share HM targets (≥500 mL/d) by day 14
• Encourage pumping log
• Assess pumping technique
• Assess for correct breast shield sizing, pumping pressures, and thorough breast emptying  (Meier 2017)
Promoting Human Milk Feedings in Preterm Infants

Maintenance of Established Lactation:

• Weekly meeting to review and update personal feeding goals
• Proactively review common scenarios that reduce HM volume during the late NICU hospitalization
• Breastfeeding followed by pumping
• Support re. returning to work
• Incorporate NICU-based breastfeeding peer counselors (Cornell 2016) and mother-to-mother support for long-term pumping

(Meier 2017)
Pumping Guidelines

• Early initiation (within 1 hour of delivery)
• Frequent (q3h) pumping with a hospital grade electric breast pump
• “Hands on Pumping” and Hand Expression (Making Enough Milk; The Key to Successful Breastfeeding. Jane Morton MD)
Keriton Milk Management System

- App based system
- Kare Mom, Kare Nurse, Konnect, Klick
- Desktops, mobile devices, ipads etc.
- Improves quality and safety of human milk and formula (bar code scanning, reports etc.)
- Innovative technology:
  - Track milk expression and supply
  - Text message to moms
  - Pictures with message
Benefits of Direct Breastfeeding

• Skin to skin contact
• Improved milk supply
• Baby led feedings: reflux, digestion and obesity
• Communication between infant and mother (? Saliva)
• Bonding, anxiety, PPD
• Maternal feeding goals****
Closing Thoughts

• Human Milk (both MOM and DHM) feeding improves clinical outcomes in preterm infants
• Research shows that the more MOM an infant receives in the NICU the greater the impact on clinical outcomes
• Study results reinforce the importance of developing a strong milk supply early on
• Resources should be allocated to improve lactation support for families as well as DHM programs
• Further research:
  – strategies to improve duration of milk expression in preterm mothers
  – Improve clinical use of DHM (targeted fortification)
BREASTFEEDING

It Rocks!