Why Not Just One Bottle: The Art and Science of Exclusive Breastfeeding

Lori Feldman-Winter, MD, MPH
Professor of Pediatrics
Cooper Medical School of Rowan University

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Disclosure

• I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.

• I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.
Objectives

1. Describe how human milk affects the cellular and molecular development of the infant's immune system
2. Understand why supplementing interferes with breastfeeding
3. Elevate the threshold for supplementing a breastfed newborn
Disease Protection in Children

“Dose Dependent”

1. AOM 50% less EBF>3-6 months
2. Atopic dermatitis less 42% EBF>3 months
3. LRTI and hospitalization less 72% with EBF>4 months
4. Asthma less 40% for EBF>3 months
5. Obesity less 4-24%; with EBF less 34%
6. T1DM less 19-27% EBF>3 months
7. T2DM less 39% with any BF vs. None
8. Cancer:
   1. ALL less 19% with BF>6 months
   2. AML less 15% with BF>6 months
9. SIDS less 36% with any BF vs. None
10. Gastro less 64% with any BF vs. None

New Evidence Linking *Early* Supplementation with ALL

<table>
<thead>
<tr>
<th>Age of formula introduction</th>
<th>Cases (%) (ALL) n=314</th>
<th>Controls (%) n=663</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Breastfeeding</td>
<td>35 (11) 279 (89)</td>
<td>40 (6) 623 (94)</td>
<td>Reference</td>
</tr>
<tr>
<td>Age of formula introduction</td>
<td></td>
<td></td>
<td>0.52 (0.32-0.86)</td>
</tr>
<tr>
<td>Never</td>
<td>75 (26)</td>
<td>191 (30)</td>
<td>Reference</td>
</tr>
<tr>
<td>≥ 6 Months</td>
<td>60 (21)</td>
<td>126 (20)</td>
<td>1.15 (0.76-1.75)</td>
</tr>
<tr>
<td>2-6 months</td>
<td>56 (19)</td>
<td>114 (18)</td>
<td>1.12 (0.73-1.71)</td>
</tr>
<tr>
<td>15 days – 2 months</td>
<td>27 (9)</td>
<td>92 (15)</td>
<td>0.65 (0.38-1.10)</td>
</tr>
<tr>
<td>&lt; 14 days</td>
<td><strong>75 (26)</strong></td>
<td><strong>108 (17)</strong></td>
<td><strong>1.57 (1.03-2.37)</strong></td>
</tr>
</tbody>
</table>

Greenop KR. Nutrition and Cancer 2015
Breastfeeding Leads to Self-Regulation

- Exclusive breastfeeding at breast: 27%
- Expressed breast milk in bottle: 47%
- Combination breastfeeding: 56%
  - Formula feeding, Breast/bottle
- All formula in a bottle: 68%

How often does your infant empty the bottle/cup after 7 months of age?

Exclusive 4 vs. 6 Months

Deaths:

- URTI
- LRTI
- GI

Liesbeth D. et al. Pediatrics June 2010
Formula Supplementation Increases Risk of Ear, Sinus and Throat Infections Beyond Infancy

<table>
<thead>
<tr>
<th>Formula Supplementation</th>
<th>N</th>
<th>%</th>
<th>AOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF&lt;6 mo with formula &lt;6 mo</td>
<td>440</td>
<td>44.6</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>BF ≥ 6 mo with formula &lt; 6 mo</td>
<td>279</td>
<td>41.9</td>
<td>0.96</td>
<td>0.69-1.32</td>
</tr>
<tr>
<td>BF ≥ 6 mo without formula &lt; 6 mo</td>
<td>389</td>
<td>34.2</td>
<td>0.70*</td>
<td>0.51-0.85</td>
</tr>
</tbody>
</table>

*P<0.01

Longitudinal data from the IFS II followed through age 6 years; AA and Hispanic mothers under-represented

Li R. Pediatrics September 2014
Epidemiological Evidence of Immune Modulation

• Non-EBF results in risk of autoimmune diseases; long after breastfeeding
  – Atopy and Asthma (response to LRTI)
  – Crohn’s and Ulcerative Colitis
  – Celiac
  – Leukemia
  – Type 1 DM
<table>
<thead>
<tr>
<th>Infant feeding</th>
<th>AE+</th>
<th>AE-</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any formula in the first year of life</td>
<td>178 (86.8)</td>
<td>892 (79.9)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Exclusive breastfeeding for ≥4 months</td>
<td>5 (2.4)</td>
<td>86 (7.7)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Introduction of solid food &lt;4 months</td>
<td>103 (49.8)</td>
<td>632 (56.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Cow's milk in the first year of life</td>
<td>184 (90.2)</td>
<td>941 (84.6)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

Dunlop, Anne L. et al. 2006. *Pediatric Allergy and Immunology.*
% Regression Score Accounted for by Modifiable Exposures

Dunlop, Anne L. et al. 2006. *Pediatric Allergy and Immunology*. 
Human Milk Influences the Development of Immune System

- **Innate defenses**
  - Surface barriers
    - Skin
    - Mucous membranes
  - Internal defenses
    - Phagocytes
    - Fever
    - NK cells
    - Antimicrobial proteins
    - Inflammation

- **Adaptive defenses**
  - Humoral immunity
    - B cells
  - Cellular immunity
    - T cells

http://classes.midlandstech.edu/carterp/Courses/bio211/chap21/chap21.htm
Gut Colonization Essential to Prevent Allergy and Establish Normal Function

• Newborn gut needs to be colonized shortly after birth

• Immune response to flora leads to:
  – Colonization with commensal bacteria
  – Development of immunologic tolerance

• Hygiene hypothesis
  – If not exposed and/or unable to properly handle flora (via HM) then allergy develops
Newborn Intestinal Immune System

- commensal bacteria
- sIgA
- TGFβ

http://www.customprobiotics.com/about_probiotics.htm
HM Provides Innate Host Defense:
• Lipids
• Mucin
• Lactoferrin
• Lysozyme
• Complement
• Leukocytes

Specific Adaptive Immunity:
• sIgA
• Anti-idiotypic Ab
• Probiotic
• TLR signaling

Enteric Bacterium Interact with Intestinal Microvillus of the Small intestine

Bacterial-epithelial “cross-talk”

- Organizes B, T, Macrophages and dendritic cells
- Regulates Ag transport
- Drives Ag specific and non-specific pathways for recognition
- Responses are both pro and anti-inflammatory

Enteromammary production

Human Milk Oligosaccharides (HMO’s)
How Prebiotics in Human Milk Work

Oligosaccharides necessary to colonize commensal bacteria

Sugars on normal cell surfaces (throat) permit bacterial adhesion (pneumococci) and infection.

Oligosaccharides thwart attempt for bacteria to enter cell

By binding sugar receptors
Immune System Priming

• Probiotic bacteria need an invitation to the environment that hosts them
  – Prebiotic - oligosaccharides, suppress of immune reaction to probiotic while participating in host defense against pathogenic bacteria

• Nature permits host defense without the need for an inflammatory response...protects the epithelium...reason to have a delayed immune system...
Stool PH as an Indicator of Normal Gut Fermentation

**Table 2. Value of stool pH**

<table>
<thead>
<tr>
<th></th>
<th>3rd day</th>
<th>1st month</th>
<th>2nd month</th>
<th>3rd month</th>
<th>4th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF</td>
<td>5.03 ± 0.7</td>
<td>5.05 ± 0.2</td>
<td>5.04 ± 0.7</td>
<td>5.06 ± 0.3</td>
<td>5.04 ± 0.4</td>
</tr>
<tr>
<td>FF</td>
<td>5.12 ± 1.4</td>
<td>5.13 ± 0.3</td>
<td>5.11 ± 0.3</td>
<td>5.12 ± 0.7</td>
<td>5.15 ± 0.6</td>
</tr>
<tr>
<td>SF</td>
<td>5.86 ± 1.7*</td>
<td>5.63 ± 0.5*</td>
<td>5.93 ± 0.7*</td>
<td>5.78 ± 0.6*</td>
<td>5.83 ± 0.7*</td>
</tr>
</tbody>
</table>

* vs breast-feed and FF feed $p < 0.001$.

BF-Exclusively HM-fed; FF-fermented formula; SF-standard formula
Oligosaccharides are *necessary* but *not sufficient* to properly colonize the infant’s intestine.

*Toll like receptors (TLR)* necessary to bind bacteria in concert with oligosaccharides (LPS on gram - bacteria).

Need certain TLR’s to be present.
Toll-like Receptors (TLR) and Their Ligands

<table>
<thead>
<tr>
<th>TLR</th>
<th>Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR1</td>
<td>Triacyl lipopeptides</td>
</tr>
<tr>
<td>TLR2</td>
<td>Lipoprotein/lipopeptides, peptidoglycan, lipoteichoic acid,</td>
</tr>
<tr>
<td></td>
<td>Double-stranded RNA</td>
</tr>
<tr>
<td>TLR3</td>
<td>Lipopolysaccharide, HSP60 etc., commensal bacteria</td>
</tr>
<tr>
<td>TLR4</td>
<td>Flagellin</td>
</tr>
<tr>
<td>TLR5</td>
<td>Diacyl lipopeptides</td>
</tr>
<tr>
<td>TLR6</td>
<td>Synthetic compounds (the immune response modifiers)</td>
</tr>
<tr>
<td>TLR7</td>
<td>Unknown</td>
</tr>
<tr>
<td>TLR8</td>
<td>CpG DNA</td>
</tr>
<tr>
<td>TLR9</td>
<td>Unknown</td>
</tr>
<tr>
<td>TLR10</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Human Milk, but Not Infant Formula Enhances TLR4- and TLR5-mediated responses

Negative Effect of Human Milk, but Not Formula, on Cell Stimulation Via TLR2 and TLR3

The Journal of Immunology, 2006, 176: 3742-3752.
Specific Toll-like Receptors necessary for proper colonization

**TLR4** binds LPS producing Gram negative pathogens up regulated by HM

**TLR1,2** down regulated by HM binds Gram + bifidobacteria

Rutgeerts P Gastroenterology 2009
Exclusive Human Milk Necessary for Proper Colonization

- **Exclusive HM**: probiotic/commensal bacteria- bifidobacteria, and lactobacillus.
- Supported by complex system of HMO (not other prebiotics)
- Flora contribute to and are a marker of normal immune development, need certain toll-like receptors for hosting.
- **Formula feeding**: bacteroides, clostridia, streptococci. *just one bottle*... leads to colonization with bacteria that induces an inflammatory response (enhanced by factors in human milk).

HM Alters Allergic Response

• Newborn responses naturally skewed toward Th2>Th1
• Colonization helps drive Th1 and induce tolerance
• Cytokines in milk enhance/divert allergic response.
• Maternal sIgA diverts antigenic response.

Chung EK et al. Arch Dis Child Fetal Neo Ed 2007
T Cell Ontogeny and Balance

Jutel M. Current Allergy Asthma Rep. 2011
Ontogeny of T Cell Function

- Delayed T cell function.
- Breastfed infants have a thymus twice the size of formula fed infants.
- Immune properties of HM are priming (signaling) the resting thymus cells.
- T cells develop in GALT sent to thymus.
FF Skews Immune Cell Composition

- Distinct differences in circulating WBC at 6 mo.
- FF skewed toward naïve T cells, decrease in NK, CTL, and B cells, slower recruitment of T cells with effector functions for innate immunity
- If EBF were given IF at 4-6 mo. Pattern resembled FF infants

Andersson Y. et.al. J of Immunology 2009
3-dimensional bolstered gene expression discriminates between breast-fed (O) and formula-fed (Δ) infants

Master genes are transcription factors associated with angiogenesis and wound repair

Human Milk Meta-genome

- Pooled DNA from cells and bacteria in HM
- Open reading frames (ORF) in HM compared to stools of mom, BF infant, and FF infant
- Changes over time LI to LII
- HM DNA may contribute to colonization and immune modulation
- **Balance** of immune *stimulatory* effects of bacterial CpG’s and immune *suppressive* effects of maternal and bacterial DNA present in HM

Link between nutrition, bacterial metabolites, and epigenetics

- Proposed mechanism between early nutrition and adult obesity

- Gut micro-flora produces differential metabolites

- Methylation can enhance histone acetylation blocks

Mischke M. 2013
Jun 15;304(12):R1065-9
Functions of the Neonatal Microbiome

• Proper immune development
  – Balance of B, T cells
  – Tolerance, immunity, anti-inflammatory
  – Reduced risk of allergy and auto-immune diseases

• Signals neonatal cellular nuclei to transcribe specific genes
  – Toll-like receptors, leading to proper microbiome
  – Master genes to protect newborn

• Contributes to genes that signal normal metabolism

Mueller NT Trends in Molecular Medicine. Feb 2015
Normal Neonatal Microbiome

• Disruptors of the establishment of the normal neonatal microbiome include:
  – Any formula feeding
  – Maternal or neonatal antibiotics
  – Cesarean delivery

• Research Questions:
  – Can the normal microbiome be restored
  – Does restoration reduce risk of micro-biome related diseases?
EBF Influences Bacterial Diversity at Weaning

**Figure 1**: (A) A comparison of species richness and (B) phylogenetic diversity between feeding groups. Non-EBF infants showed significantly higher S and PD values than EBF infants, and both values were impacted by the introduction of solid foods (*p < 0.05). (C–F) Comparison of unweighted UniFrac PCoA plots with repeated resampling (jackknifing) of microbiota from different feeding groups. ANOSIM R and P values are indicated in each figure.
Summary of Human Milk Influences on Gut Mucosa

Oral Tolerance - necessary to prevent systemic hypersensitivity, mediated through regulatory T cells, T cell anergy and clonal deletion

Gut Colonization - via maternal milk and vaginal birth hosted by appropriate down regulation of Toll-like receptors

Microbiota-Epithelial Crosstalk - structurally arranges lymphoid cells and signaling mRNA transcripts for specific TLR expression

Induction of Intestinal Immune System - induction of ILF, peyer’s patches and mesenteric lymph nodes
Supplementation in the Delivery Hospital Leads to Weaning by 6 weeks post-partum

Hospital factors affecting discharge feeding status among mothers who ever breastfed
(Adjusted for maternal race/ethnicity, foreign birth, age, education, parity)

Adjusted odds ratio

- Baby sleeps in hospital room
- Breastfed within 1st hour
- Allowed to feed on demand
- Fed only breast milk before discharge
- Baby DID NOT use pacifier
- Post-discharge help phone

Any breastfeeding, 8 wks post-partum
Exclusive breastfeeding, 8 wks post-partum

NJ PRAMS
Culture of Supplementation

- Market influence
- Nurse training and culture
- Physicians’ worry...
  - Dehydration
  - Jaundice
  - Hypoglycemia
  - Litigation!
Reasons to Supplement

- Unresponsive hypoglycemia
- Severe maternal illness *(psychosis, eclampsia, shock)*
- Mother not available *(maternal transfer)*
- Galactosemia
- Infant unable to feed at breast *(illness, congenital malformation)*
- Few maternal medications
- LBW and sufficient milk is not available
- Delayed lactogenesis II *(retained placenta, Sheehan), or primary glandular insufficiency*
- Intolerable pain
When supplements are NOT Needed

- Colostrum QNS
- Teach how to use bottle
- Growth/appetite spurts, cluster feed
- Prevent Wt. loss
- Prevent hyperbilirubinemia

- Quiet a fussy baby
- Sleepy baby
- Let mother sleep
- Prevent hypoglycemia
- Breastfeeding “too” long to prevent damage and sore nipples
Another Reason NOT to Supplement

• Joint Commissions
• **Set Measure ID:** PC-05 & PC-05a
• **Performance Measure Name:** Exclusive Breast Milk Feeding
• **Description:** Exclusive breast milk feeding during the newborn's entire hospitalization
Improving Performance on Perinatal Care Measures

Quality improvements in essential areas of patient safety, including perinatal care, rely on the performance of specific tasks. To help assess the effectiveness of patient care, The Joint Commission requires hospitals to submit data reports based on measures that meet certain criteria. These accountability measures are organized into “measure sets,” which are a unique group of action items specifically selected to optimize the care provided in each area.

Currently, general medical/surgical hospitals are required to submit data for a minimum of 4 measure sets (out of 14) via a vendor that has been evaluated and listed by The Joint Commission. This will change, however, in 2014. Beginning January 1, hospitals must submit data for 6 measure sets. According to the new guidelines, some of these sets will be mandatory for hospitals. Others will be discretionary. A number of health care organizations that are involved in perinatal care supported adoption of the measure (see the box on page 18).

Perinatal care will fall under the mandatory column for hospitals with 1,100 or more births annually. The Joint

- PC-03 Antenatal steroids
- PC-04 Health care–associated bloodstream infections in newborns
- PC-05 Exclusive breast milk feeding
- PC-05a Exclusive breast milk feeding considering mother’s choice

Beginning January 1, 2014, hospitals that see more than 1,100 births annually will be required to submit data on the Perinatal Care Measure Set.
A New Core Measure Set

The PC Core Measure Set comprises 5 main measures:

PC-01: Elective delivery
PC-02: Cesarean section
PC-03: Antenatal steroids
PC-04: Health care associated bloodstream infections in newborns
PC-05: Exclusive breast milk feeding
Mandatory in January 2014 PC-05 and PC-05a

- TJC defines exclusive breast milk feeding as newborn receiving only breast milk and no other liquids or solids except for drops or syrups consisting of vitamins, mineral, or medicines.

- Breast milk feeding includes expressed mother’s milk as well as donor human milk, both of which may be fed to the infant by means other than suckling at the breast.
Mother’s Intention to Breastfeed

• Ask on admission...How do you intend to feed your baby? (response options)
  – **Breastfeeding** (interpreted as exclusive breastfeeding, breast milk feeding)
  – **Combination** breastfeeding or breast milk feeding plus formula
  – **No breastfeeding** (formula only)
  – Unsure

• Then provide skin to skin care
  – If breastfeeding happens then revisit with question, how would you like your infant be fed while here in the hospital? (up to 4 hours)
Exclusive Human Milk Feeding – Considering Mothers’ Intention (Joint Commission PC05a)

• MEASURE: Percent of infants receiving human milk feedings exclusively throughout hospital stay (from birth to discharge), who do not have Joint Commission “allowable” reasons to be excluded (including intention)

• Exclusions: There is MD/APN/CNM/IBCLC/CLC documentation that:
  – Infant’s mother has medical contra-indication to breastfeeding (AV1)
  – Infant’s mother stated intention not to breastfeed or to partially breastfeed at admission (AV2)
  – Infant has a clinical “reason for not exclusively feeding breast milk” (AV3)
  – Infant’s mother changed her intention to exclusively breastfeed to partial / no breastfeeding (AV3)
Summary of the Core Measure

• Numerator, all breast milk (at breast or breast milk given by another method - cup, syringe, sns, bottle)

• Denominator PC-05 – all term singleton newborns without a contraindication

• PC-05a same just mom has to say she wants to breastfeed (exclusively)

• Medical indications to supplement are NOT exclusions to denominator
What is the role of the clinician?

- Present data on dashboard and at departmental meetings
- Develop action plans to decrease supplementation
- Help write or revise hospital policies
- Educate on the risks of supplementation
- Provide or refer for breastfeeding management
- Use QI strategies
Supplementing Breastfeeding

• What are medical indications for supplementation?
• Not the same as TJC defined reasons to use formula (these are medical contraindications to breastfeed)
• Weight loss?
• Jaundice?
• Hypoglycemia?
• Others?

Primum Non Noceri
“First do no harm!”
Updated CDC NIS Data

Less supplementation before 2 days from 22.3% to high of 25.6% now down to 19.4%
Updated CDC NIS Data

EBF increased from 10.3% to 18.8% at 6 months over past decade
Focus on Disparities

CDC NIS Data from 2011
Conclusions

• Exclusive breastfeeding produces optimal health outcomes—know the science
• Exclusive breastfeeding requires support in multiple dimensions
• Physicians are necessary to support exclusive breastfeeding
• The Baby-Friendly Hospital Initiative, using quality improvement methods, helps to support exclusive breastfeeding
“If you always do what you always did, you will always get what you always got.”

-Albert Einstein