Donor Human Milk and Mothers’ Own Milk: Why are Outcomes Different for VLBW Infants?

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Mothers’ Own Milk Feedings and VLBW Infants

Human Milk Feedings in the Neonatal Intensive Care Unit
Paula P. Meier, MD, Alaka Patel, MD, Harold R. Boger, MD, Tricia Johnson, PhD, Beverly Raccut, MD, and Beryl H. Begun, MD, Rush University Medical Center, Chicago, IL, USA. Department of Women, Children and Family Nursing, Rush University Medical Center, Chicago, IL, USA. Department of Pediatrics, Rush University Medical Center, Chicago, IL, USA. Department of Infant Nutrition, Rush University Medical Center, Chicago, IL, USA. Department of Health Systems Management, Rush University Medical Center, Chicago, IL, USA.

Diet and Nutrition in Critical Care, 2015

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

Savings Attributable to MOM in the NICU

Cost Savings of Human Milk as a Strategy to Reduce the Incidence of Necrotizing Enterocolitis in Very Low Birth Weight Infants
Tricia Johnson, PhD
J Perinatology 2013

Influence of own mother’s milk on bronchopulmonary dysplasia and costs

Arch Dis Child, 2016

Aloka Patel, MD
Early Nutrition Programming

- The first 1000 days is a critical window in human development that is heavily influenced by early nutrition
  - 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

Acquiring MOM from Completely Breast-Pump Dependent Mothers of VLBW Infants

- Must access and (often) self-pay for effective breast pumps or are given ineffective and inefficient breast pumps by payers
- Majority have lactation risks and many risks appear to be unmodifiable by motivational/behavioral interventions
- Require evidence-based, NICU-specific lactation care that is deemed too difficult or costly to provide in many institutions

Pasteurized Donor Human Milk has become the Global Standard when Mothers’ Own Milk is Unavailable

- Moro, et al, 2015; Perrine et al, 2013; Meier et al., 2016
The use of donor human milk has a rich history in neonatal care throughout the world.

- 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
Multi-site RCT of DHM vs formula as supplement to MOM

363 VLBW infants randomized to feeding group

Primary outcome measure = neurodevelopmental outcome at 18 months

No statistically significant differences in mean scores

27.2% of DHM-fed versus 16.2% of formula-fed infants had scores <85 (p=.02)

NEC ≥ stage 2 = 1.7 for DHM and 6.6 for formula (p = .02)

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

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Why is the impact of DHM different from MOM with respect to other morbidities?

– 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
– 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
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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
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

Colostrum Stimulates this Growth and Maturation More Effectively than Mature Human 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

In µg/ml; *n=22 (0-71 days post-birth)
**n = 10 (≤ 6 days post-birth)


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

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


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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

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

<table>
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<td>Soluble CD14</td>
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Ley et al., Pediatr Res, 2011
Underwood, in Diet and Nutrition in Critical Care, 2015.
**Human Milk is a Source of Probiotic Bacteria that are eradicated with pasteurization: The Milk Microbiome**


Martin et al. Human milk is a source of lactic acid bacteria for the infant gut. *J Pediatr* 2010; 143: 754-6.

Cabrero-Rubio et al. The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery. *AJCJL* 2012; 38 (3): 564-565.


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**Characterization of the Diversity and Temporal Stability of Bacterial Communities in Human Milk**

- 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

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**Human milk: a source of more life than we imagine**


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The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery\(^1-4\)

Alex Cabrero-Rubio, JF Camero-Cahedo, Kori Lastine, Jeppe Schouten, Rika Inoue, and Alex Wier
Minimal change in the concentration of a human milk component pre- and post-pasteurization says **NOTHING** about the bioactivity of the preserved component.

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**Cellular Abolishment**

- Lactoferrin: 57-80% reduction
- Interleukin-10: 66% reduction
- Immunoglobulins (IgA, IgG): Up to 60% reduction
- Antioxidants: Destroyed
- Adiponectin: 33% reduction
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- Soluble CD14: 88% reduction
- IGF-1, IGF-2: 40% reduction
- Proteases: Different profile
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- Lipases (all): Abolished

**Lipid and Protein Loss**

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

**Impact on Fat Concentrations**

- Fat concentrations may not be affected by pasteurization, but the lipases are completely destroyed.
- Fats cannot be digested even though they are preserved.
- Impact: slow 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
Fecal Calprotectin Concentrations Pre- and Post-Fortification of Human Milk with Bovine Products


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)

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Underwood, in Diet and Nutrition in Critical Care, 2015
Iron supplementation (as in HMF) reduces the bioactivity of lactoferrin

Bullen JJ et al, British Medical Journal, 1972

Bacterial growth with iron added to MOM

Bacterial growth in MOM without iron added

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

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

Thomas Williams, MRCPPCH, Harsh Nau, MD, PhD. Judith Simpson, MD, and Nicholas Emblion, MD

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

J Human Lactation, 2016

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)
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

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”

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

- The Institutional Cost of Providing 130 oz of Human Milk for Very Low-Birth-Weight Infants in the Neonatal Intensive Care Unit
- The Initial Cost of Providing Human Milk to Very Low-Birth-Weight Infants

Tricia Johnson, PhD

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Tricia Johnson, PhD
Evidence-Based Methods That Promote Human Milk Feeding of Preterm Infants
An Expert Review

• Review of best NICU practices that prioritize high-dose, long exposure mothers’ own milk (versus donor human milk feedings) in the NICU
• Targets the cost-effectiveness of investments into human milk acquisition
• Table 1 provides an itemization of the “cost” (in 2015 USD) per mother/infant for an average duration of hospitalization = 71 days.

Access to Hospital Grade, Electric Breast Pumps for use in the NICU and in the Home (rental)

$120 USD (90 days)

Single Use Collection Kit for Use with the Electric Pump

$32.91 (one-time purchase)
Milk Storage Containers in the NICU

- Single use, food grade, sterile human milk storage containers

$89.36 for 6 containers daily for 71 days

Breast Shield Sizing

- Many mothers need a smaller or larger size breast shield to use the breast pump comfortably, effectively, and efficiently

$7.00 (one time cost)

Toolkit for Translating the Evidence about Human Milk for NICU Infants into Best Clinical Practices

$15.00 (one time cost)
Waterless Human Milk Warmers

- For avoidance of water contamination when warming milk
- To warm milk to body temperature of the infant

$30.07 for 71 days

Purchase of Sterile Liners for the Waterless Milk Warmer (replaced each day)

$230.75 for 71 days

Creamatocrit Purchase for Quick, Easy Measurement of Lipid and Calories in Pumped Milk

$0.38
Summary

- DHM offers protection from NEC, but not sepsis, BPD, ROP and neurodevelopmental problems into toddlerhood.
- The impact of DHM is significant and is an indication to use DHM when the risk of NEC is highest. The likely protective mechanism is the "avoidance of formula" instead of a separate contribution of DHM.
- Pasteurization is one of many mechanisms by which DHM is "second best" to MOM. Other factors include: the stage of lactation, maturity of the mammary gland, freeze-cycles, endogenous digestive processes and handling and feeding practices in the NICU.
- Combining MOM and DHM into the same "human milk metric" is not evidence-based for either research or quality improvement projects.
- MOM is less expensive to acquire than either DHM or formula, but requires different resources that are often considered unnecessary or "inefficient" in today's NICU environment.
- The impact of DHM on MOM provision in the NICU is unclear on the basis of current studies.
- Clinicians must frame the evidence-based argument for prioritizing MOM over DHM with payers and hospital administrators.