Human Milk: Personalized Medicine in the NICU

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Conflicts of Interest

• None to report
Objectives

After this talk, you will be able to:

• Interpret current science of human milk to talk with NICU families about its importance

• Recall at least two examples of how human milk is personalized in mother-infant dyads

• Identify how NICU handling and delivery practices may impact bioactive components of human milk
The Big Picture

• Human milk is not *just* nutrition and immunity, it contains compounds which provide *signal* and *communication* between mother and infant

• These “non-nutritive” compounds are impacted by “everyday” practice in the NICU

• ANY human milk is better than NO human milk, but how can we get closer to the “ideal”? 
Gestational Age at Birth

- 23 weeks
- 34 weeks
- 40 weeks

**Immature and under-developed organs:**
Intestines, Heart, Lungs, Brain, Kidneys, Liver, etc.
Benefits of Human Milk for Preterm Infants

In the NICU
• Reduced incidence of late onset sepsis
• Decreased NEC and severity of NEC
• Retinopathy of Prematurity (ROP)
• Improved Neurodevelopmental Outcomes

After Discharge into Childhood
• Fewer re-hospitalizations in the first year of life
  • ↓ Metabolic Syndrome
  • ↓ Insulin Resistance
    • ↓ Blood Pressure
    • ↓ Risk of Asthma
    • ↓ Risk of SIDS
• ↓ Respiratory Tract Infections
  • ↓ Ear Infections
• ↓ Risk of Childhood Cancer
Benefits for Breastfeeding Mothers

Mothers Who Breastfeed Have Reduced Risk of Developing:

- Breast Cancer
  - Greater reduction for each birth and each month of breastfeeding
  - In women BRCA1+ → Reduces risk by 1/3
- Ovarian Cancer
- Rheumatoid Arthritis
- Type 2 Diabetes
- Cardiovascular Disease
  - High Blood Pressure, High Cholesterol
“Bioactive” Components of Milk

• Bioactivity (noun): “Any effect on, interaction with, or response from living tissue”
  – Dictionary.com

• Bioactive (adjective): “having or producing an effect on living tissue”
  – Dictionary.com
Milk Varies Between Individuals: Milk is Different for Boys and Girls

- More fat for sons, more milk for daughters (Hinde, 2009)

- Driven by first infant
  - Very high fat and high protein for sons, and more dilute for first born daughters (Hinde, 2009)

- More calcium for girls (Hinde, 2013)
  - This may explain why there is faster skeletal development in female rhesus, chimps, and humans
Milk Varies Between Individuals: Milk is Different for Boys and Girls

• Why is it different? (Hinde, 2014)
  – Developmental priorities
  – Reproductive value (in terms of grand-offspring to the mother)

• When does the difference begin?
  – Is it the fetus that signals the mammary glands during development?
  – Is it a form of hormonal co-regulation of the infant-maternal dyad?
  – Or a combo of both
Bioactive Factors in Human Milk: Molecules and Cells

• Antimicrobial Factors
  – IgA, IgM, IgG, Lactoferrin, Lysozyme, Complement C3, Leukocytes, Bifidus Factor, Lipid and Fatty Acids, Antiviral Mucins, GAGs, Oligosaccharides

• Growth Factors
  – Epidermal (EGF), Nerve (NGF), Insulin-like (IGF), Transforming (TFG), Taurine, Polyamines

• Cytokines and Anti-inflammatory Factors

• Digestive Enzymes
  – Amylase, bile acid-stimulating esterase, bile acid-stimulating lipases, lipoprotein lipase

• Hormones
  – Feedback inhibitor of lactation (FIL), insulin, prolactin, thyroid hormones, corticosteroids, ACTH, oxytocin, calcitonin, parathyroid hormone, erythropoietin

• Transporters
  – Lactoferrin, Folate, Binder, Cobalamin Binder, IgF finder, Thyroxine Binder, Corticosteroid Binder
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- **Cytokines and Anti-inflammatory Factors**
  - Tumor Necrosis Factor, Interleukins, Interferon-g, Prostaglandins, A1-Antichymotrypsin, A1-Antitrypsin, Platelet Activating Factor, Acetyl hydrolase
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**Human Milk Oligosaccharides**

Cannot be digested by humans

*Two Roles (there are more!):*

- Act as a “decoy” in the gut to prevent “bad” bacteria from attaching to mucosal surfaces, ↓ infection
- Feed the “good” gut bacteria (prebiotic)
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**Epidermal Growth Factor:** Stimulates cell proliferation and maturation

**HB-EGF (heparin-binding):** Protects against damage from hypoxia/ischemia

**NGF (nerve):** Promotes neuron growth and maturation

(Ballard & Morrow, 2013)
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*Erythropoietin: Promotes red blood cell production and intestinal development* 
(Ballard & Morrow, 2013)
Prebiotic vs. Probiotic

• Prebiotic:
  – Promotes growth and activity of beneficial bacteria (e.g. HMOs)

• Probiotic:
  – Live micro-organisms, seen as beneficial bacteria for the gut
Gut Bacteria (Microbiome) and Intestinal Health

- “Good” microbes in milk help protect infants
  - Bifidobacteria, lactobacillus
    - These bacteria might help regulate gene expression which promotes barrier protection in the gut (so the bad microbes can’t get out of the gut!) and digestion
    - Might reduce the inflammatory response in the gut
Human Milk Oligosaccharides (HMOs)

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Image From:
Moossavi et al., Cell Host & Microbe 2019 25, 324-335.e4DOI: (10.1016/j.chom.2019.01.011)
Just in: The Breastmilk “Mycobiome”

• Fungi is present in breastmilk

• Varies by delivery mode (Vaginal vs. C-section), geographic location, maternal age, and pre-pregnancy BMI

• Hypothesized bacteria-fungal interactions
Stem Cells in Human Milk

Stem Cells help the body grow, repair, renew

Properties of a Stem Cell:

Self Renewal
- Can make more of itself

Differentiation
- Can become a specialized cell
The Future of Human Milk

Human milk has long-term benefits, yet the mechanisms that link receipt of human milk to these remain unknown (e.g. cancer, neurodevelopment, cardiovascular disease)
Human Milk Stem Cells: A(n abbreviated) Timeline

First published study identifying these cells in full-term mothers’ milk
Human Milk Stem Cells: A(n abbreviated) Timeline

- Human milk cells have variable expression of pluripotency genes (typically found in hESCs)
  - OCT4, SOX2, NANOG
- In vitro differentiation into cell lines of all 3 germ layers
Human Milk Stem Cells: A(n abbreviated) Timeline

Mouse models show:
- Milk stem cells survive gut
- Found as functioning cells in multiple organs
  - Blood, thymus, liver, pancreas, spleen, brain
Human Milk Stem Cells: A(n abbreviated) Timeline

Stem-cell populations vary based on maternal/infant characteristics
Human Milk Stem Cells: A(n abbreviated) Timeline

2007: hMSC identified in milk for hospitalized preterm infants
Image from Briere et al., 2016
Milk Stem Cells are Found Throughout the Body

(Hassiotou et al., 2014; Aydin et al., 2018)
Stem Cell Therapy Improves Gut Barrier Function!

• Preterm rat pups received an intraperitoneal injection of stem cells or a control fluid and were then subjected to “experimental” NEC
  
  – Rats who received the stem cells had **less gut permeability**
  
  – **Concerns:**
    • Stem cell therapies can cause tumors and immunologic responses (not breastmilk stem cells though…)

(McCulloh et al., 2018)
Can Stem Cells “Heal” Intraventricular Hemorrhage?

- Germany
  - 31 VLBW infants with intraventricular hemorrhage (all received breastmilk)
  - 16 received nasal drops of breastmilk daily for 28 days

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<table>
<thead>
<tr>
<th>Condition</th>
<th>Intranasal Breastmilk</th>
<th>Comparative Group</th>
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<tbody>
<tr>
<td>Severe Porencephalic Defects</td>
<td>21% (3/14)</td>
<td>58% (7/12)</td>
</tr>
<tr>
<td>Progressive Ventricular Dilatation</td>
<td>71% (10/14)</td>
<td>91% (11/12)</td>
</tr>
<tr>
<td>Surgery for Post hemorrhagic Hydrocephalus</td>
<td>50% (7/14)</td>
<td>67% (8/12)</td>
</tr>
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**The researchers did not find any statistical significance, which means that these differences could be due to chance**

(Keller et al., 2018)
• Pathways of breast milk uptake in oral cavity and nasal passages
Human Milk is Protective in Infants with Congenital Heart Disease

• Exclusive human milk diet:
  – Lower risk of NEC
  – Better weight gain

(Davis & Spatz, 2018)
Exosomes and Intestinal Cell Health in Times of Stress

- Human milk contains exosomes
  - These vesicles have protein, lipid, and microRNA

- Exosomes were isolated from human milk

- Exosomes were added to Intestinal epithelial cells (in a dish) and exposed to a type of oxidative stress (hydrogen peroxide)
  - The exosomes protected the epithelial cells!

(Martin et al., 2018)
What Can You Do Today?

- Use fresh human milk whenever possible
- Get those infants to their mom’s breast! (First oral feeding should be at-breast!)
- Help and encourage mothers to provide as much as direct-breastfeeding as possible
- Delay the use of bottles when possible
- Help mothers transition to direct breastfeeding and understand what is “typical”
- Talk with families about human milk and its role as a personalized medicine
  - It is not “just” nutrition
References


