Mammalian lactation patterns and milk composition have evolved over millions of years to support the survival, growth, and development of mammalian offspring.
Human Infant

- Largest brain of all mammals
- Because the brain is large, the head is large
- If the human fetus were to remain in utero and reach the maturity of other mammals, the head would be too large for normal delivery
- Thus, the human is the most “immature” of all mammals at the time of term birth

Human Milk has evolved to support metabolic activity and specific development of the brain:

- Provide ready substrate to support the metabolic activity of the largest brain in the mammalian kingdom
  - High concentrations of lactose and triglycerides
  - Provide unique fatty acid profiles that facilitate
    - optimal structural development and myelination
- Provide a unique proteome that prioritizes neurodevelopment over body growth

Beck KL et al, 2015; Hassiotou F2014; Keunen, 2015; Sherman 2015

Human Milk has evolved to:

- Grow the human body slowly
  - Lowest protein of all mammalian milk
- Protect, develop and program many body systems through synergistic functions:
  - immunomodulatory, anti-inflammatory, gut-colonizing, and epigenetic mechanisms

Early Nutrition Programming

**DOHAD:** Developmental Origins of Health and Disease

The first 1000 days is a critical window for human development:
- 270 days of gestation
- 365 days = 1st year post-birth
- 365 days for 2nd year post-birth

- Organs, immunomodulatory and enzymatic pathways develop and are influenced by early diet
- Early diet and growth trajectories influence childhood and adult health by multiple mechanisms

### Human Milk Feedings in the Neonatal Intensive Care Unit

- Dose-dependent reduction the risk / incidence / severity of:
  - NEC
  - Late Onset Sepsis
  - Bronchopulmonary Dysplasia
  - Retinopathy of Prematurity
  - Neurodevelopmental problems at 20 months CA
  - Rehospitalization after NICU discharge

### Mothers of VLBW Infants are Completely Breast-Pump Dependent

- Must access and self-pay for effective breast pump
- Majority have lactation risks
- Many lactation risks are unmodifiable by motivational and behavioral interventions
- Require evidence-based, NICU-specific lactation care that is deemed too difficult or costly to provide in many institutions

Copyright Rush Mothers’ Milk Club, 2016. All rights reserved.
Pasteurized Donor Human Milk is the Global Standard when Mothers’ Own Milk is Unavailable

Moro, et al, 2015; Perrine et al, 2013

The use of donor human milk has a rich history in neonatal care throughout the world

What is the evidence for the use of DHM?

Why are outcomes dissimilar for MOM and DHM?

What is the concern about the “human milk-fed” metric?

Does the introduction of a DHM feeding program impact the provision of MOM?

Are limited resources invested into acquiring and creating a DHM infrastructure instead of into evidence-based practices to acquire MOM?
• DHM (versus formula) reduces the risk, incidence/severity of NEC
• DHM has no favorable impact on other morbidities, including late onset sepsis, chronic lung disease, retinopathy of prematurity and/or neurodevelopmental outcome, for which MOM is protective
• DHM is associated with slower growth rates when compared to MOM or formula

The lack of impact on other morbidities suggest that the mechanism protecting VLBW infants from NEC is the absence of bovine-based products instead of DHM bioactivity

Clinical Outcomes

Experimental Mechanisms

Infant Formula: Separate Detrimental Impact

- Increases Intestinal Permeability: Undigested casein attracts neutrophils which separate the tight junctions, allowing entry of bacteria and toxins into the mucosa
- Direct Cytotoxicity of Epithelial Cells: Components in digested and undigested formula are directly cytotoxic to intestinal cells in animal studies and incubated intestinal cell lines
Why is the impact of DHM different from MOM with respect to outcomes?

Mechanisms of Protection with MOM that are Reduced or Lost in DHM

- Longitudinal changes in HM composition
  - Appear to mirror the biology of the recipient infant
- Differences in mammary maturity and HM product
  - PT MOM more protective with respect to most components
- Losses with freeze-thaw cycles
- Losses with pasteurization
- Losses with digestive processes
- Addition of fortifiers not tested previously with DHM
The most profound “lack of fit” occurs when donor human milk replaces mothers’ own colostrum and transitional milk during the early post-birth period. Early mothers’ own milk mirrors the preterm infant’s biology:

- High protein as a function of protective and developmental (not nutritive) proteins
- Preterm colostrum is more like amniotic fluid than it is like mature milk
- Multitude of gut-colonizing mechanisms

Intended to nourish a term infant who is past the need for “front-loaded protection”:

- Relatively low levels of protective proteins, many of which further altered with processing
- Absence of fundamental gut-colonizing mechanisms

Bioactive Proteins are Highest During the Early Lactation Period—Mirror the Biology of the Newborn


Total Protein in Term and Preterm Milk Over 1st Month of Lactation

Dvorak B, Pediatric Research, 2003
Genes in the mammary gland upregulate bioactive immunoprotective proteins in early lactation

- Colostrum
- Transitional Milk
- Mature Milk


Secretory IgA as a Proportion of Total Protein in Term and Preterm Milk


Growth Factors During the First Month of Lactation and Impact of Mammary Maturity

Stalakai CG et al., Pediatric Research 1999

Copyright Rush Mothers’ Milk Club, 2016. All rights reserved.
Growth Factors Target Enterocytes to Markedly Increase Surface Area and Stimulate Epithelial Cell Migration and Turnover in the GIT

Tapper et al., 1979; Walker, 2010

Colostrum Stimulates this Growth and Maturation More Effectively than Mature Human Milk

Human Milk (11-30 days)

Tapper et al., 1979; Walker, 2010

Lactoferrin concentrations decline by as much as 50% between 0-5 days and 11-30 days post-birth in term milk
Soluble CD14 mediates bacterial-enterocyte cross-talk in the immature intestine

- Soluble CD-14 is a pattern recognition receptor serving as co-receptor for TLR-II and TLR-IV
  - Mediates bacterial-enterocyte "cross-talk"
- Present in serum, amniotic fluid, breast milk, and other fluids, but not in infant formulas


Myoinositol supplementation reduces the risk of BPD and ROP

- Essential nutrient for human cells
- Promotes maturation of surfactant phospholipids
- RCTs reveal efficacy of supplementation
- Human milk has high concentrations EARLY in lactation and preterm milk has higher concentrations than term milk
- Human milk-fed infants have higher serum concentrations


Myoinositol concentrations mirror the biology of the infant with highest concentrations in early lactation in preterm milk

Myo-inositol declines significantly over the course of lactation

Bioactive milk hormones that regulate (and perhaps, program) metabolism decrease markedly from birth to two months of age

Mechanisms of Protection with MOM that are Reduced or Lost in DHM

- Longitudinal changes in HM composition
  - Appear to mirror the biology of the recipient infant
- Differences in mammary maturity and HM product
  - PT MOM more protective with respect to most components
- Losses with freeze-thaw cycles
- Losses with pasteurization
- Losses with digestive processes
- Addition of fortifiers not tested previously with DHM
Stem Cells are highly specific to the mother-infant dyad (including infant gestational age)


- The human infant consumes millions of cells each day
- They are the highest in hindmilk at the end of the feeding
- Once inside the recipient infant, they:
  - Survive the stomach
  - Enter the blood and remain in the blood after breastfeeding ends
  - Migrate to body organs and differentiate into liver, pancreatic and brain cells
  - Reach the spleen, liver and thymus

Hassioutou F, Hartmann PE, Adv Nutr 5: 770-778, 2014

Slow weight gain on donor human milk is more than low protein that is corrected by “super-fortification”

Significant lipid (up to 58.9%) and protein (13.6%) loss with each successive process in the path of donor milk use

<table>
<thead>
<tr>
<th>Component</th>
<th>Pasteurization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactoferrin</td>
<td>Abolished</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>57-80% reduction</td>
</tr>
<tr>
<td>Immunoglobulins (sIgA, IgG)</td>
<td>66% reduction</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Up to 60% reduction</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Destroyed</td>
</tr>
<tr>
<td>Insulin</td>
<td>33% reduction</td>
</tr>
<tr>
<td>Soluble CD14</td>
<td>46% reduction</td>
</tr>
<tr>
<td>IL-1, IGF-2</td>
<td>88% reduction</td>
</tr>
<tr>
<td>Proteases</td>
<td>40% reduction</td>
</tr>
<tr>
<td>Amylase</td>
<td>Different profile</td>
</tr>
<tr>
<td>Lipases (all)</td>
<td>15% reduction</td>
</tr>
<tr>
<td></td>
<td>Abolished</td>
</tr>
</tbody>
</table>

Loy et al., Pediatr Res., 2011
Underwood, in Diet and Nutrition in Critical Care, 2015


Martin et al. Human milk is a source of lactic acid bacteria for the infant gut. J Pediatr 2003; 143: 754-8

Cabrero-Rubio et al. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. AJCL, 2012, 82 (2), 564-565.


• The milk microbiome is exceptionally mother-infant specific, and is accompanied by an array of prebiotic oligosaccharides that serve as “food” for the probiotic bacteria.
• No study of probiotics has compared impact for DHM and MOM in recipient infants, including whether exogenous probiotics compete with MOM oligosaccharides.
### Component Pasteurization

<table>
<thead>
<tr>
<th>Component</th>
<th>Pasteurization</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular</td>
<td>Abolished</td>
<td>Minimal change in the concentration of a human milk component pre- and post-pasteurization says NOTHING about the bioactivity of the preserved component</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>57-80% reduction</td>
<td></td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>66% reduction</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins (sIgA, IgG)</td>
<td>Up to 60% reduction</td>
<td></td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Destroyed</td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td>33% reduction</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>46% reduction</td>
<td></td>
</tr>
<tr>
<td>Soluble CD14</td>
<td>88% reduction</td>
<td></td>
</tr>
<tr>
<td>IGF-1, IGF-2</td>
<td>40% reduction</td>
<td></td>
</tr>
<tr>
<td>Proteases</td>
<td>Different profile</td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>15% reduction</td>
<td></td>
</tr>
<tr>
<td>Lipases (all)</td>
<td>Abolished</td>
<td></td>
</tr>
</tbody>
</table>

- Fat concentrations may not be affected by pasteurization, but the lipases are completely destroyed.
- Fats cannot be digested even though they are preserved.
- Impact: slower weight gain on donor human milk with adequate fat concentrations.
- Solution: Fortify with more protein???
Even if absolute concentration does not decrease, the bioactivity can be reduced or abolished.

Anti-infectives may show minimal concentration change, but bioactivity is affected.

Mechanisms of Protection with MOM that are Reduced or Lost in DHM:

- Longitudinal changes in HM composition
  - Appear to mirror the biology of the recipient infant
- Differences in mammary maturity and HM product
  - PT MOM more protective with respect to most components
- Losses with freeze-thaw cycles
- Losses with pasteurization
- Losses with digestive processes
- Addition of fortifiers not tested previously with DHM

Mechanisms of Protection with MOM that are Reduced or Lost in DHM

- Longitudinal changes in HM composition
  - Appear to mirror the biology of the recipient infant
- Differences in mammary maturity and HM product
  - PT MOM more protective with respect to most components
- Losses with freeze-thaw cycles
- Losses with pasteurization
- Losses with digestive processes
- Addition of fortifiers not tested previously with DHM
Fecal Calprotectin Concentrations Pre- and Post-Fortification of Human Milk with Bovine Products

**Fecal Calprotectin Concentrations**


**Why is the impact of DHM different from MOM with respect to outcomes: Cumulative impact with Lactoferrin as an example**

- Longitudinal changes in HM composition
- Differences in mammary maturity and HM product
- Losses with freeze-thaw cycles
- Losses with pasteurization
- Losses with digestive processes
- Misfit between own mothers’ milk and donor components
- Addition of fortifiers not tested previously with DHM


**Lactoferrin concentrations decline by as much as 50% between 0-5 days and 11-30 days post-birth, and stabilize at about 30% of baseline by 2 months**

Lactoferrin concentrations decrease as much as 50% after 3 months of freezing (bioactivity also decreases)

Rollo DE et al, J Perinatol 2014

<table>
<thead>
<tr>
<th>Component</th>
<th>Pasteurization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular</td>
<td>Abolished</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>57-80% reduction</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>66% reduction</td>
</tr>
<tr>
<td>Immunoglobulins (slgA, IgG)</td>
<td>Up to 60% reduction</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>Destroyed</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>33% reduction</td>
</tr>
<tr>
<td>Insulin</td>
<td>46% reduction</td>
</tr>
<tr>
<td>Soluble CD14</td>
<td>88% reduction</td>
</tr>
<tr>
<td>IGF-1, IGF-2</td>
<td>40% reduction</td>
</tr>
<tr>
<td>Proteases</td>
<td>Different profile</td>
</tr>
<tr>
<td>Amylase</td>
<td>15% reduction</td>
</tr>
<tr>
<td>Lipases (all)</td>
<td>Abolished</td>
</tr>
</tbody>
</table>

Ley et al., Pediatr Res, 2011
Underwood, in Diet and Nutrition in Critical Care, 2015.

Iron supplementation (as in HMF) reduces the bioactivity of lactoferrin

Bacterial growth with iron added to MOM

Bacterial growth in MOM without iron added

Bullen JJ et al, British Medical Journal, 1972

Copyright Rush Mothers’ Milk Club, 2016.
All rights reserved.
What is the impact of a DHM program in the NICU on the rates of MOM provision in VLBW infants?

Use of Donor Human Milk and Maternal Breastfeeding Rates: A Systematic Review

J Human Lactation, 2016

Thomas Williams, MPH, FCPH, Harish Nair, MD, PhD, Judith Simpson, MD, and Nicholas Embleton, MD

Impact of Donor Milk Availability on Breast Milk Use and Necrotizing Enterocolitis Rates

J Peds 2016

• Multiple ways of measuring the “impact” makes interpretation difficult
• Overall rates not reduced, but early data suggest a racial disparity for African-American mothers of VLBW infants (who switch to DHM)

Original Research

“It’s Somebody Else’s Milk”: Unraveling the Tension in Mothers of Preterm Infants Who Provide Consent for Pasteurized Donor Human Milk

J Human Lactation, 2015

Anita Esquerra-Zwiers, MSN, RN, Beverly Rossman, PhD, RN, Paula Meier, PhD, RN, Janet Engstrom, PhD, RN, CNM, WHNP-BC, Judy James, BSN, RN, and Alisha Patel, MD

• Mothers less concerned about safety and quality than the fact DHM is “somebody else’s milk”
• Are told it is the one thing they can do, but it is no longer true
• Resent being asked for consent prior to own attempts to express milk
• Want separate consent process (not bundled in with UAC and ventilator) and personal communication with MDs and RNs

Use of Human Milk Feeding Nomenclature is Misleading

- Combined use of MOM and DHM in the same metric without specifying relative proportions of the two milks
- Failure to demonstrate positive outcomes and/or poor growth with primarily DHM allows generalization to MOM
- Research example: probiotic supplementation
- Quality improvement example: Best practices to acquire DHM and MOM are different and compete for limited funds
Human Milk from an Economic Perspective

Cost of Human Milk vs Formula and Donor Human Milk Feeding

- The "upstart" costs of a human milk feeding program in the NICU are thought prohibitive.
- Mothers do not maintain adequate milk output because of the lack of evidence-based lactation services that are specific to breast pump dependent mothers.
- Donor human milk is the default when "our mothers just can't establish and maintain lactation".

Johnson et al., 2013

Economic Benefits and Costs of Human Milk Feeding: A Strategy to Reduce the Risk of Prematurity-Related Morbidities in Very-Low-Birth-Weight Infants

Tricia Johnson, PhD

Summary

- Donor human milk offers protection from NEC, but not sepsis, BPD, and neurodevelopmental problems into toddlerhood.
- The impact of donor human milk is likely the "avoidance of formula" instead of a separate contribution to outcome.
- Contrary to common assumptions, pasteurization is only one of many mechanisms by which donor human milk is remarkably "second best" to mothers' own milk. Other primary factors are the stage of lactation and maturity of the mammary gland.
- Combining mothers' own milk and donor human milk into the same "human milk metric" is not evidence-based for either research or quality improvement projects.
- Own mothers' milk is less expensive to acquire than either donor human milk or formula, but requires different resources that are often considered unnecessary in today's NICU environment.
- The impact of donor human milk on mothers' own milk feeding in the NICU is unclear.
- Clinicians must frame the evidence-based argument for prioritizing mothers' own milk over donor human milk with payers and hospital administrators.