Optimizing Nutrition in Infants at High Risk for Developing Allergy

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Presented by
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Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

This activity is supported by an educational grant from
Mead Johnson Nutrition.

Faculty Disclosures

Tatyana Hofmekler, MD, MSc

faculty has no relevant financial relationships to disclose

Learning Objectives

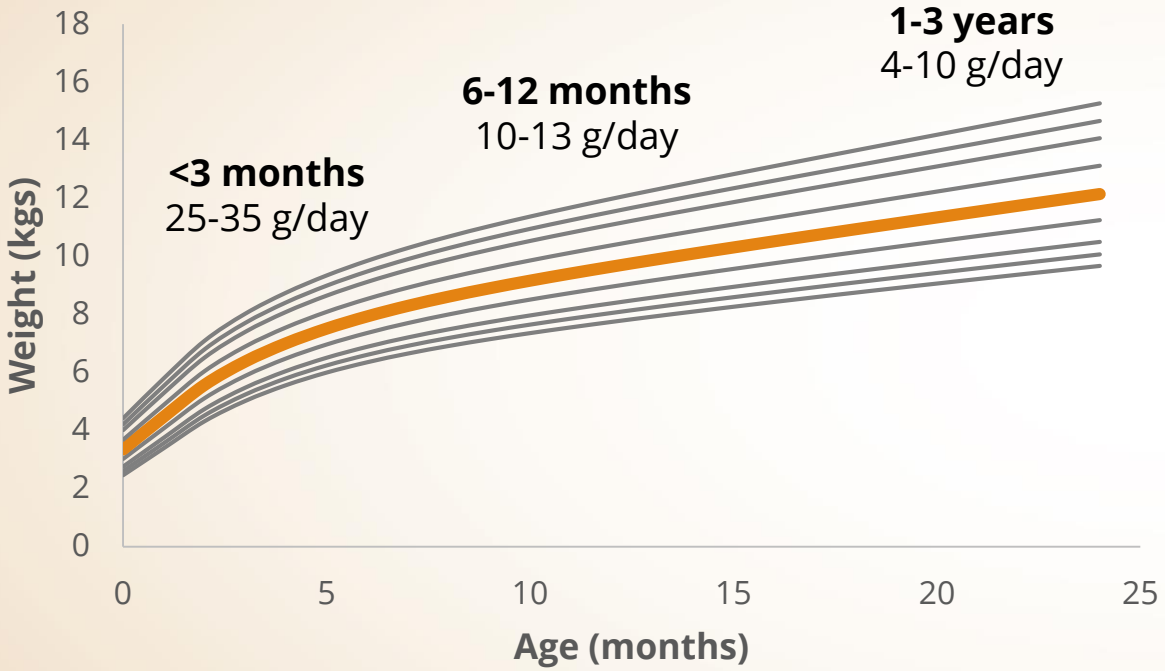
- Understand the role of human milk in preventing allergy development
- Recognize factors that predispose infants to allergy
- Identify formula options that support the nutritional needs of infants with food allergy

OBJECTIVE 1: HUMAN MILK AND ALLERGY

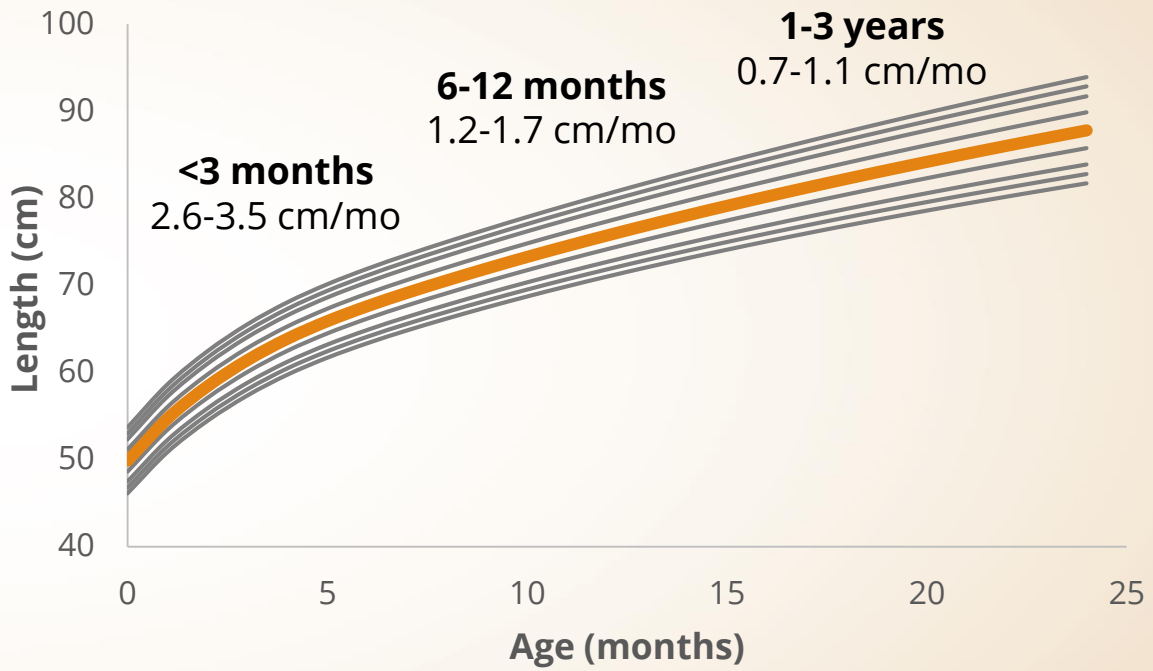
- Expected growth patterns for infants and children
- Benefits of human milk and breastfeeding
- Role of human milk in developing and maintaining normal food tolerance

Normal Growth Patterns in Infancy

Weight-for-Age Percentiles, Birth to 24 Months†



Length-for-Age Percentiles, Birth to 24 Months†



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

†For boys.

WHO Growth Charts. https://www.cdc.gov/growthcharts/who/boys_length_weight.htm. Updated September 9, 2010.

Rapid Growth in Infancy

Weight doubles by 4-6 months

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

Recommended Energy Intake Corresponds With Growth

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

1. Faulhaber D. *Pediatric Manual of Clinical Dietetics*. 2nd ed. 2003.
2. Fomon SJ, et al. *Am J Clin Nutr*. 1982;35(5):1169-1175.
3. Otten JS, et al. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. 2006.

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

1. National Center for Health Statistics: WHO Growth Charts. 2010.
2. National Center for Health Statistics: Clinical Growth Charts. 2017.

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

World Health Organization. https://www.who.int/mediacentre/news/statements/2011/breastfeeding_20110115/en/. Published January 15, 2011.

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)

Andreas NJ, et al. *Early Hum Dev*. 2015;91(11):629-635.

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Cytokines
TGFβ
Protective against atopic diseases

Nutritional Factors

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- Oligosaccharides
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Immunoglobulins
IgA
Potentially protective against cow's milk allergy[1]

1. Böttcher MF, et al. *Clin Exp Allergy*. 2002;32(9):1293-1298.
2. Andreas NJ, et al. *Early Hum Dev*. 2015;91(11):629-635.

Components of Human Milk

Immune Modulators

Immune cells
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Nutritional Factors

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

Oligosaccharides
Human Milk Oligosaccharides
Anti-inflammatory

Andreas NJ, et al. *Early Hum Dev*. 2015;91(11):629-635.

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)

Fatty Acids
DHA and EPA
Anti-inflammatory

Andreas NJ, et al. *Early Hum Dev*. 2015;91(11):629-635.

Developing Gut Immune System

Maternal Factors
Age
Parity
Genetics
Immune status
Diet
Environment

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

External Factors
Infant diet
Environment

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

Immature **Infant Gut Immune System** *Tolerant vs Intolerant*

1. Adapted from Rajani PS, et al. *Front Pediatr*. 2018;6:218.
2. Andreas NJ, et al. *Early Hum Dev*. 2015;91(11):629-635.

The Microbiome and Infant Health

- The microbiome is established within the first 2 years of life[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[1,2]

Gut dysbiosis precedes allergy development

1. Abrahamsson TR, et al. *J Allergy Clin Immunol*. 2012;129(2):434-440.
2. Azad MB, et al. *Clin Exp Allergy*. 2015;45(3):632-643.
3. Macfarlane GT, Macfarlane LF. *Dig Dis*. 2009;27 Suppl 1:90-98.

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

1. Kramer MS, et al. *JAMA*. 2001;285(4):413-420.
2. Greer FR, et al. *Pediatrics*. 2008;121(1):183-191.
3. Kramer MS, Kakuma R. *Cochrane Database Syst Rev*. 2012;(8):CD003517.

Summary: Human Milk and Allergy Development

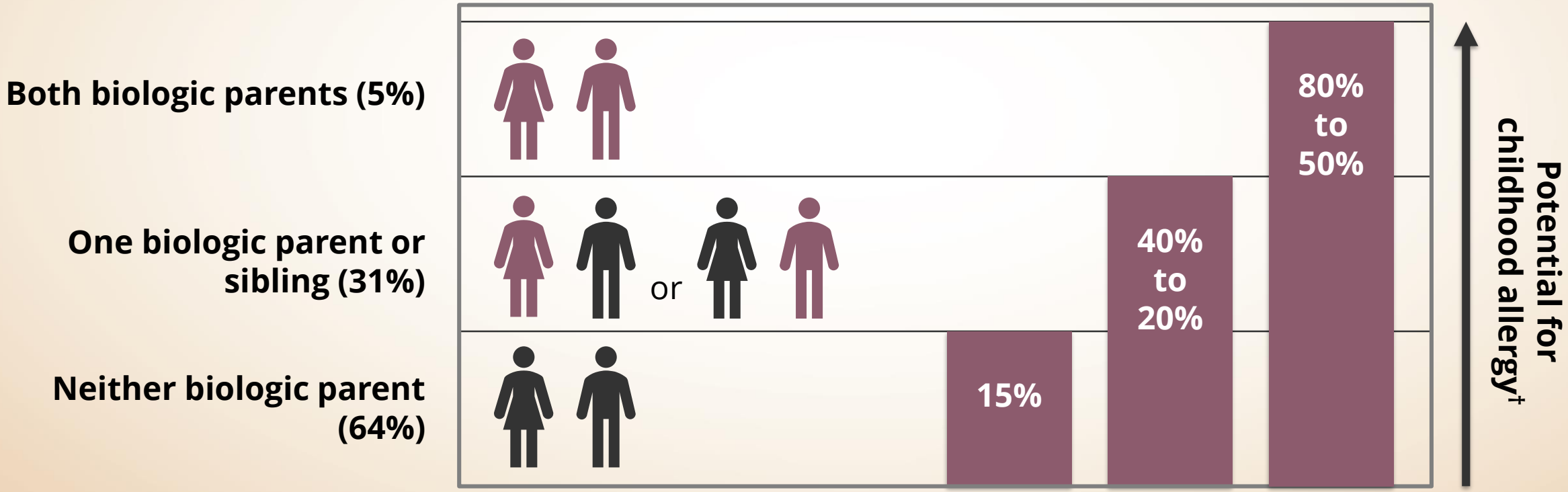
- Rapid growth in the first 6 months of life requires high caloric intake
- Breast feeding is recommended as sole nutrition in the first 6 months of life
- Various components of breastmilk are anti-inflammatory, protective against atopy and allergy
- Breast milk varies depending on maternal and infant 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



†Approximate numbers in developed countries

1. Bousquet J, Kjellman NI. *J Allergy Clin Immunol*. 1986;78(5 Pt 2):1019-1022.
2. Halken S, Høst A. *Allergy*. 2000;55(9):793-802.
3. Kjellman NI. *Acta Paediatr Scand*. 1977;66(4):465-471
4. Exl NM, Fritsché R. *Nutrition*. 2001;17(7-8):642-651.

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.

1. Bousquet J, Kjellman NI. *J Allergy Clin Immunol*. 1986;78(5 Pt 2):1019-1022.
2. Halken S, Høst A. *Allergy*. 2000;55(9):793-802.
3. Kjellman NI. *Acta Paediatr Scand*. 1977;66(4):465-471
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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

IgE-Mediated	Non-IgE-Mediated
• Can involve skin, respiratory, gastrointestinal, and cardiovascular symptoms • Onset is rapid • Anaphylaxis may occur	• Symptom onset is slower and symptoms are more chronic • More common in infancy • Includes food protein induced enterocolitis syndrome and enteropathy

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**

Ho MH, et al. *Clin Rev Allergy Immunol*. 2014;46(3):225-240.

Therapy for Milk Protein Sensitivity

If Breastfeeding

Eliminate all dairy and soy (ie, foods with casein and whey)[†]

Assess symptoms
If symptomatic proceed to the next step

Consider formula-feeding options

If Formula-Fed

Consider soy formula trial

Semi-elemental formula

Elemental formula

[†]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.

Fomon S. *J Nutr*. 2001;131(2):409S-420S.

Four Tiers of Formula: Overview

Tier 1: "Routine" cow's milk-based formula

Tier 2: 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)

Tier 3: Protein hydrolysate formulas or semi-elemental formulas

Tier 4: Amino acid elemental formulas and metabolic/specialty formulas[†]

[†]Medical documentation required.

Cohen S, Crane K. Formula algorithm for infants on Georgia WIC. 2017.

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

Green Corkins K, Shurley T. *Nutr Clin Pract*. 2016;31(6):723-729.

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

Human Milk	Cow's Milk-Based Formula
• Predominantly **whey-based** (about 70% whey) • Primary whey protein is **alpha-lactalbumin** • Includes other whey proteins involved in host defense	• Predominantly **casein-based** (82% casein) • Primary whey protein is **beta-lactoglobulin**, the protein associated with cow's milk allergy

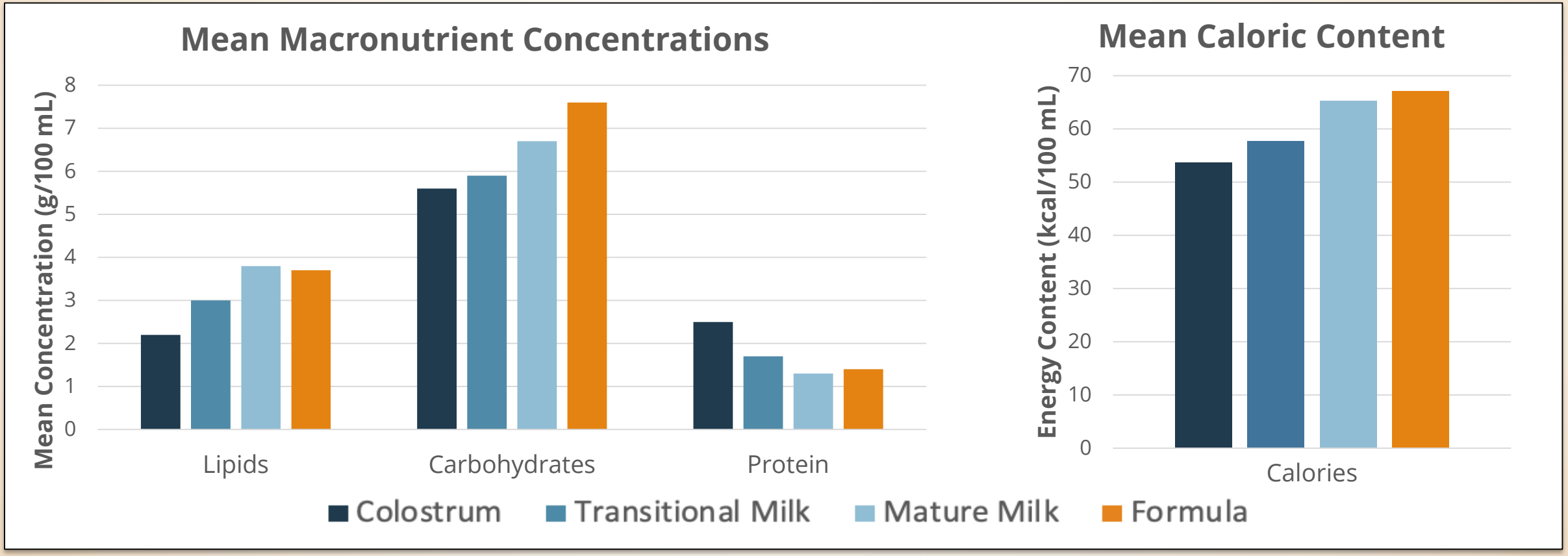
Macronutrient Composition: Fats

Breast Milk	Cow's Milk-Based Formula
• Provides 50% of calories • Composition facilitates fat digestion and absorption (contains bile salt-stimulated lipase) • Contain **Docosahexaenoic acid (DHA)** and **arachidonic acid (ARA) –** important for neuronal tissue structure and cognitive development	• Fat blends in formula are modified to contain greater medium- and intermediate-chain fatty acids to improve fat absorption • Many are supplemented with DHA and ARA

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



Hester SN, et al. *J Nutr Metab*. 2012;2012:891201.

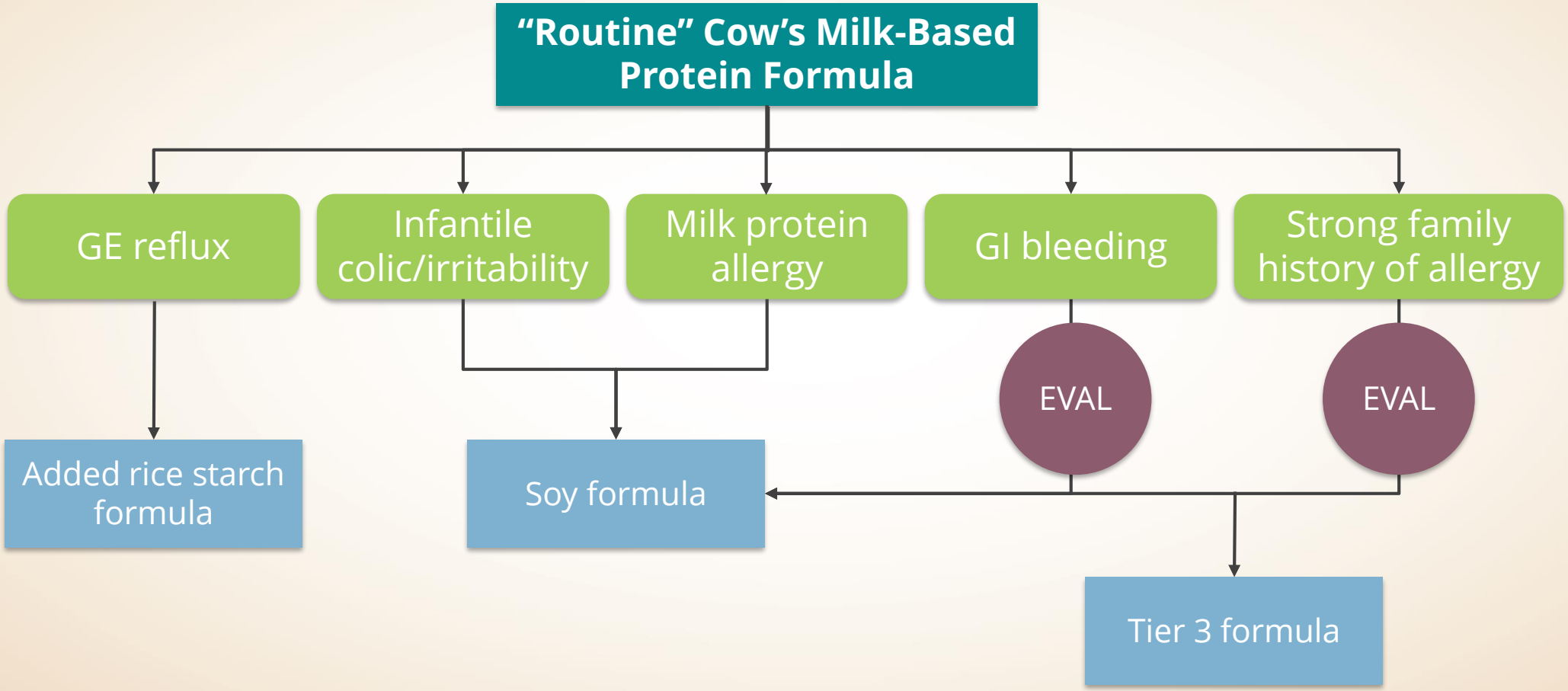
Things to Consider Among Standard Cow's Milk-Based Formulas

- 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

Green Corkins K, Shurley T. *Nutr Clin Pract*. 2016;31(6):723-729.

TIER 2: MILK ALTERNATIVES

Tier 2 Formulas



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

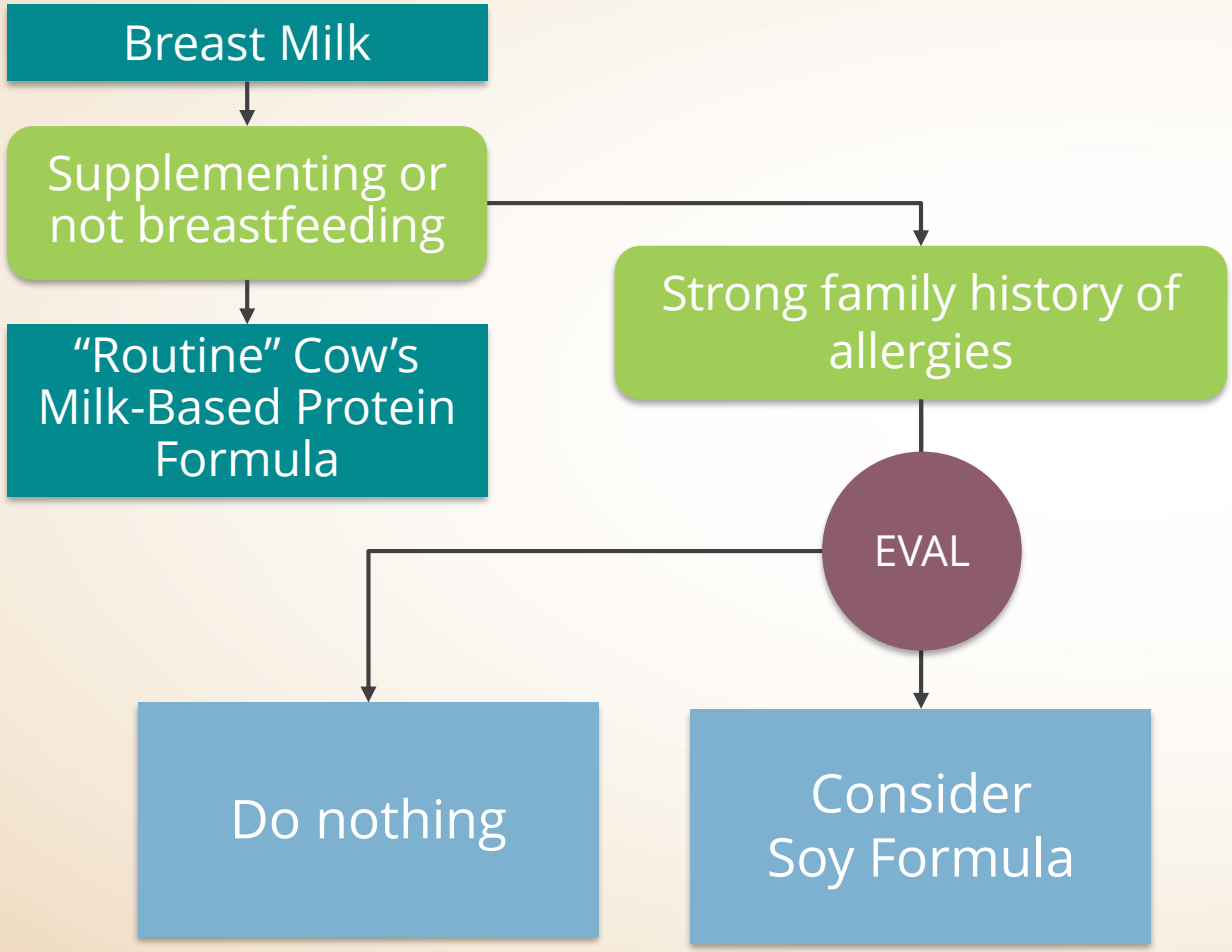
1. Green Corkins K, Shurley T. *Nutr Clin Pract*. 2016;31(6):723-729.
2. Bhatia J, et al. *Pediatrics*. 2008;121(5):1062-1068.

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

1. Green Corkins K, Shurley T. *Nutr Clin Pract*. 2016;31(6):723-729.
2. Bhatia J, et al. *Pediatrics*. 2008;121(5):1062-1068.

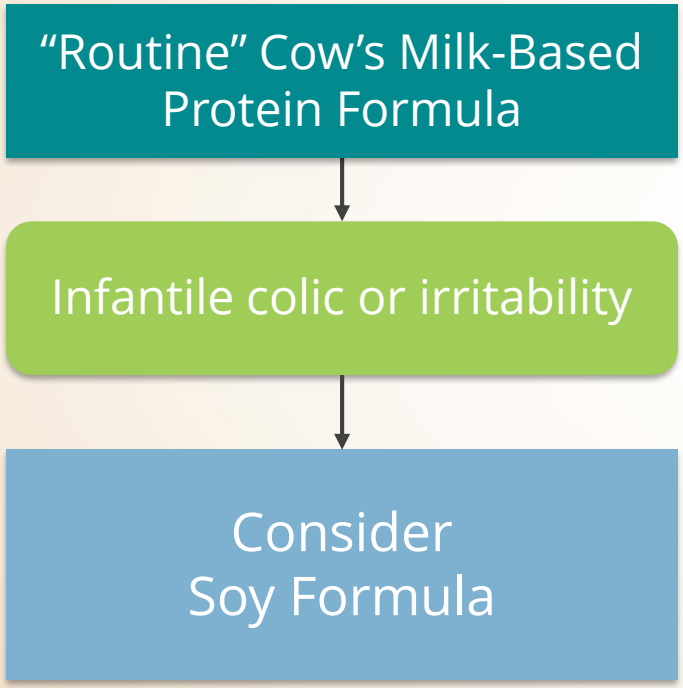
Common Condition: Family History of Allergies



- 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

Cohen S, Crane K. Formula algorithm for infants on Georgia WIC. 2017.

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

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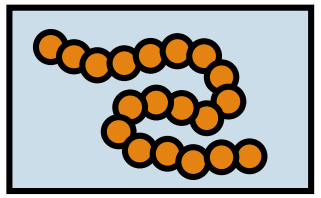
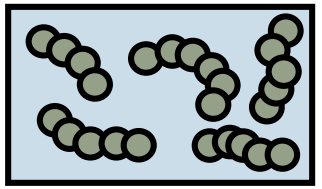
TIER 3: SEMI-ELEMENTAL OR HYDROLYSATE FORMULAS

Removing the Protein Allergen: Hydrolysate (Tier 3) and Elemental Formulas (Tier 4)

Most Allergenic

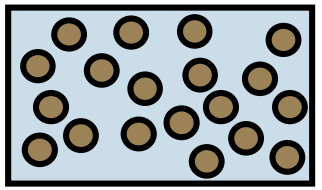


All **routine formulas (eg, cow's milk-based, soy)** are made of complete protein chains that trigger allergic reactions.



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

Least Allergenic

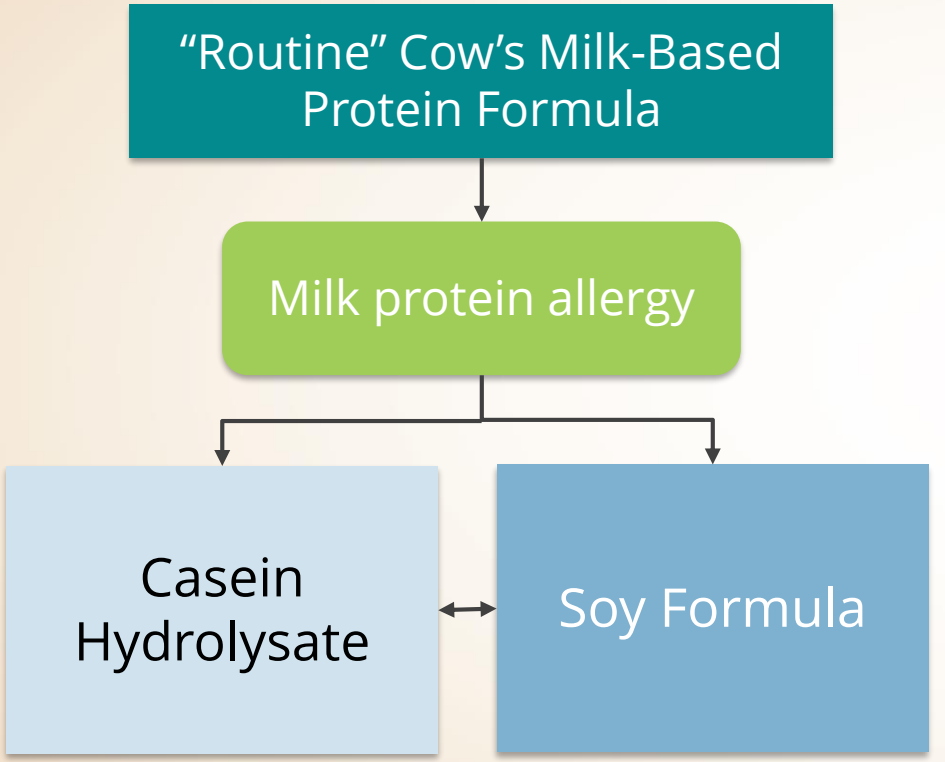


Amino acid–based (elemental) formulas are made with individual non-allergenic amino acids. They are very well tolerated and classified as hypoallergenic.

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)



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

- 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

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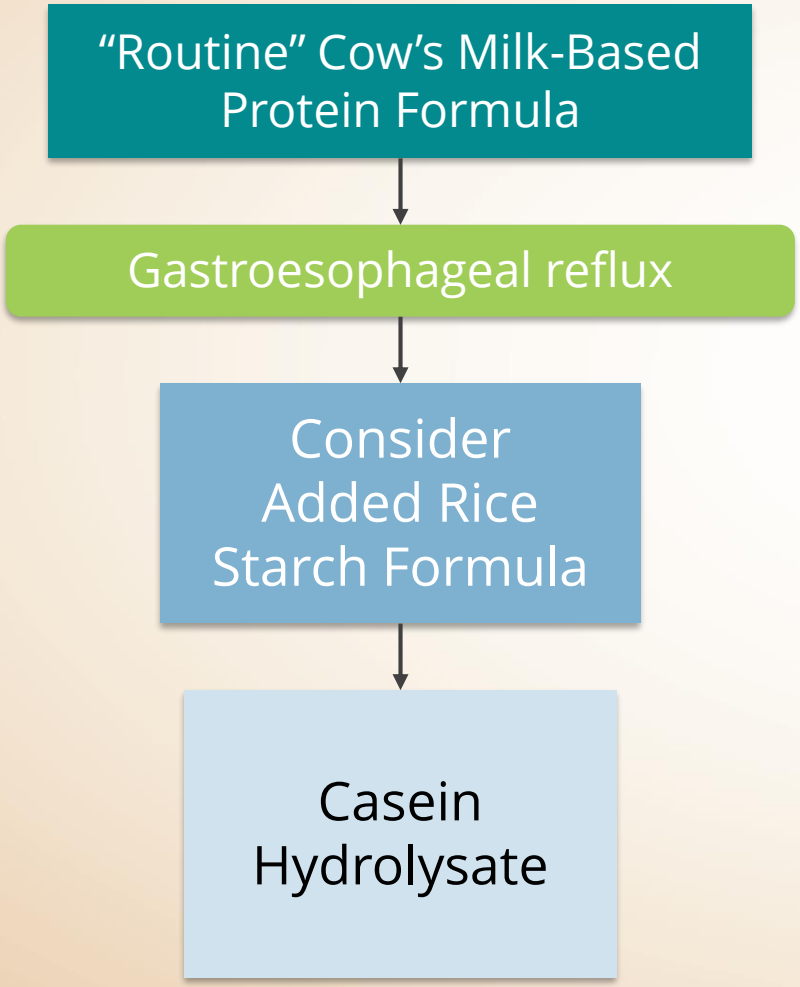
Common Condition: Gastroesophageal Reflux



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[1]

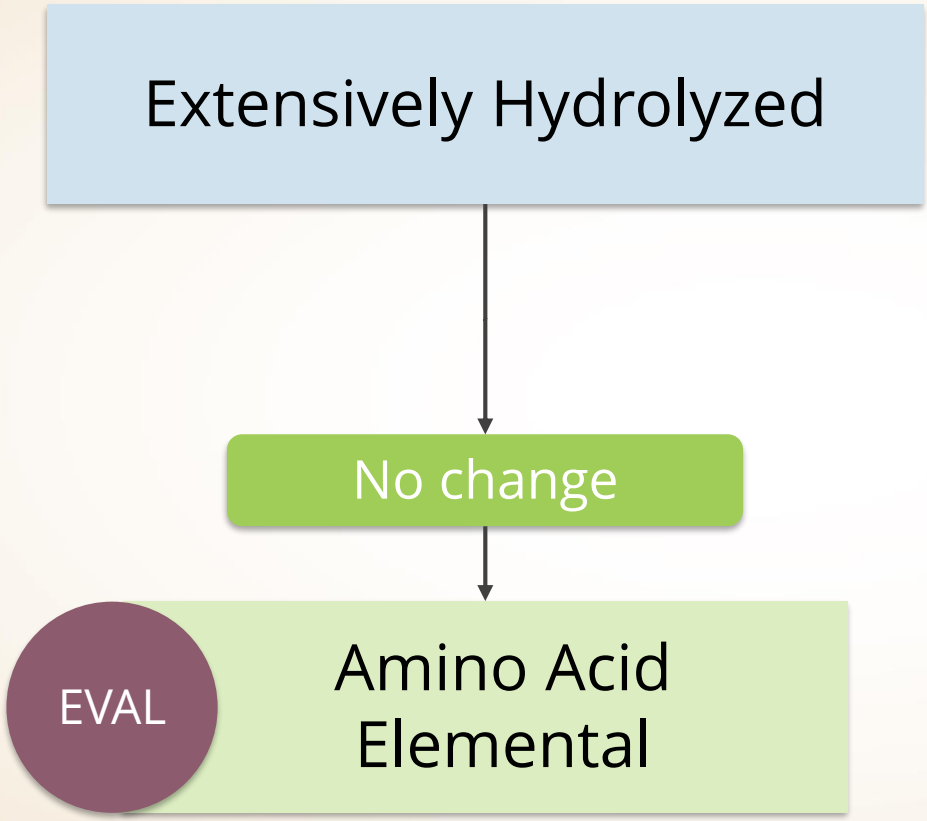
1. Mousa H, Hassan M. *Pediatr Clin North Am*. 2017;64(3):487–505.
2. Cohen S, Crane K. Formula algorithm for infants on Georgia WIC. 2017.

TIER 4: AMINO ACID ELEMENTAL FORMULAS

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

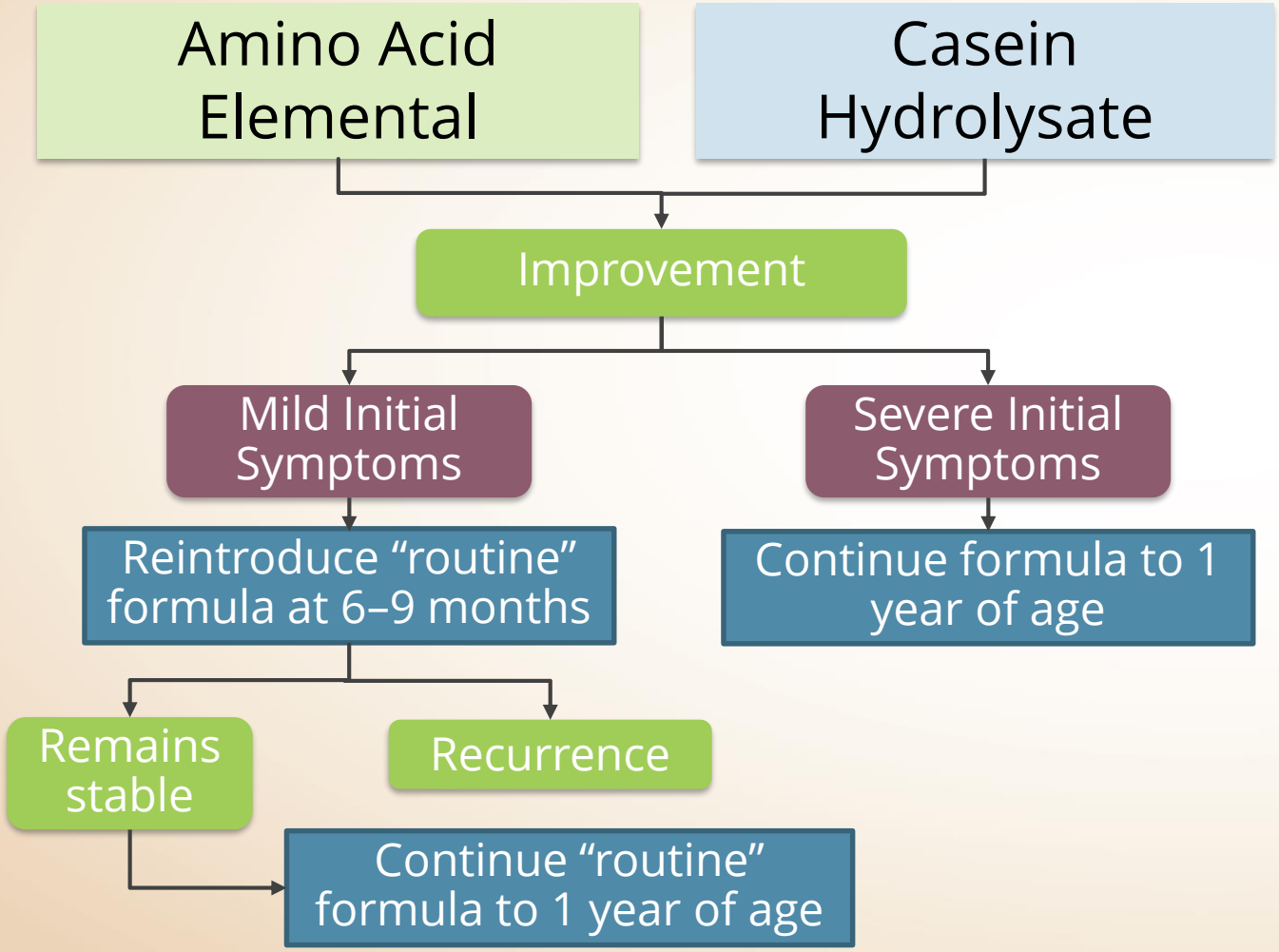
Amino Acid Elemental Formulas



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

Cohen S, Crane K. Formula algorithm for infants on Georgia WIC. 2017.

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

Cohen S, Crane K. Formula algorithm for infants on Georgia WIC. 2017.

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
- 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