Optimizing Nutrition in Infants at High Risk for Developing Allergy

Presented by
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Faculty Disclosures

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faculty has no relevant financial relationships to disclose
Learning Objectives

- Understand the role of human milk in preventing allergy development
- Recognize factors that predispose infants to allergy
- Identify formula options that support the nutritional needs of infants with food allergy
OBJECTIVE 1: HUMAN MILK AND ALLERGY

• Expected growth patterns for infants and children
• Benefits of human milk and breastfeeding
• Role of human milk in developing and maintaining normal food tolerance
Normal Growth Patterns in Infancy

The first year of life—and particularly the first 6 months—are a period of very rapid growth.

†For boys.

Rapid Growth in Infancy

**Newborn**
- **Growth**: ~1 cm/week and 20–30 g/day
- **Energy**: 110 kcal/kg daily
- **Weight**: ~3.5 kg

**1 Year**
- **Growth**: 0.5 cm/week and 10 g/day
- **Energy**: 110 kcal/kg daily
- **Weight**: Triples

Weight doubles by 4-6 months
**Recommended Energy Intake Corresponds With Growth**

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight Gain (g/day)</th>
<th>Length Gain (cm/mo)</th>
<th>Energy Intake (kcal/kg)</th>
<th>Protein Intake (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 months</td>
<td>25–35</td>
<td>2.6–3.5</td>
<td>108</td>
<td>1.52</td>
</tr>
<tr>
<td>3–6 months</td>
<td>15–21</td>
<td>1.6–2.5</td>
<td>98</td>
<td>1.2</td>
</tr>
<tr>
<td>6–12 months</td>
<td>10–13</td>
<td>1.2–1.7</td>
<td>102</td>
<td>1.05</td>
</tr>
<tr>
<td>1–3 years</td>
<td>4–10</td>
<td>0.7–1.1</td>
<td>90</td>
<td>0.95 (4–8 years)</td>
</tr>
<tr>
<td>4–6 years</td>
<td>5–8</td>
<td>0.5–0.8</td>
<td>70</td>
<td>0.95 (9–13 years)</td>
</tr>
<tr>
<td>7–10 years</td>
<td>5–12</td>
<td>0.4–0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evaluating Infant and Child Growth

- Monitoring growth of children
  - **WHO growth charts**\(^1\) – Ages 0 to 2 years
  - **CDC growth charts**\(^2\) – Ages 2 years and older

- Infants should follow a set pattern of growth along a percentile curve
  - Large-for-gestational age and small-for-gestational age children tend to normalize to a new percentile curve within first 2 to 3 months

**Poor growth is always a cause for concern and should be evaluated promptly**

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Optimal Feeding Practices

Breast is Best
The World Health Organization recommends that human milk be the sole source of nutrition for healthy term infants until 6 months of age.

- Breastfeeding reduces the risk of chronic illnesses, such as obesity, hypertension, and dyslipidemia
- Breast milk composition serves as basis for formula, but cannot be duplicated

Components of Human Milk

Immune Modulators
- Immune cells
- Immunoglobulins
- Cytokines
- Chemokines
- Lactoferrin
- Secretory components
- Foreign food antigens
- Viruses and bacteria

Nutritional Factors
- Growth factors
- Oligosaccharides
- Fatty acids
- Hormones
- Enzymes (peroxidase, lysozymes)
Components of Human Milk

**Immune Modulators**
- Immune cells
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**Nutritional Factors**
- Growth factors
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- Enzymes (peroxidase, lysozymes)

**Cytokines**
- TGFβ
  - Protective against atopic diseases
Components of Human Milk

**Immune Modulators**
- Immune cells
- Lactoferrin
- **Immunoglobulins**
  - Secretory components
- Cytokines
- Foreign food antigens
- Chemokines
- Viruses and bacteria

**Nutritional Factors**
- Growth factors
- Hormones
- Oligosaccharides
- Enzymes (peroxidase, lysozymes)
- Fatty acids

**Immunoglobulins**
- IgA
  - Potentially protective against cow’s milk allergy

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Components of Human Milk

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Nutritional Factors
- Growth factors
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- Fatty acids
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- Enzymes (peroxidase, lysozymes)

Oligosaccharides
- Human Milk
- Anti-inflammatory

Components of Human Milk

**Immune Modulators**

- Immune cells
- Immunoglobulins
- Cytokines
- Chemokines
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- Secretory components
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**Nutritional Factors**

- Growth factors
- Oligosaccharides
- Hormones
- Enzymes (peroxidase, lysozymes)
- Fatty acids

**Fatty Acids**

- DHA and EPA
- Anti-inflammatory

Developing Gut Immune System


**Breast Milk Components**
- Growth factors
- Oligosaccharides
- Cytokines and chemokines
- Glycoproteins and lactoferrin
- Immunoglobulins
- Fatty acids
- Microbiome
- Cells and stem cells
- Dietary antigens
- Exosomes and miRNAs

**Gut Immune Factors**
- Antigen repertoire
- Mucosal barrier
- Immune microenvironment
- Gut microbiome
- pH
- Innate stimulation

**Maternal Factors**
- Age
- Parity
- Genetics
- Immune status
- Diet
- Environment

**External Factors**
- Infant diet
- Environment

**Infant Gut Immune System**

The Microbiome and Infant Health

• The microbiome is established within the first 2 years of life\textsuperscript{3}
  • Bifidobacteria dominate during the early stages
  • Healthy microbiome has a high diversity

• High gut diversity is associated with reduced risk of atopic diseases
  • Living on farms
  • Avoiding antibiotics
  • Vaginal delivery

• Atopy, eczema, and food allergies are associated with low gut diversity\textsuperscript{1,2}

Gut dysbiosis precedes allergy development

Benefits of Human Milk and Allergy Development

- Exclusive breastfeeding up to 4 months of age is associated with reduced risk of eczema, wheezing, and cow’s milk allergy later in life
  - Breastfeeding beyond 4 months **does not** reduce the risk of asthma or other atopic diseases
  - Breastfeeding up to 1 year of age may also reduce risk of gastrointestinal illnesses
- Most studies on breastfeeding have been too small to study the effect on food allergy development
- Maternal avoidance of foods during pregnancy or breastfeeding is currently **not recommended** unless there is known infant allergy/intolerance
- Variation of breast milk among mothers make studying breast milk’s effects difficult

Summary: Human Milk and Allergy Development

- Rapid growth in the first 6 months of life requires high caloric intake
- Breast feeding is recommended as sole nutrition in the first 6 months of life
- Various components of breastmilk are anti-inflammatory, protective against atopy and allergy
- Breast milk varies depending on maternal and infant health/age and other factors
- Breast milk likely plays an important factor in infant microbiome development
- Unclear evidence of breast milk’s effect on food allergy
OBJECTIVE 2: IDENTIFYING INFANTS AT RISK TO DEVELOP ALLERGIES

• Identify infant groups at high risk for developing food allergies
• Discuss allergy management strategies when breastfeeding
Infants at High Risk for Developing Allergies

Family atopic history is a strong indicator of food allergy development

- Both biologic parents (5%)
  - Potential for childhood allergy
    - 80% to 50%

- One biologic parent or sibling (31%)
  - or
  - Potential for childhood allergy
    - 40% to 20%

- Neither biologic parent (64%)
  - Potential for childhood allergy
    - 15%

1 Approximate numbers in developed countries
Infants at High Risk for Developing Allergies

• Approximately 55% of allergy incidence is diagnosed among children whose parents have no atopic history

• Only 9% of children diagnosed with food allergies have 2 biologic parents with atopic history

If the biologic parents have a history of food allergy, it is a good indicator the child will have allergy. If the biologic parents do not have atopic history, it is not a good indicator of allergy status in the child.

Common Symptoms and Comorbidities: Atopic Dermatitis

• Approximately 35% of children with atopic dermatitis have food allergies

• Among asthma, allergic rhinitis and atopic dermatitis, the allergic dermatitis will be the biggest predictor or risk for having food allergies

Adapted from Hill DA, Spergel JM. *Ann Allergy Asthma Immunol.* 2018;120(2):131–137.
## Types of Allergies

<table>
<thead>
<tr>
<th>IgE-Mediated</th>
<th>Non-IgE-Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can involve skin, respiratory,</td>
<td>Symptom onset is slower and symptoms are more chronic</td>
</tr>
<tr>
<td>gastrointestinal, and cardiovascular</td>
<td>More common in infancy</td>
</tr>
<tr>
<td>symptoms</td>
<td>Includes food protein induced enterocolitis syndrome and enteropathy</td>
</tr>
<tr>
<td>Onset is rapid</td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis may occur</td>
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</table>

**Mixed Allergies:** Eosinophilic diseases and atopic dermatitis
Gastrointestinal Presentation of Allergies in Infancy

- Gastrointestinal symptoms/comorbidities include:
  - Esophageal reflux or regurgitation
  - Stool irregularities (diarrhea, mucous in the stool, blood in stool)
  - Problems with growth

- Blood or mucous in the stool may be the only symptom in children with food allergies and may not have pain associated
  - May also be associated with gastrointestinal tract impairment, which requires **intervention of a specialist**
Therapy for Milk Protein Sensitivity

If Breastfeeding
Eliminate all dairy and soy (ie, foods with casein and whey)†
Consider formula-feeding options

If Formula-Fed
Semi-elemental formula
Assess symptoms
If symptomatic proceed to the next step
Elemental formula
Consider soy formula trial

†For example, foods with casein and whey might include bakery goods, high-protein beverages, dairy products, breath mints, coffee creamer, beef, fortified cereals, non-broth-based soups, nutrition bars, processed meats, chocolate, salad dressings, “lactose free” products
Summary: Infants at Risk for Allergies

- Infants with both parents with food allergies have a high risk to have food allergies
- Having parents without food allergies is NOT protective against developing food allergies
- Patients with atopic dermatitis have a higher risk for food allergies
- Food allergies in infancy can present as growth problems, “reflux” or spitting up, or stool irregularities
- Milk protein intolerance is a common allergy in infancy
OBJECTIVE 3: FORMULA OPTIONS

- Explore nutritional composition of cow’s milk-based formulas
- Compare non-milk-based formulas and indications for their use
Indications for Formula Feeding

Formula can be used as a supplement or substitute for human milk for:

• Mothers who choose not to or are unable to breastfeed

• Infants for whom breastfeeding is contraindicated (HIV, active tuberculosis)

• Breastfed infants that do not adequately gain weight
**Defining and Regulating Infant Formula Standards**

1938

**Food and Drug Cosmetic Act**
“A food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.”

1980

**Infant Formula Act**
Set standards for nutrient concentrations (minimums and maximums of vitamins and minerals determined with help from the American Academy of Pediatrics)

1985

**Infant Formula Act Amended**
Infant formula was defined as a separate class of food, increasing quality control testing.

## Four Tiers of Formula: Overview

<table>
<thead>
<tr>
<th>Tier 1:</th>
<th>“Routine” cow’s milk-based formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tier 2:</td>
<td>Cow’s milk alternatives (eg, soy milk) and modified cow’s milk-based formulas (eg, lactose-reduced milk, added rice starch formulas, partially hydrolyzed milk)</td>
</tr>
<tr>
<td>Tier 3:</td>
<td>Protein hydrolysate formulas or semi-elemental formulas</td>
</tr>
<tr>
<td>Tier 4:</td>
<td>Amino acid elemental formulas and metabolic/specialty formulas†</td>
</tr>
</tbody>
</table>

†Medical documentation required.

TIER 1: COW’S MILK-BASED FORMULA
Components of Cow’s Milk-Based Formulas

- **Macronutrients** – protein, carbohydrates, and fats
  - Butter fat is removed from milk
  - Carbohydrates (lactose) and vegetable oils are added
  - Protein content is decreased (34–15 g/L)
  - Long chain fatty acids are added (eg, soy, coconut, palm, sunflower, safflower)

- **Micronutrients** are highly regulated
  - Vitamins and minerals

- **Other ingredients** are added
  - Nucleotides
  - Pre- and probiotics
  - Amino acids

Cow’s Milk Macronutrients: Proteins

- The primary group of milk proteins are **caseins**
  - Highly digestible in the intestine
  - High source of amino acids

- All other milk proteins are known as **whey proteins**
  - Major whey proteins are **beta-lactoglobulin** and **alpha-lactalbumin**
  - Less digestible in the intestine
  - Undigested whey protein may stimulate a localized or systemic immune response
### Macronutrient Composition: Protein

<table>
<thead>
<tr>
<th>Human Milk</th>
<th>Cow’s Milk-Based Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Predominantly <strong>whey-based</strong> (about 70% whey)</td>
<td>• Predominantly <strong>casein-based</strong> (82% casein)</td>
</tr>
<tr>
<td>• Primary whey protein is <strong>alpha-lactalbumin</strong></td>
<td>• Primary whey protein is <strong>beta-lactoglobulin</strong>, the protein</td>
</tr>
<tr>
<td>• Includes other whey proteins involved in host defense</td>
<td>associated with cow’s milk allergy</td>
</tr>
</tbody>
</table>
### Macronutrient Composition: Fats

<table>
<thead>
<tr>
<th>Breast Milk</th>
<th>Cow’s Milk-Based Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provides 50% of calories</td>
<td>• Fat blends in formula are modified to contain greater medium- and intermediate-chain fatty acids to improve fat absorption</td>
</tr>
<tr>
<td>• Composition facilitates fat digestion and absorption (contains bile salt-stimulated lipase)</td>
<td>• Many are supplemented with DHA and ARA</td>
</tr>
<tr>
<td>• Contain <strong>Docosahexaenoic acid (DHA)</strong> and <strong>arachidonic acid (ARA)</strong> – important for neuronal tissue structure and cognitive development</td>
<td></td>
</tr>
</tbody>
</table>
Cow’s Milk Macronutrients: Carbohydrates

• In **breast milk**, carbohydrates are composed of lactose and lactose-based oligosaccharides
  • A small proportion of unabsorbed lactose leads to softer stool consistency, more nonpathogenic fecal flora, and improved absorption of minerals
  • Oligosaccharide structure mimics bacterial antigen receptors and prevents bacterial attachment to host mucosa

• **Cow’s milk-based formula** is typically lactose-based
Macronutrient Composition and Energy Content of Standard Infant Formula

Mean Macronutrient Concentrations

Mean Caloric Content

Things to Consider Among Standard Cow’s Milk-Based Formulas

- All formulas are iron fortified
- Comparison of organic to conventional cow’s milk-based formulas
  - No significant difference in macronutrient composition, quality, or safety
  - No difference in hormone levels
  - Neither contain antibiotics
- Each brand has a unique formulation

TIER 2: MILK ALTERNATIVES
Tier 2 Formulas

“Routine” Cow’s Milk-Based Protein Formula

- GE reflux
  - Added rice starch formula
- Infantile colic/irritability
  - Consider soy or a hydrolysate formula
- Milk protein allergy
- GI bleeding
  - EVAL
- Strong family history of allergy
  - EVAL

Tier 3 formula
Soy Formulas

• Formulas are plant-based and are whey, casein, and lactose-free

• There are limited applications for soy formulas, but they account for **25% of the formula market** in the United States
  • They are recommended for galactosemia, hereditary lactase deficiency, post-infectious diarrhea, and those who want a vegetarian diet
  • They are **not recommended** for premature infants

• Soy formula and phyto-oestrogen research has been conflicting but there have been some questions raised if early exposure leads to changes in bone health or reproductive health

Soy Formulas: Risks and Benefits

• There is no conclusive evidence that dietary soy isoflavones have adverse effects on development, reproduction, or endocrine function.

• Soy formulas can be allergenic
  • Of patients with cow’s milk protein intolerance, 10%–14% will react to soy.

• Benefit of soy formulas is their cost, which is considerably less than a hydrolysate or elemental formula.

Common Condition: Family History of Allergies

- For infants with a strong family history of allergies – consider a soy formula if symptoms present
- However, no evidence that avoiding an allergen will prevent an allergy
- Early exposure to allergenic foods prevents allergy later in life

Breast Milk

Supplementing or not breastfeeding

“Routine” Cow's Milk-Based Protein Formula

Strong family history of allergies

EVAL

Do nothing

Consider soy or a hydrolysate formula

Common Condition: Infantile Colic

- Characterized by inconsolable irritability for a period of approximately 2 to 4 hours per day between 3 weeks and 4 months of age
- When irritability is more prolonged or occurs outside those time parameters, other conditions should be considered
  - Allergies
  - Gastroesophageal reflux
  - Infection

“Routine” Cow’s Milk-Based Protein Formula

Infantile colic or irritability

Consider soy or a hydrolysate formula
TIER 3: SEMI-ELEMENTAL OR HYDROLYSATE FORMULAS
Removing the Protein Allergen: Hydrolysate (Tier 3) and Elemental Formulas (Tier 4)

All routine formulas (e.g., cow’s milk-based, soy) are made of complete protein chains that trigger allergic reactions.

Hydrolysate formulas break the protein chain into pieces. This is better tolerated by many, but can still trigger an allergic reaction.

Amino acid–based (elemental) formulas are made with individual non-allergenic amino acids. They are very well tolerated and classified as hypoallergenic.
Partially Hydrolyzed Formulas

- Partially hydrolyzed protein formulas (either casein and whey, or 100% whey)

- Partially hydrolysate formulas are **lactose free** and contain higher concentrations of **medium-chain triglyceride (MCT) oil**, which helps with malabsorption disorders

- These formulas are indicated for infants with soy or cow’s milk allergies or intolerance, surgical short gut, cholestasis, or bile acid deficiency

- **Not appropriate** for “happy spitters”
Common Condition: Milk Protein Allergy (IgE- or Non-IgE-mediated)

- May present with gastrointestinal bleeding, hematochezia, vomiting, rash (atopic dermatitis), wheezing, or cough
- Casein hydrolysate formulas should manage most milk protein intolerance in patients
- Many—but not all—infants with milk protein allergy are likely to tolerate soy
  - Use clinical signs to determine if soy should be tried
- Most infants with milk protein allergy outgrow it by age 9 months but could persist to age 36 months

Note: goat’s milk is not a safe alternative to cow’s milk for children with cow’s milk allergy

Reflux is common in children, but concerns arise when this leads to weight loss, failure to thrive, or feeding difficulties. In a subset of cases, reflux may be a presentation of milk protein intolerance and therefore casein hydrolysate should be used.

Amino Acid Elemental Formulas

- Contain individual nonallergenic amino acids
- Typically well tolerated and classified as hypoallergenic
- Do have a high osmotic load and may cause diarrhea as a result
Amino Acid Elemental Formulas

For infants that do not respond to casein hydrolysate/hydrolyzed casein with MCT oil formula, an amino acid formula may be indicated.

Amino Acid Elementals – Next Steps

- If infants respond to amino acid elemental or casein hydrolysate formula, next steps depend on severity of initial reaction
- It is appropriate to have a plan to re-introduce a “step down” formula at a set time

Amino Acid Elemental

- Improvement
  - Mild Initial Symptoms
    - Reintroduce “routine” formula at 6–9 months
  - Severe Initial Symptoms
    - Continue formula to 1 year of age

Casein Hydrolysate

- Improvement
  - Mild Initial Symptoms
    - Reintroduce “routine” formula at 6–9 months
  - Severe Initial Symptoms
    - Continue formula to 1 year of age

Key Takeaways

- When possible, exclusive breastfeeding should be encouraged until 6 months of age
- Although cow’s milk formula has been fortified to meet the nutritional needs of infants, human milk appears to have additional benefits, including support for the development of the immune system and gut microbiome
- Routine cow’s milk formula is suitable for the majority of infants
Key Takeaways (continued)

- Soy milk is an appropriate choice for infants allergic to cow’s milk, but soy reactivity is common in patients with cow’s milk protein allergy. There is conflicting evidence about the effect of soy formula on bone health and reproductive health of infants.

- Partially hydrolyzed casein formulas are appropriate choices for infants who are allergic to cow’s milk and do not tolerate soy.

- Elemental formulas should be reserved for infants who do not tolerate partially hydrolyzed formulas.