Making Sense of Infant Formulas, Milk Fortifiers and Additives

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Components of infant formula
- Start with first principles
- What are the goals?
- What do we need to provide nutrients?

What is the goal of infant nutrition?
- Optimal nutrient delivery
- Optimal health
- Optimal long-term outcomes

Goals of Growth
- “Postnatal growth” should approximate that of in utero growth of a normal fetus” (AAP 1985)

Infant formula
- Human milk is extremely variable
- Matching components inexact due to varying absorption and interaction with other components
- Mere matching of components in human milk is insufficient; proof that the component is beneficial is required

Nutrition Risk Factors
- Decreased nutrient stores
- Increased nutrient requirements
- Reduced tolerance to parenteral nutrition
- Hyperglycemia, lipid intolerance
- Reduced tolerance to enteral feedings
- Abdo distension, aspirates, NEC
- Suboptimal intake secondary to medical condition
- Respiratory Distress Syndrome/Chronic Lung Disease
- Increased energy requirements
- Congenital Heart Disease, Fluid Restriction
- Malnutrition/malnutrition in enteral volume
- GERD
- Short Bowel Syndrome
Components of Infant Formula Milk

- Macronutrients
- Micronutrients
  - Minerals and vitamins
  - Trace elements
- Nucleotides
- Prebiotics

Sources for formula milk

- Fat
  - Source: Plant based blend
  - Blend of vegetable oils
  - DHA: fungal source
- Protein
  - Source: Bovine based
  - Whole protein
  - Whey dominant
- Carbohydrate
  - Source: Bovine based
  - Lactose
  - Elemental: glucose polymers

Macronutrients

- Fat
  - Source: plant based
  - Blend of oils such as safflower, soy, coconut
  - Constitutes approximately 50% of the calories (4.4-6.0g/100 kcal) compared with human milk (5.7 g/100 kcal)
  - Mainly triglycerides

Macronutrients

- Protein
  - Source: bovine milk based
  - Changed to whey dominant since typical bovine milk is casein dominant
  - Additional carnitine and taurine

Macronutrients

- Carbohydrates
  - Source: bovine milk
  - Lactose like human milk
  - oligosaccharides?
  - Soy formulas contain sucrose or glucose polymers

Enteral Administration of Fat

- How does fat get digested?
- Differences between human milk and formula
- How much should we give?
  - Formula – not highly variable
  - Human milk – most variable macronutrient
Long chain polyunsaturated fatty acids (LCPUFA)
- OMEGA-3 (ω-3)
- LINOLENIC ACID
- FISH OIL
- DHA (docosahexanoic acid)
- EPA
- OMEGA-6 (ω-6)
- LINOLEIC ACID
- ARA (arachidonic acid)

Nucleotides
- Structure
  A nucleotide consists of a base (either a purine, such as adenine, or a pyrimidine, such as cytosine) linked to a sugar (either ribose or deoxyribose) and one, two or three phosphates.
- Functions
  Nucleotides form the basis of DNA and RNA, are important in tissues with rapid turnover (for example, gut and immune system) and are metabolic regulators (involved in energy transfer, ‘acid’ handling, synthesis and breakdown of large molecules.)

Nucleotides
- growth enhancement of babies born light for gestational age
- fewer episodes of diarrhea
- improved immunological functions in babies’ blood with greater antibody responses to diphtheria and haemophilus influenzae immunisations
- changes in lipid metabolism

TERMINOLOGY
- PREBIOTICS
- PROBIOTICS
- POSTBIOTICS
- SYMBIOTICS

Probiotics
- Probiotics are defined as live microorganisms that when given in adequate amounts confer a health benefit on the host

Postulated benefits of probiotics
- Alleviation of symptoms of lactose malabsorption
- Increase in natural resistance to infectious diseases of the intestinal tract
- Suppression of cancer
- Reduction in serum cholesterol concentrations
- Improved digestion
- Stimulation of gastrointestinal immunity

Collins and Gibson, Am J Clin Nutr 1999;69(5):1052S-7S.
How do probiotics work?
- lower colonic pH
- produce antimicrobial compounds and antitoxins
- compete with other bacteria for nutrients and adhesion receptors
- increase mucin production
- decrease intestinal permeability
- immunomodulation; increased immunoglobulins

Health benefits of probiotics
- Lactose intolerance
- Diarrhea
- Acute diarrhea
- Antibiotic related diarrhea
- Traveler’s diarrhea
- Allergies
- Respiratory illness
- Inflammatory bowel disease
- Irritable bowel disease
- Dental caries
- Cystic fibrosis

Are probiotics safe?
- No deaths ascribed to probiotic use
- BUT...
- Lactobacillus has caused bacteremia, pneumonia, endocarditis, local suppurative infections, neonatal sepsis and meningitis
- S. boulardii has caused fungemia

Remaining issues with probiotics
- Which probiotic should we use?
- How much probiotics should we give?
- How long should we give it?
- How early should we start?
- Do we want to permanently alter the flora?
- What is the most important outcome to measure?

Prebiotics
- Prebiotics are non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve the health of the host
- Human milk contains numerous prebiotics primarily in the form of oligosaccharides
Mechanisms of prebiotics
- lower intestinal pH
- production of bacterial products
- adherence to the cell surface
- competition of fermentable substrates or receptors
- strengthen intestinal barrier
- release of gut protective metabolites
- binding of toxic metabolites
- immunologic mechanisms
- regulation of the intestinal motility and mucus production

How do prebiotics work?
- Non-digestible
- Fermented by selective bacteria
- Synthesize nutrients
- Help with gut maturation
- Produce short chain fatty acids
- Decrease pH
- Support immune development

Human Milk Oligosaccharides (HMO)
- Small chain sugars (>200 variations)
- Resist digestion
- Substrate for beneficial intestinal microflora
- Support favorable bacteria population in infant colon (“BIFIDOGENIC”)
- Beneficial microflora stimulate the developing immune system
- Measurable amounts are absorbed and can affect neutrophil function

Human Milk is an Ideal Synbiotic

Effects of the HMO

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Postulated effects of HMO</th>
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<td>Prebiotic, bifidogenic</td>
<td>Colon</td>
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<td>Antimicrobial, antiinflammatory</td>
<td>Lymphopharynx, sternum, small intestine, colon, urinary tract</td>
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<td>Glycemic-modifying</td>
<td>Intestinal? Others?</td>
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<td>Immunomodulatory</td>
<td>Inflamed tissue immune system</td>
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Prebiotics: Oligosaccharides
- Third largest component in human milk!
- 7-12 g/L, 10-100 fold any other animal
- Oligosaccharides start with lactose on the reducing ends
- Biosynthetic pathway poorly understood
- Most cannot be synthesized

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Human Oligosaccharides
- Day 4, highest oligosaccharide levels (up to 20g/L)
- Days 30 and 120, reduction by 20% and 40%
- Human milk contains 60-90% with Gal-Glc oligos and 10-40% Fruc-Glc oligos

Core Structure of Oligosaccharides
A. Core Structure of Neutral Human Milk Oligosaccharides
\[\text{Gal}[1-3]4\text{GlcNaAc}[1-1]3\text{Gal}[1-4]\text{Glc}\]
B. Core Structure of Neutral Milk Oligosaccharides of Some Domestic Animals
\[\text{Gal}[1-3]4\text{GlcNaAc}[1-1]3\text{Gal}[1-4]\text{Glc}\]
- e.g. goat, horse

C. Core Structure of Galacto-Oligosaccharides
\[\text{Gal}[1-3]4\text{GlcNaAc}[1-1]3\text{Gal}[1-4]\text{Glc}\]

Synthesized oligosaccharides
- Galacto-oligosaccharides (GOS)
- Chemically synthesized from lactose
- Available in infant formula in North America
- Studied in over 1000 infants
- Has GRAS status (generally regarded as safe)

GOS/FOS effect
- Altered microflora: increased Bifidobacter and Lactobacillus
- Increased secretory IgA
- Reduced respiratory infections, fever
- Reduced allergic symptoms (wheezing, urticaria, atopic dermatitis)

Human milk alone is insufficient to meet preterm infant growth
- Energy needs
- Protein needs
- Mineral needs
- Iron needs
- Vitamin needs

Aceto et al., J Nutr 2007;137(7 Suppl 2):847S-9S.
Table of comparison of preterm infant fortifiers

<table>
<thead>
<tr>
<th></th>
<th>Percent HMF</th>
<th>Enfamil HMF</th>
<th>Similac HMF</th>
<th>Apream 5</th>
<th>P-24</th>
<th>Enfamil ISMO</th>
<th>Probactis HMF</th>
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</thead>
<tbody>
<tr>
<td>Energy (kcal)</td>
<td>69</td>
<td>65</td>
<td>82</td>
<td>84</td>
<td>86</td>
<td>66</td>
<td>82</td>
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<tr>
<td>Fat (%)</td>
<td>5.0</td>
<td>4.0</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
<td>3.6</td>
<td>4.8</td>
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<tr>
<td>Carbohydrates (g)</td>
<td>6.7</td>
<td>7.1</td>
<td>8.3</td>
<td>9.5</td>
<td>9.3</td>
<td>8.5</td>
<td>7.1</td>
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<tr>
<td>Protein (g)</td>
<td>1.9</td>
<td>2.4</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
<td>2.4</td>
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<tr>
<td>Calcium (mg)</td>
<td>29</td>
<td>119</td>
<td>146</td>
<td>54</td>
<td>119</td>
<td>184</td>
<td>136</td>
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<tr>
<td>Phosphorus (mg)</td>
<td>93</td>
<td>39</td>
<td>76</td>
<td>34</td>
<td>34</td>
<td>34</td>
<td>80</td>
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<tr>
<td>Magnesium (mg)</td>
<td>7.8</td>
<td>7.4</td>
<td>9.6</td>
<td>8.4</td>
<td>8.7</td>
<td>8.4</td>
<td>8.4</td>
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<tr>
<td>Sodium (mEq)</td>
<td>1.6</td>
<td>1.6</td>
<td>1.8</td>
<td>1.7</td>
<td>1.8</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Zinc (ug)</td>
<td>255</td>
<td>405</td>
<td>1225</td>
<td>415</td>
<td>385</td>
<td>1015</td>
<td>835</td>
</tr>
<tr>
<td>Copper (ug)</td>
<td>31</td>
<td>65</td>
<td>213</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>112</td>
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<tr>
<td>Vitamins</td>
<td>Yes</td>
<td>Multi</td>
<td>Multi</td>
<td>Multi</td>
<td>Multi</td>
<td>Multi</td>
<td>Multi</td>
</tr>
</tbody>
</table>

Human milk does not meet requirements of VLBW infants

Postdischarge Nutrition

- **Formula**
  - Standard term formula (20 kcal/oz)
  - Increased calorie term formula (22-24 kcal/oz)
  - Postdischarge formula (22 kcal/oz)

- **Human milk**
  - Human milk alone
  - Fortified human milk with postdischarge powder
  - Supplemental bottles of postdischarge formula
  - Liquid fortifier

Comparison of postdischarge milk

<table>
<thead>
<tr>
<th>Per 100 kcal</th>
<th>Preterm Formula</th>
<th>Post Discharge Formula</th>
<th>Term Formula</th>
<th>Breast Milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g)</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Fat (%)</td>
<td>6.1</td>
<td>6.1</td>
<td>6</td>
<td>5.2</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
<td>51.3</td>
<td>51.3</td>
<td>51</td>
<td>19</td>
</tr>
<tr>
<td>Calcium (mg)</td>
<td>105</td>
<td>105</td>
<td>105</td>
<td>50</td>
</tr>
<tr>
<td>Phosphorous (mg)</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Sodium (mEq)</td>
<td>1.8</td>
<td>1.8</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Chloride (mEq)</td>
<td>2.3</td>
<td>2.3</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Vitamin A (IU)</td>
<td>1250</td>
<td>1250</td>
<td>1250</td>
<td>533</td>
</tr>
<tr>
<td>Energy (kcal per 100 mL)</td>
<td>81</td>
<td>81</td>
<td>81</td>
<td>67</td>
</tr>
</tbody>
</table>

Merko, Sunnybrook Hospital, Toronto

What is good in infant formula

- Balanced macronutrients
- Good tolerance for most babies
- Excellent overall growth
- Liquid feeds are clean
### What are we missing?
- Immune protection (aside from nucleotides)
- Reduction of infection
- Reduction in immune disease
- Maybe not enough DHA
- Preterm: reduction in NEC
- Prebiotics: one versus greater than 150 variations
- No prebiotic or probiotic for preterm infants

### Problems with infant formula
- Clinical problems
  - Bovine protein intolerance
  - Altered mineral absorption
  - Plant palm olein oils in term formula
- Preterm infants
  - Increased incidence of NEC

### Human milk remains the optimal feeding for preterm and term infants