Milk as Medicine

• AAP Policy:
  • Breastfeeding & Use of Human Milk 2012
    • Human milk is species specific
    • All substitute feeding preparations differ markedly from it, making human milk uniquely superior for infant feeding
    • Its the reference or normative model against which all feeding methods must be measured

AAP SECTION ON BREASTFEEDING
http://pediatrics.aappublications.org/content/early/2012/02/22/peds.2011-3552.full.pdf+html
Pediatrics originally published online February 27, 2012; DOI: 10.1542/peds.2011-3552

Milk as Medicine

• “Milk as Medicine”
  • A substance or preparation of treating disease, something that effects well-being
  • The science and art of dealing with the maintenance of health and the prevention, alleviation or cure of disease
  • Professionals referencing human milk as a “medicine” that “only a mother can provide”


Milk as Medicine

• “Milk as Medicine”
  • “Major components of human milk are not primarily for nutrition, but for host defense”

*Hanson, LA (2004). Immunobiology of human milk.*
"Lack of breast milk may be the commonest immunodeficiency of infancy."

**Milk as Medicine**

**Dose-Response Benefits of Breastfeeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Lower Risk</th>
<th>Breastfeeding</th>
<th>Comments</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>77</td>
<td>NICU stay</td>
<td>Premature; exclusive HM</td>
<td>0.23</td>
<td>0.15-0.34</td>
</tr>
<tr>
<td>SIDS</td>
<td>36</td>
<td>≥1 mo</td>
<td>-</td>
<td>0.64</td>
<td>0.57-0.71</td>
</tr>
<tr>
<td>RSV Bronchiolitis</td>
<td>74</td>
<td>≥4 mo</td>
<td>-</td>
<td>0.28</td>
<td>0.24-0.32</td>
</tr>
<tr>
<td>Otitis media</td>
<td>23</td>
<td>Any</td>
<td>-</td>
<td>0.77</td>
<td>0.64-0.91</td>
</tr>
<tr>
<td>Otitis media</td>
<td>50</td>
<td>≥3 or 6 mo</td>
<td>Exclusive BF</td>
<td>0.50</td>
<td>0.39-0.67</td>
</tr>
</tbody>
</table>

**Milk as Medicine**

**Dose-Response Benefits of Breastfeeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Lower Risk</th>
<th>Breastfeeding</th>
<th>Comments</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>40</td>
<td>≥3 mo</td>
<td>Atopic family history</td>
<td>0.60</td>
<td>0.43-0.82</td>
</tr>
<tr>
<td>Asthma</td>
<td>26</td>
<td>≥3 mo</td>
<td>No atopic family history</td>
<td>0.7</td>
<td>0.60-0.82</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>27</td>
<td>≥3 mo</td>
<td>Exclusive BF (≥1 family history)</td>
<td>0.84</td>
<td>0.69-1.02</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>42</td>
<td>≥3 mo</td>
<td>Exclusive BF (≥1 family history)</td>
<td>0.56</td>
<td>0.41-0.79</td>
</tr>
</tbody>
</table>

**Milk as Medicine**

**Dose-Response Benefits of Breastfeeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Lower Risk</th>
<th>Breastfeeding</th>
<th>Comments</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay</td>
<td>77</td>
<td>Exclusive BF (≥1 mo)</td>
<td>Compared with BF (≥1 mo)</td>
<td>1.95</td>
<td>1.86-3.09</td>
</tr>
<tr>
<td>URTI</td>
<td>63</td>
<td>≥4 mo</td>
<td>Exclusive BF</td>
<td>0.30</td>
<td>0.20-0.51</td>
</tr>
<tr>
<td>URTI</td>
<td>72</td>
<td>≥4 mo</td>
<td>Exclusive BF</td>
<td>0.28</td>
<td>0.14-0.54</td>
</tr>
<tr>
<td>URTI</td>
<td>75</td>
<td>Exclusive BF (≥4 mo)</td>
<td>Compared with BF (≥6 mo)</td>
<td>4.27</td>
<td>1.27-14.35</td>
</tr>
</tbody>
</table>

**Milk as Medicine**

**Dose-Response Benefits of Breastfeeding**

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Lower Risk</th>
<th>Breastfeeding</th>
<th>Comments</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac Disease</td>
<td>52</td>
<td>≥2 mo</td>
<td>Gluten exposure when breastfeeding</td>
<td>0.48</td>
<td>0.41-0.69</td>
</tr>
</tbody>
</table>

American Academy of Pediatrics. "Milk as Medicine" originally published online February 27, 2012; DOI: 10.1542/peds.2011-15932
“Milk as Medicine”

- “Human milk is an evolutionary wonder whereby the lactating mother produces a species-specific nutritional and biologically active product that confers the best health to the human offspring”.


- For the purpose of my discussion today, either is OK… I just mean for as long as we have been having babies.

- Evolutionary Biology

  - For millennia woman have delivered and babies have been born –
    - At term
    - With labor after/with
    - Rupture of membranes
    - Vaginally delivered
    - Breastfed
    - Remained with their mother
    - Microbiome was colonized

- Evolutionary Discordance

  - Changing clinical practices
    - Preterm delivery
    - Elective C/S
    - Labor with/without ROM
    - Hyper-hygienic measures
    - Maternal/infant antibiotics
    - Limited mother/infant contact
    - Exposure to colostrum breast milk feeding

- Immunonutrition

  “The modulation of the immune and inflammatory responses in critically ill patients with the use of enteral feedings enriched with immune-enhancing ingredients”.

Milk as Medicine

Compelling Evidence to Support the Use of Human Milk Diets in the NICU

Immunity  Microbiome  Anti-Oxidants  NEC  Intolerance  Growth

“IT MIGHT LOOK LIKE I'M DOING NOTHING.... BUT ON A CELLULAR LEVEL I AM REALLY QUITE BUSY!”

It might look like I'm doing nothing.... but on a cellular level I am really quite busy!


Milk as Medicine

• “Critical Exposure Periods”
  – For the use of Human Milk
    • Colostrum as the transition from amniotic fluid
    • Transition from colostrum to mature milk feedings
    • Human milk feedings throughout the NICU stay
    • Human milk feedings after NICU, after discharge

Evolutionary Biology

Mucosal Immunologic System (MIS)
  – Provides a complex mechanical barrier and an inherent defense against pathogens that constantly threaten the human body

Mucosal Immunologic System (MIS)
  – Evidence suggests that these systems do not work independently, but an integrated network of tissue, cells, and signaling molecules

Milk as Medicine

• Mucosal Immunologic System (MIS)
  – The lining of the GI tract provides the largest interface with the external environment and is critical to host defense.

  - Epithelial Cells
  - Mucous Secretions

Gastrointestinal

Pulmonary


Milk as Medicine

• Colonization of the Microbiome
  • First Stage: Birth to 1 Week of Age
    • Role of mode of delivery is major determining factor
    • Composition of infant’s evolving microbiota initially defined by mother
    • Role of ROM, labor, SVD exposes the infant to maternal GI flora
    • Establishing colonization


Milk as Medicine

• Neonatal Microbiome
  – Delivery Mode: Colostrum Microbiome

WARNING
Mom’s Bottom About to Appear. REALLY!


Milk as Medicine

• Neonatal Microbiome
  – Delivery Mode: Milk Microbiome


Milk as Medicine

• Colonization of the Microbiome
  • Second Stage: 1-4 Weeks of Age
    • Role of infant’s diet is a major determining factor
    • Human milk has lower buffering capacity - acidic milieu potentiates growth of nonpathogenic bacteria
    • Human milk (including colostrum) has specific antibodies and oligosaccharides to support growth of commensal bacteria in the infant’s gut

Milk as Medicine

**Human Milk Oligosaccharides (HMO)**

- The high concentration and structural complexity of HMO are unique to human breast milk
- HMO provides the newborn with a variety of bioactive factors that promote a healthy **colonization of the neonatal gut** and support the maturation of the neonatal immune system


---

**Macronutrients/HMOs**

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Bovine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/L)</td>
<td>8</td>
<td>32</td>
</tr>
<tr>
<td>Fat (g/L)</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>Lactose (g/L)</td>
<td>70</td>
<td>48</td>
</tr>
<tr>
<td>Oligosaccharides (g/L)</td>
<td>5-15</td>
<td>0.05</td>
</tr>
<tr>
<td>Identified HMOs</td>
<td>100+</td>
<td>~40</td>
</tr>
<tr>
<td>Sialylated</td>
<td>50-80%</td>
<td>~1%</td>
</tr>
<tr>
<td>Fucosylated</td>
<td>10-20%</td>
<td>~70%</td>
</tr>
</tbody>
</table>

Bode L (2012). Human milk oligosaccharides; every baby needs a sugar mama. *Glycobiology* 22(9); 147-162.


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**Human Milk Oligosaccharides (HMO)**

- Composed of 5 monosaccharides
- HMO mount/composition vary between women over the course of pregnancy
- Wide range of interpersonal variation
- Not every woman synthesizes the same set of HMOs
- Composition mirrors maternal blood group characteristics

Bode L (2012). Human milk oligosaccharides; every baby needs a sugar mama. *Glycobiology* 2299); 147-162.


---

**Human Milk Oligosaccharides (HMO)**

- Resist the low pH in stomach
- Are non-digestible
- Reach the small intestine/colon intact
- Appear in urine of preterm breastfed infants, but not in the urine of formula-fed infants
- This finding suggests they are absorbed and reach the systemic circulation

Bode L (2012). Human milk oligosaccharides; every baby needs a sugar mama. *Glycobiology* 2299); 147-162.

Milk as Medicine

• Human Milk Oligosaccharides (HMO)
  – Immune Function
  – Anti-adhesive antimicrobials
  – Serve as soluble decoy receptors
  – To prevent attachment of pathogens on the mucosal/epithelial surfaces
  – Lower the risk of bacterial, viral, protozoan parasite infection
  – Stimulate developing and distant immune system responses

Bode L (2012). Human milk oligosaccharides; every baby needs a sugar mama. Glycobiology 22(9): 147-162

Milk as Medicine

• Human Milk Oligosaccharides
  – “Probiotic – Epithelial Crosstalk”
  – Shapes the immune system
  – Strengthen host mucosal defenses
  – Tighten mucosal physical barriers
  – Regulates host metabolic pathways
  – Improve mineral absorption
  – Regulates immune-inflammatory processes connecting the intestine, liver, muscle, and brain


Milk as Medicine

• Neonatal Gut Microbiome
  • Abnormal Bacterial Colonization


Milk as Medicine

• AAP Policy:
  • Breastfeeding & Use of Human Milk 2012
    – The potent benefits of human milk are such that all preterm infants should receive human milk
    – Mother’s own milk, fresh or frozen, should be the primary diet
    – If mother’s own milk is unavailable, despite significant lactation support, pasteurized donor milk should be used
    – Supports the use of banked human milk as the “first alternative” to own mother’s milk


Milk as Medicine

• Milk “Traffic” Chain (Dr. Jae Kim, MD)

Donor Milk

It should be nutritionally standardized

Analysis of Donor Milk


- 25% of samples had less than 17 kcal/oz
- 30% of the samples were above 20 kcal/oz

Reported

<table>
<thead>
<tr>
<th>Protein</th>
<th>Fat</th>
<th>Lactose</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0% to 1.2%</td>
<td>3.5% to 4.2%</td>
<td>7.2% to 7.3%</td>
<td>20 kcal/oz</td>
</tr>
</tbody>
</table>

Donor Milk

- 1.16% ± 0.25%
- 3.2%
- 7.8%
- 19 kcal/oz

Milk as Medicine

Critical Dosage

For the use of Human Milk

- Definitions of “Breastfeeding”
- Definitions of “human milk fed”
- Calculating the percentage of human milk feedings
- “Exclusive human milk diet”

Hair, K. et al. J Pediatr 2014; DOI: 10.1016/j.jpeds.2014.07.005

Hair et al. BMC Research Notes 2013, 6:459

EHMD and Extrauterine Growth Failure

Objective

- To evaluate growth velocities and incidence of extrauterine growth restriction in infants ≤ 1250 g birth weight receiving an EHMD with early and rapid advancement of fortification using a donor human milk derived fortifier

Method

- Single center, prospective observational cohort of 104 preterm infants weighing ≤1250 g birth weight receiving an EHMD during and after the NICU stay.

Hair et al. BMC Research Notes 2013, 6:459

<table>
<thead>
<tr>
<th>Hair Human Milk + HMF 80* (n=104)</th>
<th>Sullivan Human Milk + HMF 40** (n=71)</th>
<th>Sullivan Human Milk + HMF 100** (n=67)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain (g/kg/d)</td>
<td>24.8 ± 5.4</td>
<td>14.6 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length (cm/wk)</td>
<td>0.99 ± 0.23</td>
<td>0.93 ± 0.53</td>
<td>0.008</td>
</tr>
<tr>
<td>HC (cm/wk)</td>
<td>0.72 ± 0.14</td>
<td>0.72 ± 0.22</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Hair et al. BMC Research Notes 2013, 6:459

TCH initiates fortification at 60ml/kg/day with EHM fortifier at 24 cal/oz; then automatically advances to EHM fortifier with 26 cal/oz at 100ml/kg. If babies are not growing at 15g/kg/day then they will automatically advance to EHM fortification at 28 cal/oz.
• EHMD and Extrauterine Growth Failure
  – The weight gain in this study was calculated differently than in real world clinical setting. Growth was measured at the begin of the hospital till the end and growth was measured on average over the entire time.
  – Study only evaluated infants who were able to achieve full feeds and therefore excluded a small number of infants.

• Oxidative Stress
  – Due to the abrupt change to a hyperoxic extra-uterine environment, $P_2O_2$ levels are suddenly five times higher than intrauterine values.
  – Elevated levels of vitamin E oxidation product in infants cord blood is > than found in maternal serum.
  – Normal, full term, healthy infants without resuscitation show metabolic evidence of oxidative stress.

• Oxygen Radical Disease of Neonatology

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colostrum</th>
<th>Mature Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation</td>
<td>1061.6 ± 500.6</td>
<td>915.3 ± 511.4*</td>
</tr>
<tr>
<td>Ischemia</td>
<td>915.3 ± 511.4*</td>
<td>816.3 ± 379.4*</td>
</tr>
<tr>
<td>Reparation</td>
<td>816.3 ± 379.4*</td>
<td>862.7 ± 457.7*</td>
</tr>
<tr>
<td>Chronic Lung Disease/BPD</td>
<td>862.7 ± 457.7*</td>
<td>724.7 ± 302.4*</td>
</tr>
<tr>
<td>Leukomalacia</td>
<td>Retinopathy of Prematurity</td>
<td>Chronic Lung Disease/BPD</td>
</tr>
<tr>
<td>Intraventricular Hemorrhage</td>
<td>Necrotizing Enterocolitis</td>
<td>Patent Ductus Arteriosus</td>
</tr>
<tr>
<td>Necrotizing Enterocolitis</td>
<td>Cerebral Palsy</td>
<td></td>
</tr>
</tbody>
</table>

Inflammation Infection Ischemia Reparation
Increased ROS Production Deficient Antioxidant Defenses

• ROS’s
  – Play a role in normal growth and development.
  – Aerobic metabolism, fetal growth
  – Granulocyte function.

• ROS’s
  – Activate complex array of physiologic processes.
  – Amplified inflammatory response
  – Outpouring of cytokines, chemokines
  – Increased reactivity of endothelium
  – Promotion of a pro-coagulation state
  – Altered nitric oxide synthesis
  – Stimulates necrotic & apoptotic cell death mechanisms.

• Antioxidants in Colostrum and Mature Milk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colostrum</th>
<th>Mature Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Antioxidant Capacity (μmol/L)</td>
<td>1061.6 ± 500.6</td>
<td>915.3 ± 511.4*</td>
</tr>
<tr>
<td>DPPH Radical Scavenging Activity (% in μmol/L)</td>
<td>50.4 ± 19.7</td>
<td>40.8 ± 20.0*</td>
</tr>
</tbody>
</table>

Values are presented as Mean ± SD and * indicate significant difference in comparison with colostrums. 

Milk as Medicine

- Colostrum
  - Secretion from
- **Paracellular pathways in mammary epithelium**
  - Profile of growth factors similar to amniotic fluid
    - Antibodies, IgA
    - Anti-inflammatory factors
    - Growth factors
    - Anti-infective components
    - Oligosaccharides
    - Antioxidants
- Absorption of factors via oropharyngeal associated lymphoid tissues (OFALT) and then pass through the open paracellular pathways in infant’s GI tract


Milk as Medicine

Dr. Biren Modi, MD
- Pediatric Surgeon
- Associate Director of the Center for Advanced Intestinal Rehabilitation at Boston Children’s Hospital
- 2016 VON Meeting
  - October 3, 2015

Milk as Medicine

- NEC By BW

Mortality of NEC in CHD

- Mortality in NEC vs. Medical NEC by Birth Weight
  - Surgical NEC vs. Medical NEC
  - Mortality rates
- CHD: 34%
- NEC: 28%
- CHD and NEC: 55%

**Milk as Medicine**

- **“Critical Dose Response”**
  - For the use of Human Milk
    - A relationship in which a change in the amount, intensity or duration of exposure is associated with a change in the risk of a specified outcome
    - In a linear dose-response relationship, the response is proportional to the dose

- **Benefit of Human Milk Diet to Reduce NEC**

**The Arc of Human Milk Feeding and NEC Studies**

- Schanler, R.J. et al. (2003) 398; doi:10.1038/sj.jp.7211758; published online 19 April 2007.

**Incidence of Surgical NEC or Death**

- Hum 100: HMF @ 100 mL/kg/d
- Hum 40: HMF @ 40 mL/kg/d
- HMF: Hum 100 + Hum 40
- BCN: Bovine-based Powdered HMF: @100 mL/kg/d

*Not included in OMM Study Protocol

**Incidence of NEC or Death**

- Hum 100: HMF @ 100 mL/kg/d
- Hum 40: HMF @ 40 mL/kg/d
- HMF: Hum 100 + Hum 40
- BCN: Bovine-based Powdered HMF: @100 mL/kg/d

**Milk as Medicine**

- **“Dose Response”**
  - For the use of Human Milk - Remaining NEC Free

  Probability of Remaining NEC Free vs. Cow Milk-Based Diet

  For every 10% increase in CMBD, there is a 12% increase in NEC.
Milk as Medicine

• **“Dose Response”**
  – For the use of Human Milk - Remaining SEPSIS Free
  
  ![Graph showing probability of remaining sepsis free vs. cow milk-based diet](Image)

  For every 10% increase in CMBD, there is a 17.9% increase in SEPSIS


• **“Dose Response”**
  – For the use of Human Milk - Remaining NEC SX Free

  ![Graph showing probability of remaining NEC surgery free vs. cow milk-based diet](Image)

  For every 10% increase in CMBD, there is a 21% increase in SURGICAL NEC


Milk as Medicine

• **EHMD: Multicenter Retrospective Cohort Study**
  – **Objective**
    • To compare clinical outcomes in 1,587 Extremely Premature infants (birth weight <1250 g) before and after an institutional change to the use of an exclusive human milk–based diet (EHMD) including fortifiers from a diet that included cow milk-based (CMD) products (formulas and/or fortifiers).

  ![Graph showing probability of remaining sepsis free vs. cow milk-based diet](Image)


Milk as Medicine

• **EHMD: Multicenter Retrospective Cohort Study**
  – **Method**
    • Conducted at four geographically disparate hospitals: Texas, California, Illinois, and Florida. Each of the four hospitals reviewed charts from an equal period before and after implementing an exclusive human milk-based protocol.

  ![Graph showing probability of remaining sepsis free vs. cow milk-based diet](Image)


Milk as Medicine

• **EHMD and Extrauterine Growth Failure**
  – **Study Hospital’s Feeding Protocols**

  **Texas Children’s Hospital**
  - <1000 g BW to 24 weeks PMA
  - Prolact+ fortification initiated at 60 mL/kg/day with Procal® HMF
  - At 150 mL/kg/day fortification increased to Prolact+6 HMF
  - If weight gain was <15 g/kg/day, fortification increased to Prolact+8 HMF if low weight gain continued.

  **Good Samaritan San Jose**
  - <1000 g BW to 24 weeks PMA
  - Prolact+ fortification initiated at 100 mL/kg/day with Procal® HMF
  - At 150 mL/kg/day fortification increased to Prolact+6 HMF, Procal® HMF as needed

  **Winnie Palmer Hospital**
  - ≤750 g BW and ≤26 weeks gestational age to 32 weeks PMA
  - Prolact+ fortification initiated at 100-120 mL/kg/day with Procal® HMF
  - If weight gain was deemed suboptimal by the attending doctor based on growth curve velocity, an additional 2-4 cal/oz of fortification was added to the feeds for a total of 6-8 kcals/oz


Milk as Medicine

<table>
<thead>
<tr>
<th></th>
<th>CMD</th>
<th>EHMD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEC</td>
<td>16.7%</td>
<td>6.9%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>Mortality</td>
<td>17.2%</td>
<td>13.6%</td>
<td>p = 0.04</td>
</tr>
<tr>
<td>BPD</td>
<td>56.3%</td>
<td>47.7%</td>
<td>p = 0.0015</td>
</tr>
<tr>
<td>ROP</td>
<td>9.0%</td>
<td>5.2%</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>PDA</td>
<td>64.7%</td>
<td>55.1%</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>Late-Onset Sepsis</td>
<td>30.3%</td>
<td>19.0%</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

Milk as Medicine

• EHMD: Multicenter Retrospective Cohort Study
  – Limitations
    • Other treatment changes may have occurred over this period and could account for some of the differences noted in this study
    • One of the differences noted was a decrease in late onset sepsis, as there was widespread emphasis on decreasing central line-associated bloodstream infections during this period


Milk as Medicine

• Endorsement of Human Milk Feeding

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