



Optimizing Nutrition in Infants at High Risk for Developing Allergy

Overview

Tatyana Hofmekler, MD, MSc, discusses the role of human milk in preventing allergy development, as well as identifying formula options that support the needs of infants with food allergies or those at high risk for food allergies. Topics covered include an overview of nutritional and growth considerations for children; benefits of human milk and breastfeeding; identification of infants at high risk for developing allergies; the nutritional composition of infant formula options; and comparison of non-cow's milk-based formulas and their indications for use.

Target Audience

This activity was developed for pediatric physicians, nurses, nurse practitioners, dietitians, allergists and other health care providers who have an interest in newborns, infants and toddlers.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- 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.

Faculty

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Contact Information

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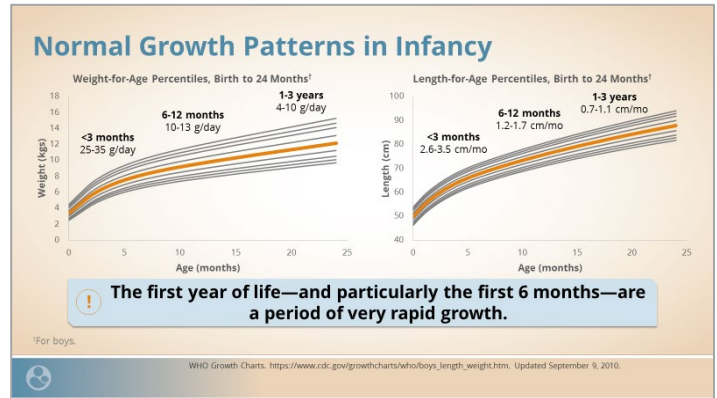


Dr. Tatyana Hofmekler: We have 3 main learning objectives. Number 1 is to understand the role of human milk in allergy development. Number 2 will be to recognize factors that predispose infants to allergy. Finally, number 3 will be to identify formula options that support the nutritional needs of infants with food allergy.

Human Milk and Allergy

I will go ahead and start addressing objective number 1. When discussing human milk and allergy, and the relationship to allergy, we're going to talk about 3 main factors. We will discuss the expected growth patterns for infants and children. We will discuss the benefits of human milk and breastfeeding, and then we will discuss the role of human milk in developing and maintaining normal food tolerance.

On this slide [Slide 1], you will see the graphs of expected growth for infant boys ages 0–24 months. This is from the WHO growth charts.¹ These are very useful charts that are needed for us to plot out the expected growth patterns for infants. It is important to know what the expected and the normal patterns of growth will be because then we can identify children that have deviated from the norms.



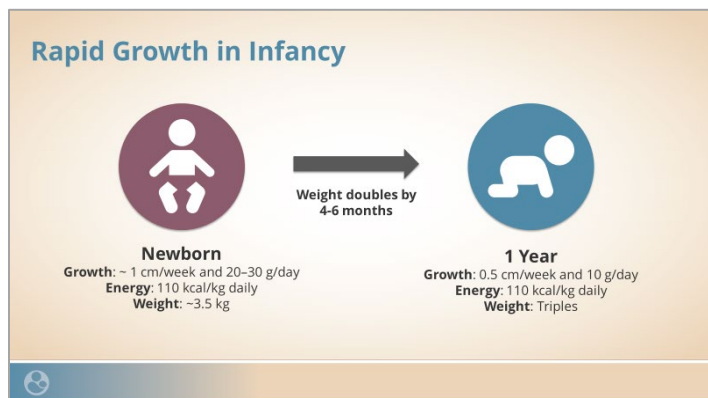
Slide 1 – Normal Growth Patterns in Infancy

The WHO growth charts are useful to track kids from ages 0–24 months. They have different percentile curves that children will typically follow. There are charts for the expected growth for the weight-for-age, weight-for-length, and head circumference.

What I'd like you to understand is that in the first 6 months of life, as we all know, children should grow rapidly. In the first 3 months of life, we expect about 30 g of weight gain per day, and about 2.5 cm of linear growth per month. These are very fast growth rates.

Because there is such fast expected growth in the first several months of life, there are high energy requirements. In the first year of life, children should eat at least 100 kcal/kg per day to support this rapid weight gain. As weight gain increases, we expect the child's weight to double in the first 4–6 months of life, and then triple by about 1 year of age. Again, this is a time of very fast growth and high energy requirements.

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Slide 2 – Rapid Growth in Infancy

Here is a chart that further highlights the energy requirements of infants [Slide 3]. In the first 2 columns, there is this rapid expected weight gain and length gain in the first several months of life. This drops down around the time the child reaches school age. Similarly, as can be expected, you have really high energy needs of about 100 or 110 kcal/kg in the first several months of life before requirements drop down to about 70 kcal/kg once children reach 7-10 years.²

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(1):1168-1175.
3. Orem JS, et al. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. 2006.

Slide 3 – Recommended Energy Intake Corresponds With Growth

While the WHO growth charts are very helpful in the first 2 years of life, and the CDC growth charts are used for children 2 years and older, all infants should follow a set pattern of growth along these percentile points. There will be small deviations of course. For example, large-for-gestational-age infants and small-for-gestational-age infants may shift a few percentile points in the first months of

life. They then tend to normalize to a new percentile point by 2-3 months of age and will develop a new growth pattern from that set point that follows an expected growth curve.

Evaluating Infant and Child Growth

- Monitoring growth of children
 - WHO growth charts¹ – Ages 0 to 2 years
 - CDC growth charts² – 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.

Slide 4 – Evaluating Infant and Child Growth

However, a deviation from the norm resulting in poor growth should always be a concern and should be promptly evaluated. In some cases, this can be an indication of an allergy, which we'll talk about a little later.

To maintain expected growth, the WHO recommends that human milk be the sole source of nutrition for healthy term infants until 6 months of age. There are many different benefits to breastfeeding. We know that breastfeeding reduces the risk of many chronic illnesses, such as obesity, hypertension, and dyslipidemia.³

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.

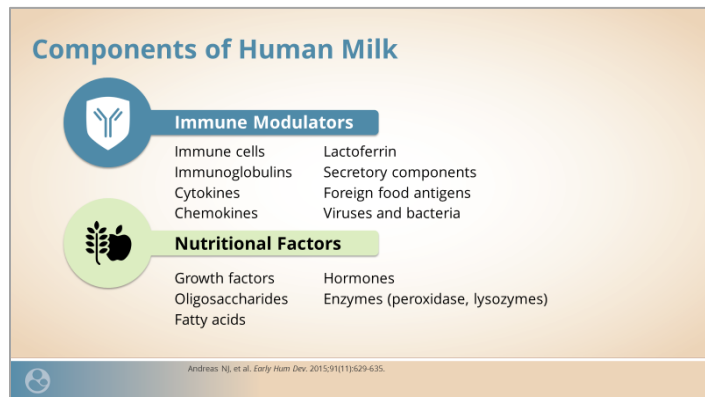
Slide 5 – Optimal Feeding Practices

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Right now, breast milk is really known to be the best source of nutrition. The nutritional composition of human milk serves as the basis for infant formula, but it can never be duplicated.

There are very many different components of human milk that are still being studied and understood. We will highlight a few of them as they relate to allergies.

There are various immune modulators in breast milk, including immune cells, immunoglobulins, cytokines, chemokines, lactoferrin, secretory components, foreign food antigens, and viruses and bacteria, which are all transferred from the mother to the infant. There are also nutritional factors, such as growth factors, oligosaccharides, fatty acids, hormones, and enzymes, such as peroxidases and lysozymes, in breast milk.⁴



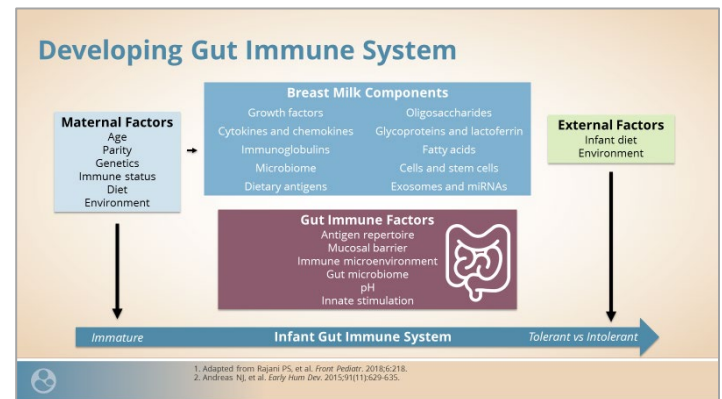
Slide 6 - Components of Human Milk

Among the immune modulators listed, cytokines include $TGF\beta$, which has been shown to be protective against atopic diseases. Immunoglobulin A is high in breast milk, and we know it's likely protective against cow's milk allergy.

Human milk oligosaccharides are anti-inflammatory, and also found in human milk. Fatty acids, such as DHA and EPA, are anti-inflammatory, and naturally found in human milk.

All of these components are found in human milk, but not all of them can be replicated in formula.

This is a complicated slide [Slide 7], but what we're trying to highlight is that the developing gut is exposed to different substances from a variety of sources, which contributes to the development of a healthy gut and subsequently a healthy and tolerant immune system.



Slide 7 - Developing Gut Immune System

Many allergens are first introduced to our systems through the GI tract, which has an important connection to our immune system. In the bottom left-hand corner, we're showing that infants are born with immature guts. The immature gut is influenced by many factors, as the infant gut immune system is developed. Internal and external factors then influence whether the infant gut immune system develops into a tolerant or an intolerant immune system.

These are the factors that we think play a role into developing a tolerant vs an intolerant immune system. There are many different maternal factors that either directly affect the infant's immune system, either through genetics, or the mother's diet.

Various maternal factors also directly influence the breast milk components. We know breast milk will change a great deal in comparison from one mother to another mother, and even at different times and ages of the child. The different breast milk components will change, and so all those factors further influence the infant gut immune system.



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Finally, there are inherent factors that are specific to the child, such as the antigen repertoire, the pH of the intestinal system, the microbiome, or the bacterial makeup of various either stimulants that the child may be experiencing. Of course, there are external factors, such as diet outside of breast milk, and environmental factors, that will influence the infant gut immune system.

All of this is just to show that it's a complicated system. Definitely there are many maternal factors that either directly influence the child's immune system or will influence the immune system through various components of breast milk.

The Microbiome and Infant Health

- The microbiome is established within the first 2 years of life³
 - 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. Aasi MB, et al. *Clin Exp Allergy*. 2015;45(3):524-543.
3. Macfarlane GT, Macfarlane LP. *Dig Dis*. 2009;27 Suppl 1:90-98.

Slide 8 - The Microbiome and Infant Health

Additionally, the infant's microbiome is a very important part in developing infant health. The gut microbiome is a term that describes the bacterial makeup of the intestinal tract. We all know that the microbiome is established for most infants in the first 2 years of life, so the first 2 years of life are very important for future health, gut health, and immune health.

In a healthy microbiome in an infant, *Bifidobacteria* dominate the early stages. We also know that high diversity of the microbiome is a good thing and may be protective.

High gut diversity is associated with a reduced risk of atopy later on in life. The things that we know influence and increase gut diversity include the following: living on a farm, avoiding antibiotics early

on in life, and vaginal delivery. Atopy, eczema, and food allergies are all associated with low gut diversity.^{5,6}

Interestingly, we know that gut dysbiosis happens before an allergy develops. That means we know that gut dysbiosis—meaning an irregular amount or composition of bacteria—happens before we actually see allergy symptoms develop.

This is what we know regarding human milk and allergy development. We know that exclusive breastfeeding in the first 4 months of life is associated with a reduced risk of eczema, wheezing, and cow's milk allergy later in life. However, breastfeeding beyond 4 months of life does not reduce the risk of asthma or other atopic diseases. Breastfeeding in the first year of life does reduce risk of GI illnesses.⁷

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;(6):CD003517.

Slide 9 - Benefits of Human Milk and Allergy Development

Unfortunately, most studies on breastfeeding have been too small to study the effects of food allergy development. We also know that maternal avoidance of foods during their pregnancy or breastfeeding is currently not recommended, unless there is a known infant allergy or intolerance.⁷

Unfortunately, what I mentioned earlier, that there is large variation in breast milk composition across mothers as well as different times that mothers are breastfeeding and the age of the child. Because there is such a large variation in these different

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factors, it makes studying the effects of breast milk difficult.

As a summary, there is rapid growth in the first 6 months of life that require high caloric intake. Breastfeeding is recommended as the sole nutrition in the first 6 months of life. Various components of breast milk are anti-inflammatory and protective against atopy and allergy.

Breast milk composition varies depending on maternal health, infant health and age, and other factors. Breast milk likely plays an important role in the infant microbiome development, but it is unclear exactly how breast milk affects food allergy development later on.

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 breast milk 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 affect on food allergy

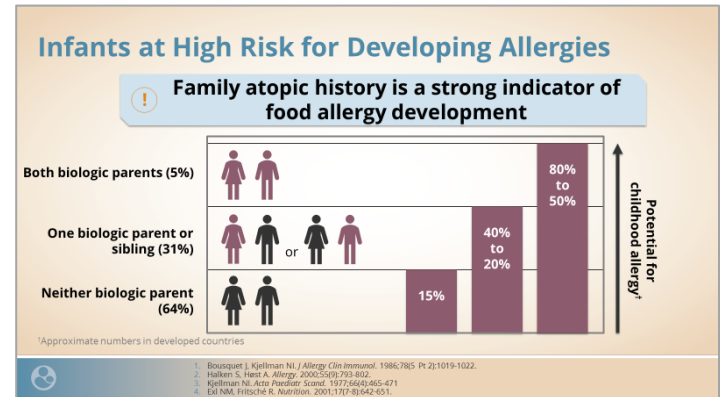
Slide 10 – Summary: Human Milk and Allergy Development

Identifying Infants at Risk to Develop Allergies

We will move on to objective 2, which is identifying infants at high risk for developing allergies. In this objective, we will talk about ways to identify infant groups at high risk for developing food allergies. We will discuss allergy management strategies when breastfeeding, as well.

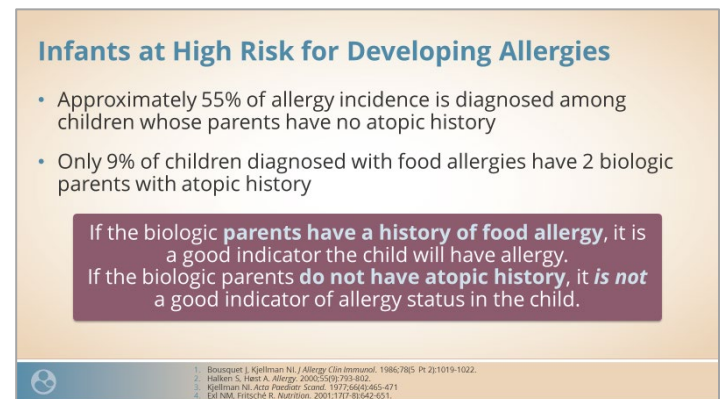
Unfortunately, what we have learned is that genetics do play an important role, as they do in many things, in developing a risk for allergies in infants. A family atopic history is a strong indicator of food allergy development. If both parents have a food allergy, this places their infants at the highest risk. If there is 1 family member or sibling with

atopy, then it still places the infant at risk, but not quite as high a risk. Definitely, parents without atopy will have children with the lowest risk for developing allergies.



Slide 11 – Infants at High Risk for Developing Allergies

However, we also know that approximately half of allergy incidence is diagnosed in children whose parents have no atopic history at all. Only 9% of children diagnosed with food allergies have 2 biologic parents with atopy. The other way I would summarize this is that if the biologic parents have a history of food allergy, it is a pretty good indicator that the child will have an allergy as well. However, if the biologic parents do not have an atopic history, that is not protective against the child not having an allergy.



Slide 12 – Infants at High Risk for Developing Allergies

There are common presentations and copresentations of food allergy, such as atopic

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dermatitis. Approximately 35% of children with atopic dermatitis will have food allergies. Atopic dermatitis is probably one of the highest predictive factors for food allergies later in life. For example, considering kids with asthma, allergic rhinitis, or atopic dermatitis, the dermatitis will be the highest predictor that there will be a food allergy later on.

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.

Slide 13 – Common Symptoms and Comorbidities: Atopic Dermatitis

It's important to remember that there are different kinds of allergies. There are IgE-mediated and non-IgE-mediated allergies. Then there are allergies that are mixed and fall into both categories. IgE-mediated allergies can involve the skin, respiratory system, gastrointestinal, and cardiovascular symptoms. The symptom onset is usually pretty fast, so a child who is exposed to an allergen will have a reaction quickly afterwards, within an hour or so, and anaphylaxis can occur.

Types of Allergies

IgE-Mediated	Non-IgE-Mediated
<ul style="list-style-type: none"> • Can involve skin, respiratory, gastrointestinal, and cardiovascular symptoms • Onset is rapid • Anaphylaxis may occur 	<ul style="list-style-type: none"> • 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

Slide 14 – Types of Allergies

Non-IgE-mediated allergies are associated with symptoms that occur more slowly, with a later onset. These are also much more common in infancy. Examples will include things like food protein-induced enterocolitis syndrome, or FPIES, and enteropathy.

As I mentioned, there are some conditions that have an overlap of both IgE and non-IgE-mediated allergies. That would include things like eosinophilic esophagitis, or eosinophilic GI disease, and atopic dermatitis.

There can be various presentations of allergies in infancy. GI symptoms can include things such as gastroesophageal reflux, or regurgitation. It can also include symptoms such as stool irregularities, where an infant has profuse diarrhea, mucous in the stool, or blood in the stool. There can also be problems with growth. That's why it's important to understand what normal growth patterns look like.

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;44(3):225-240.

Slide 15 – Gastrointestinal Presentation of Allergies in Infancy

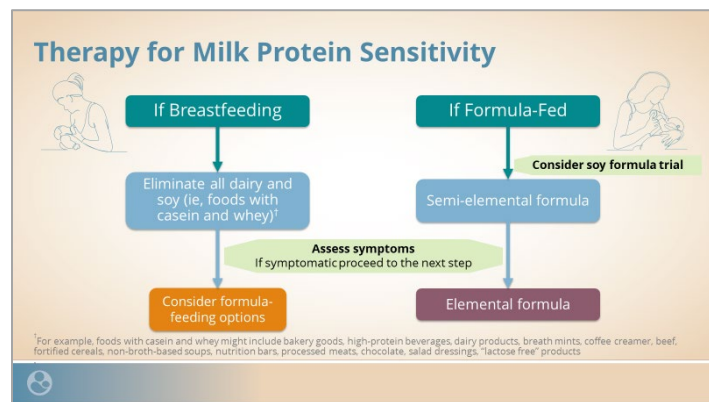
In some kids, blood or mucous in the stool may be the only symptom, and there may not be a whole lot of pain or discomfort associated with it. I would say whenever there is a significant amount of blood in the GI tract, I would recommend that a specialist evaluate the child.

The most common allergy and sensitivity in infancy is cow's milk protein sensitivity or allergy. This is a quick breakdown of an approach to addressing this [Slide 16]. We will talk about selecting infant

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formulas for cow's milk allergy in more detail in the upcoming slides.

But if a child is breastfeeding, then we can ask the mother to eliminate either all dairy and soy, and sometimes just exclusively just dairy elimination. Then, if there is an improvement, the mother can continue breastfeeding and eliminating dairy and soy from her diet. However, if the symptoms persist, then sometimes other food options may need to be eliminated from mom's diet, or you may need to consider other feeding options, such as formula.



Slide 16 – Therapy for Milk Protein Sensitivity

If a child is formula-fed and appears to have cow's milk allergy, then generally the child should transition either to a soy formula or a semi-elemental formula. Soy formula sometimes works, but sometimes it does not work. We'll talk about that in more detail later on. If a semi-elemental formula doesn't improve symptoms, then an elemental formula can be tried.

As a summary for this section, infants with both parents with food allergies have a high risk to having food allergies, as well. Having parents without food allergies, however, is not protective against developing food allergies.

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

Slide 17 – Summary: Infants at Risk for Allergies

Patients with atopic dermatitis have a higher risk for food allergies than other atopic diseases. Food allergies in infancy can present as either growth problems, reflux, spitting up, or just irregular stooling conditions, such as mucous and blood. Milk protein intolerance is the most common allergy that we see in infants.

Formula Options

Moving on to objective number 3, we will discuss various formula options. We'll explore nutritional components of cow's milk-based formulas, compare non-milk-based formulas, and indications for their use.

As a reminder, formula can be used as a supplement or a substitution for human milk for various reasons. Sometimes mothers cannot or choose not to breastfeed. Sometimes there are infants where breastfeeding is contraindicated. For example, an HIV infection in mom or active tuberculosis are contraindications for breastfeeding. In other cases, there are breastfed infants that simply do not gain adequate weight, and then we sometimes opt to supplement with formula.

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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

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 algorithms for infants on Georgia WIC. 2017.

Slide 18 – Indications for Formula Feeding

As a reminder, formulas are well regulated, and they are safe products. As early as 1938, formulas were protected by the Food and Drug Cosmetic Act. In 1980, additional laws were passed that further regulated the amount of vitamins and minerals in all infant formulas. These standards were set in place by the Academy of Pediatrics. In 1985, the Infant Formula Act was further amended, defining infant formula as its own class of food, increasing the quality control testing.

Slide 20 – Four Tiers of Formula: Overview

Tier 1 will be the routine cow's milk-based formulas. Those are the most common ones you'll see on your shelves in the grocery stores. Tier 2 will be cow's milk alternatives, so either soy milk formulas, modified cow's milk-based formulas, such as lactose-reduced milks, or formulas with added rice-starch formula in them. Tier 3 will be the protein hydrolysate formulas, or semi-elemental formulas. Those will definitely be more difficult to find at your stores. Then, Tier 4 are the amino acid elemental formulas, and the specialty formulas.⁸

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.

Slide 19 – Defining and Regulating Infant Formula Standards

There are many different formulas out there, and I would like to categorize formulas into 4 broad tiers. That helps us keep them straight, and keep track of them, and what they would be best used for.

Tier 1: Cow's Milk-Based Formula

I would like to discuss the basic components of the Tier 1 cow's milk-based formulas first. As with anything, the basic components will include the macronutrients, such as the protein, carbohydrates, and fats. They will also include the micronutrients, which are the vitamins and minerals. These are the components that are regulated by legislation, for which there are strict guidelines. Then there are other ingredients that are sometimes added in, such as nucleotides, pre- and probiotics, and amino acids.

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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, Sharley T. *Nutr Clin Pract*. 2016;31(6):723-729.

Slide 21 – Components of Cow's Milk-Based Formulas

Going back to the macronutrients, when cow's milk-based formula is made, actual cow's milk is used, and butter fat is removed from the milk. Carbohydrates, such as lactose, and vegetable oils are then added back in. Protein content is reduced relative to regular cow's milk, and long-chain fatty acids are added, such as soy, coconut, palm, sunflower, and safflower oils.

Let's talk about the types of protein found in formula and breast milk. The primary proteins in formula are casein, and these are highly digestible and a good source of 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

Slide 22 – Cow's Milk Macronutrients: Proteins

All other milk proteins are known as whey proteins. The major whey proteins are beta-lactoglobulins and alpha-lactoglobulins. These are less digestible than casein. Sometimes, if there is undigested whey

protein in the GI tract, it may stimulate a localized or systemic immune response.

Comparing the protein content between human milk and cow's milk-based formulas, human milk is predominantly whey-based, specifically alpha-lactoglobulin, which is less reactive than beta-lactalbumin. There will be other whey proteins, as well, and they are involved in the host defense system.

Macronutrient Composition: Protein

Human Milk	Cow's Milk-Based Formula
<ul style="list-style-type: none"> • Predominantly whey-based (about 70% whey) • Primary whey protein is alpha-lactalbumin • Includes other whey proteins involved in host defense 	<ul style="list-style-type: none"> • Predominantly casein-based (82% casein) • Primary whey protein is beta-lactoglobulin, the protein associated with cow's milk allergy

Slide 23 – Macronutrient Composition: Protein

In cow's milk-based formula, proteins are predominantly casein-based, but there is some whey protein. The type of whey protein that's usually present is beta-lactoglobulin, and this protein is associated with cow's milk allergy.

Moving on to talk about the fat content. Comparing breast milk to cow's milk-based formula, breast milk will have about half of its calories come from fats, and the natural composition of breast milk will have different factors in it that help digest and break down the fat, because the breast milk will naturally have bile salt-stimulated lipase that can break down the fat. Breast milk will also have DHA and ARA, and so these are very important fats for neuronal tissue structure and cognitive development.

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Macronutrient Composition: Fats

Breast Milk	Cow's Milk-Based Formula
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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

Slide 24 – Macronutrient Composition: Fats

The fats found in cow's milk-based formulas tend to be shorter medium- and intermediate-chain fatty acids. The fats are broken down to medium-chains because bile salt-stimulated lipases are not found in formula, so medium-chain fatty acids are easier to absorb. Most formulas are supplemented with DHA and ARA as well.

In breast milk, carbohydrates are composed of lactose and lactose-based oligosaccharides. A small portion of unabsorbed lactose leads to the softer poop consistency found in infants, as well as more nonpathogenic fecal flora and improved absorption of minerals. Interestingly, oligosaccharide structures mimic bacterial antigen receptors, and so they prevent bacteria attaching to the infant's mucosa. Cow's milk-based formula is typically lactose-based.

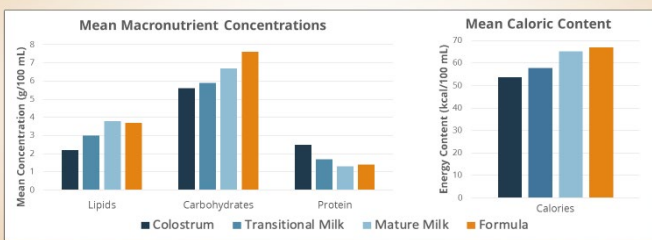
Cow's Milk Macronutrients: Carbohydrates

- 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

Slide 25 – Cow's Milk Macronutrients: Carbohydrates

This is a nice chart that highlights [Slide 26], once again, the different amounts of macronutrients in formula vs breast milk, and then the caloric changes, as well. What you'll see is, as the breast milk changes from colostrum to transitional milk—to mature milk—the amount of lipids will increase, and in mature milk, you'll have a slightly higher amount of fat than in formula.⁹

Macronutrient Composition and Energy Content of Standard Infant Formula



Slide 26 – Macronutrient Composition and Energy Content of Standard Infant Formula

In regard to carbohydrates, this also increases as the breast milk changes from colostrum to mature milk, and formula will have a higher amount of carbohydrates than most mature milk. Protein amount does drop in breast milk as it transitions from colostrum to mature milk, and formula does have a slightly higher amount of protein than mature milk. As a result, formula tends to have higher caloric content than mature milk.

A few other things to keep in mind about the standard cow's milk-based formulas. All formulas are iron fortified. There have been comparisons of organic to conventional cow's milk-based formula, and so far, there have not been significant differences found in the macronutrient composition, quality, or safety. Furthermore, no differences have been found in hormone levels, and neither type of formula contains antibiotics. Definitely, there are slight variations between brand and the formulations.¹⁰

Optimizing Nutrition in Infants at High Risk for Developing Allergy

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

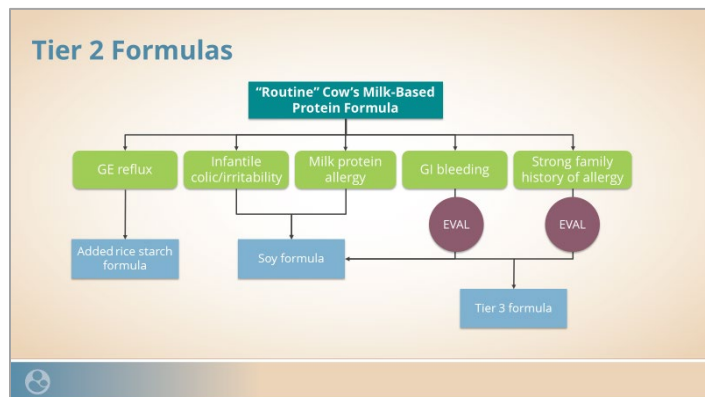
- All formulas are iron fortified
- Comparison of organic to conventional cow's milk-based formulas
 - No significant difference in macronutrient composition, quality, or safety
 - No difference in hormone levels
 - Neither contain antibiotics
- Each brand has a unique formulation

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

Slide 27 – Things to Consider Among Standard Cow's Milk-Based Formulas

Tier 2: Milk Alternatives

Let's move on to the Tier 2 milk alternatives. Tier 2 formulas are designed to address many of the symptoms that happen in infancy. As an example, you'll see that most infants will start out with this routine cow's milk-based protein formula [Slide 28].



Slide 28 – Tier 2 Formulas

If an infant exhibits symptoms of a condition such as reflux, there are formulas with added rice starch in them to address this symptom. The rice starch becomes more condensed and thicker once it reacts with the acid in the stomach, and so it is less likely to reflux back up.

Soy formula is another Tier 2 formula that can be used for various situations, such as infantile colic and irritability. Colic is not well understood, but sometimes soy formula can be used for that. There

are situations where you would suspect a milk protein allergy. In some situations, soy can be used for that. We'll talk about that in more detail.

Also, there are situations where there is a very strong family history of allergies or GI bleeding. In those situations, there usually needs to be some sort of an evaluation. Sometimes soy is appropriate. Sometimes moving on to Tier 3 is appropriate.

Because soy formula is probably one of the most commonly used in this section, I'll discuss this in more detail. Soy formulas are formulas that are plant-based, and they are whey, casein, and lactose-free. Technically, there is very limited application for soy formulas, but they do account for [approximately 12%] of the formula market in the US.^{11,12}

Soy Formulas

- Formulas are plant-based and are whey, casein, and lactose-free^{1,2}
- There are limited applications for soy formulas, but they account for **approximately 12% of the formula market** in the United States^{3,4}
 - They are recommended for galactosemia, hereditary lactase deficiency, post-infectious diarrhea, and those who want a vegetarian diet²
 - They are **not recommended** for premature infants²

1. Green Corkins K, Sharley T. *Nutr Clin Pract*. 2016;31(6):723-729.
2. Bhatia J, et al. *Pediatrics*. 2008;121(5):1062-1068.
3. Rossen LM, et al. *Clin Pediatr (Phila)*. 2014;53(12):78-285.
4. McCarver G, et al. *Birth Defects Res B Dev Reprod Toxicol* (2011) 92:421-48.10.1002/bdrb.20314

Slide 29 – Soy Formulas

They're really only recommended for a few instances, such as galactosemia (which is quite rare), hereditary lactase deficiency (also quite rare), post-infectious diarrhea, and those who want a vegetarian diet. They are not recommended for premature infants.¹³

There is no conclusive evidence that dietary soy isoflavones have any adverse effect on development, reproduction, or endocrine function on infants. Keep in mind that soy formulas can be allergenic. Of the patients with cow's milk protein intolerance, about 10–14% of them will react to soy. However, that does still leave a large segment of

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those patients that may be fine with soy. The benefit of soy, however, is their cost, which is considerably less than those Tier 3 and Tier 4 formulas, the hydrolysate or elemental formulas.^{10,13}

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, Sharley T. *Nutr Clin Pract.* 2016;31(6):723-729.
2. Bhatta J, et al. *Pediatrics.* 2008;121(5):1062-1068.

Slide 30 – Soy Formulas: Risks and Benefits

Let's talk a little bit more detail about situations such as when there is a high family history of allergies. There are some situations where infants with a strong family history of allergies may benefit from soy formula. This may be the case if there are some symptoms that are present or if there is a significant risk for an allergy to develop.

Common Condition: Family History of Allergies

```

graph TD
    BM[Breast Milk] --> S[Supplementing or not breastfeeding]
    S --> R["'Routine' Cow's Milk-Based Protein Formula"]
    S --> SFH[Strong family history of allergies]
    R --> DN1[Do nothing]
    SFH --> EVAL((EVAL))
    EVAL --> DN2[Do nothing]
    EVAL --> CSF[Consider Soy Formula]
    
```

- 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.

Slide 31 – Common Condition: Family History of Allergies

However, please keep in mind that at this time, there is no evidence that avoiding an allergen will prevent an allergy from developing later on. In fact, early exposure to allergenic foods probably prevents allergies later on in life.

Let's also discuss infantile colic, which I touched on a little bit earlier. Infantile colic is not very well understood. We do know that it can be normal for some infants to cry for long periods of time. As of right now, we're defining colic as times where infants are inconsolable and very irritable for periods of 2–4 hours per day between 3 weeks and 4 months of life.

Common Condition: Infantile Colic

```

graph TD
    R["'Routine' Cow's Milk-Based Protein Formula"] --> ICI[Infantile colic or irritability]
    ICI --> CSF[Consider Soy Formula]
    
```

- 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

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

Slide 32 – Common Condition: Infantile Colic

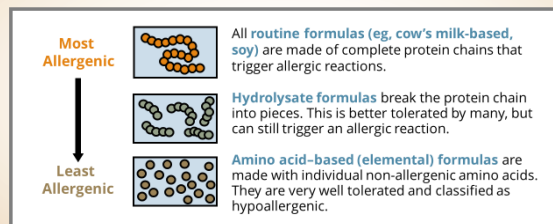
When irritability is so prolonged that it's outside of those parameters, or if it's affecting other situations, like the growth of a child, or the development of a child, other conditions should be considered, such as allergies, severe gastroesophageal reflux, or infections. But in some situations when we're dealing with colic, or an irritable infant, a soy formula may be a reasonable attempt.

Tier 3: Semi-Elemental or Hydrolysate Formulas

Moving on, let's discuss the semi-elemental, or hydrolysate, formulas. This is the Tier 3. I like this diagram to help visually explain exactly how Tier 3 and Tier 4 formulas work [Slide 33]. Our immune system reacts to proteins. That is that first, orange strand that you will see. Routine cow's milk-based formula will have long strands of proteins that our immune system can react to.

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



Slide 33 – Removing the Protein Allergen: Hydrolysate (Tier 3) and Elemental Formulas (Tier 4)

Hydrolysate formulas have those proteins broken down into smaller segments of smaller chains of amino acids. For most infants, that is sufficient to eliminate the allergic reaction. However, some infants are still very sensitive, and need to advance to the amino acid-based, or elemental, formula, where the proteins are broken down into individual amino acids. That is the Tier 4 formula. The Tier 3 formulas are the hydrolysate formulas in the middle.

Partially hydrolyzed formulas, or the semi-elemental formulas, have either casein or whey, or 100% whey proteins, that are broken down. These are lactose-free, and contain higher concentrations of MCT oil, or medium-chain triglyceride oil, which helps with malabsorption disorders.

Partially Hydrolyzed Formulas

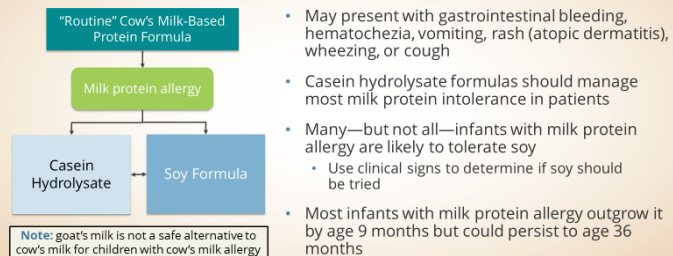
- Partially hydrolyzed protein formulas (either casein and whey, or 100% whey)
- Partially hydrolysate formulas are **lactose free** and contain higher concentrations of **medium-chain triglyceride (MCT) oil**, which helps with malabsorption disorders
- These formulas are indicated for infants with soy or cow's milk allergies or intolerance, surgical short gut, cholestasis, or bile acid deficiency
- Not appropriate** for "happy spitters"

Slide 34 – Partially Hydrolyzed Formulas

In addition to milk protein intolerance, there are other indications for these formulas. If infants have surgical short guts (where they're missing parts of their intestinal tract), liver diseases such as cholestasis, or bile acid deficiencies, then usually a partially hydrolyzed formula with a higher MCT oil is appropriate for those children. These formulas are not appropriate for the "happy spitters."

Probably the most common use for these types of formulas is the milk protein allergy. This can be IgE- or non-IgE-mediated milk protein allergy. In these situations, please remember that children can present with either GI bleeding, hematochezia, vomiting, rash (such as atopic dermatitis), wheezing, or cough. These hydrolyzed formulas should manage most of the milk protein intolerance in these kids.

Common Condition: Milk Protein Allergy (IgE- or Non-IgE-mediated)



Slide 35 – Common Condition: Milk Protein Allergy (IgE- or Non-IgE mediated)

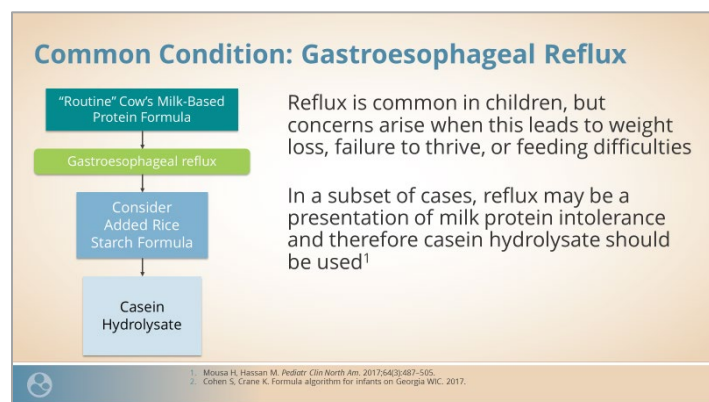
Many, but not all, infants with milk protein allergies are likely to tolerate soy. However, some 10–14% of milk-allergic children will react with soy, and so that would not be appropriate for them. Definitely, clinical signs should be used to figure out if soy is appropriate for children. Also keep in mind that many, if not most, infants with milk protein intolerance outgrow it by the age of 9 months, but it could persist as long as 36 months of age.⁸

Here, on the left, is a nice diagram about the progression of formulas [slide 35]. If milk protein

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allergy is diagnosed, and the child is on a routine formula, then a clinical decision needs to be made whether or not to try a soy formula, or to go ahead onto the casein hydrolysate formula.

Keep in mind that goat's milk formula is not a safe alternative. Any mammalian milk has the ability to cross-react in any infant with milk protein allergy. Mammalian milk has a much higher chance to be allergenic than a soy formula.



Slide 36 – Common Condition: Gastroesophageal Reflux

Moving on to gastroesophageal reflux. Reflux is common in children, and this is a very common and natural physiology in most children. There are rare instances where reflux is so severe that it's leading to weight loss, or failure to thrive, or feeding difficulties. In this subset of cases, then it is worth considering whether or not a milk protein hydrolysate formula should be used, because this could be a presentation of an allergy, as well.

Tier 4: Amino Acid Elemental Formulas

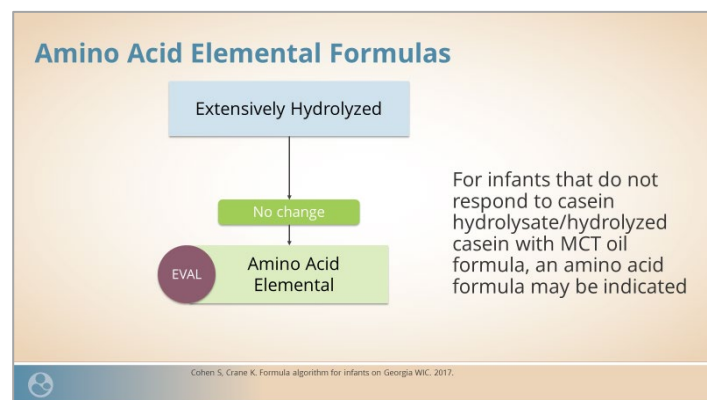
Let's move on to the amino acid-based, or elemental, formulas. This is the last tier. These formulas contain individual non-allergenic amino acids. Typically, these are very well tolerated formulas, and classified as hypoallergenic. These formulas do have a high osmotic load and may cause diarrhea, as well. That is a possible side effect that's worth mentioning to our patients before we start these formulas for them.

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

Slide 37 – Amino Acid Elemental Formulas

Most—but not all—patients that end up on an amino acid or elemental formula have been on an extensively hydrolyzed formula in the past. If their symptoms do not improve, then the elemental formula is used.⁸



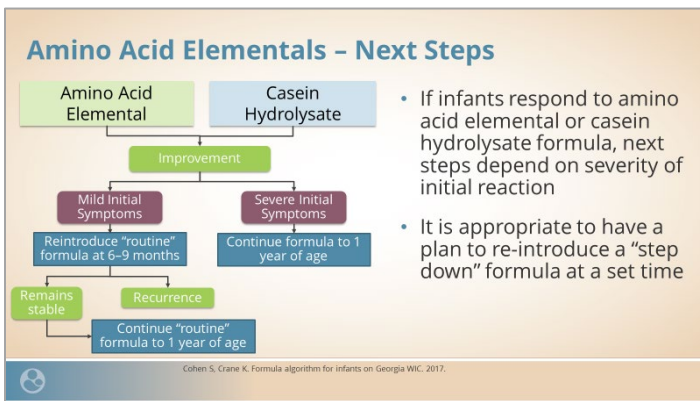
Slide 38 – Amino Acid Elemental Formulas

It is reasonable to have a plan, with any patient that's either on a Tier 3 or a Tier 4 formula, when to do a step-up approach and when to go back to a routine formula. This involves some clinical input. If symptoms are mild, then it may be worth considering introducing a lower tier formula at 6–9 months of age; however, if symptoms were severe, you might choose to continue that formula for 1 full year.

It is important to try to go back to a more routine formula at some point because many of these conditions that we talk about will change as the

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child grows. It might mean that the child will still not tolerate cow's milk, and you have to go back to that very specific formula, but regardless, it's reasonable to have a plan for when you try to go back to a more routine formula.



Slide 39 – Amino Acid Elementals – Next Steps

Let's discuss a few takeaways from this whole presentation. 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. Routine cow's milk formula is suitable for the majority of infants. Soy milk is an appropriate choice for infants allergic to cow's milk, but soy reactivity is common in pediatric patients with cow's milk protein allergy.

Partially hydrolyzed casein formulas are an appropriate choice 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.

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

Slide 40 – Key Takeaways

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

Slide 41 – Key Takeaways (continued)

Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Hofmekler's responses from the July 10 and July 24, 2019, audio webcasts.

My patients frequently ask about raw milk and the GABRIELA Study. What are your recommendations about the consumption of raw, unpasteurized milk to prevent allergy development?

Dr. Hofmekler: The GABRIELA Study was done in Europe, and it looked at various school-age children, many of whom grew up on farms. The study looked at their exposure to unpasteurized milk, if that influenced their allergies later on. What it found is that, yes, exposure to unpasteurized, raw milk

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seemed to decrease chances for allergy development later on.¹⁴

I think it's important to note a few things about the study. Number one, this study was particularly looking at asthma, and it's a retrospective study for much older infants. We also know that there are many, many risks that go along with using unpasteurized milk, or raw milk. There are many different infections, and infants are much more susceptible to these infections, which can be deadly to them.

I think that GABRIELA Study further confirms and supports the notion that early exposure to allergens is probably protective against allergies, or atopic diseases later on. However, we have to still do this in a very safe manner.

I always think there is a pendulum that swings, and at one point, we were being very, very clean about things, and not exposing infants to "allergenic foods" earlier on, and we now think that it probably increased the risk of allergies later on in life. I think that's an established factor.

If this GABRIELA Study shows that early exposure to raw milk might influence and decrease asthma later on, that's interesting. That further supports this notion that early exposure to allergenic foods is a good thing. However, it carries significant risks, and unpasteurized milk is unsafe for children, and carries the risk of severe infections that could be deadly.

I do recommend against that. Hopefully, this pendulum will swing to a safer point, where we're still comfortable with exposing our children to various antigens, and various "allergenic foods" earlier on, while not putting them directly at risk for significant infections.

Is there a concern with phytoestrogens in soy formula?

Dr. Hofmekler: No. That's a good question, and as of right now, phytoestrogens have been shown to be at normal levels in infants that drink soy formula or soy milk later on. You would have to consume gallons and gallons and gallons of soy formula to have any slight change in any hormonal status. It is very safe to consume.

A breastfed 5-month infant presents with mucous-laden stool and a handful of bloody stools, very irritable, with silent reflux and wet cough. Mom has done at least 8 weeks of 6 food elimination diets without improvement. There is a delay getting into the pediatric gastroenterologist. Do I recommend a Tier 3 or 4 formula at this point?

Dr. Hofmekler: That's also a good question. I think it depends clinically on how the child is doing. If the child is growing, but slightly irritable, it might be reasonable to just do the Tier 3 formula. If it's been 7 or 8 weeks that the mother has already been trying to change the formula around, and the child is not growing very well, then it might be reasonable to just go ahead and go to that Tier 4 formula. If you're very worried about the child, I would just go directly to that Tier 4 formula while waiting to get an evaluation with the pediatric gastroenterologist.

The other thing I will mention is that most of the time, when we see infants with bloody stools, and we rule out infectious etiologies, most of the time it is milk protein intolerance, or some kind of an allergic process that's causing the bloody stools. There are, in rare instances, autoimmune issues that can cause bloody stool as well. Sometimes, it might not just be allergies. Most of the time, it is, but in some instances, there are rare cases of things like inflammatory bowel disease that occur very early

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on. Still, getting evaluated by a pediatric gastroenterologist is a good idea.

Can you share any source or background on the recommendation to reintroduce cow's milk formula early, at 6–9 months, in children with mild cow's milk allergy?

Dr. Hofmekler: There's been good evidence that about [up to 85%] of milk-allergic patients will [develop tolerance to milk by age 4 years].¹⁵ What I usually do with my patients is that at 6–9 months of age, when infants are eating table foods or baby foods, I might have them start out with baked milk products.

If they do small bits of muffins, and they seem to be doing okay with that, then maybe I'll have them do small amounts of yogurt. If they're doing small amounts of yogurt, and those initial symptoms that they had in the first couple months of life are not returning, and they seem to be happy and thriving, then probably at that point they could be tried on either a regular cow's milk-based formula. Or you can decide whether to just supplement with those table foods, and give them the exposure to milk products, and then later on, when they're 1 year of age, they can transition to whole milk, and continue on their table foods with the milk exposure.

For infants who require a formula bridge until their mother's milk comes in, is there a benefit for using hydrolyzed formula or donor human milk over cow's milk-based formula?

Dr. Hofmekler: No, I don't know of any evidence that would support using a hydrolyzed formula. Regarding donor breast milk vs formula, probably donor milk could theoretically provide additional benefits, immunological benefits, and easier digestibility. But if it's going to be for a very short period of time, as we're waiting for mom's milk to come in, it may be reasonable to also use formula

as well. Probably there may be a slight benefit from using donor milk, but it would be a very small benefit, if you just consider that it's going to be pretty temporary.

In the WIC Formula Algorithm, it recommends soy formula for milk protein allergy before going with the hydrolyzed casein formula. Is this primarily due to cost? Is casein a better choice if cost is not an issue?

Dr. Hofmekler: Yes. The algorithms do definitely put a lot of thought into cost-benefits of formulas. As I mentioned, soy is way cheaper, and way easier to obtain than the casein hydrolysate formulas. Many infants will do okay with a soy formula. However, there is still a high incidence of this cross-reactivity to the casein hydrolysate formula. If you have an infant that you are very sure has milk protein intolerance, and they are having bloody stools, mucous in the stools, or irritability, it would also be reasonable to just go directly to the casein hydrolysate formula, and then later on decide whether you want to step down to a soy trial, just to save them some money.

If the reintroduction of routine formula at 6–9 months is successful, would it be appropriate to introduce solid foods containing cow's milk protein at that time, as well? Would it also be appropriate to transition to 3.25% cow's milk once the infant is 9 months of age?

Dr. Hofmekler: Let me answer this in a backwards way. I would hold off on cow's milk until age 1 year. I think it's appropriate for term infants that they should get that formula as their sole source of nutrition up to age 1 year, and if it's a premature infant, which we really didn't talk about in this presentation, they should really continue with their specialized formula until 1 year. That just provides them more calcium and phosphorus, and a better caloric intake than if they go directly to a cow's milk-

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based formula at age 9 months. Yes, I would definitely try to hold off until closer to 1 year.

I addressed this a couple of questions back, slightly. Around 6–9 months of age, as infants are already starting to use solid foods, I use that as an opportunity to try exposure to milk products. I find that easier, and it's a slightly more gradual introduction. I usually use that as the way to test if our milk protein issues are improving.

I first try to use the baked goods, because they're more likely to be less allergenic, such as muffins, or something that milk is already baked into. Then, if that seems to be okay, then maybe try some yogurt. If that's okay, then try the transition to a regular cow's milk formula.

If trying an elemental formula for severe reflux that is not responding to meds, is there a timeframe that you would expect to see improvement if the formula change is working?

Dr. Hofmekler: If a formula is going to help, probably about a week or so. Because most likely the reason a formula would help "reflux" or regurgitation of contents is if there's an allergic process that's going on. It should probably be within about a week, maybe 2 weeks at the most, that you would expect an improvement.

What is the purpose of the addition of MCT to some infant formulas? How does this promote weight gain?

Dr. Hofmekler: MCTs, or medium-chain triglycerides, are easier to absorb, so they can be absorbed passively or actively. If you can think back to chemistry classes, the fat globules need to be surrounded by products so that they can help absorption. In contrast, medium-chain triglycerides can be absorbed either passively through diffusion

into your intestinal tract, or through enzymatic reactions, which can help the absorption that way.

Fats have 2 ways to be absorbed. Because MCTs are much easier to be absorbed and have multiple methods of absorption, they are frequently added to formulas. It's just an easier process of absorption, so that it's easier to get the required calories.

MCT formulas, or formulas with higher amounts of MCTs, are especially beneficial for kids that have liver issues, because if they don't have the bile acids to break down those fats, then you can only rely on that passive diffusion for absorption. Or if there are any kind of issues with intestinal tract, like parts of the intestinal tract are missing, it's the same thing. It's just an easier absorption process.

For formula-fed infants, are formulas containing probiotics essential to preventing allergies? Can probiotics be added to formulas to reduce the chance of allergy development?

Dr. Hofmekler: There are some promising results regarding probiotics and allergies, but there are also some results that don't show a whole lot of change one way or another. At this point, I think we have to wait and see, and decide how it's going to unfold for us in the future, because there are just so many bacteria, and we don't know which dose, and which type, would be most beneficial.¹⁶

I think that this is something that we are going to be learning more and more about in the upcoming years. There are some data that certain probiotics given to children with cow's milk allergy at a young age may help prevent [atopy] later on.¹⁷ However, I will say the data are still coming out to understand exactly how much and which specific strains of probiotics are needed to help prevent allergy.¹⁶ There are some formulas currently that have strains of probiotics that are added in that have been studied and those are probably reasonable

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approaches. There are not many strains of probiotics separate from the formula that are really studied and known to prevent allergy formation later on.

So, yes, there are some formulas already premixed with certain strains of probiotics, and they're probably beneficial. As to adding in a separate probiotic, I think there are still questions as to whether or not that's going to be beneficial because we still have to find out which strains of probiotics are appropriate and how much. So this is probably something that we will have more information on in the next several years, and it definitely has promise, but right now it's hard to make specific recommendations about probiotics.

How do you decide between casein and whey hydrolyzed formulas for children with allergies?

Dr. Hofmekler: Most of the hydrolyzed formulas are casein based, and the casein is hydrolyzed. Many of them are very similar across brands. However, there will be slight variation formula to formula. The main thing I would consider when comparing hydrolyzed formulas is the MCT component. Some formulations of hydrolysate formulas will have higher amounts of MCT oil in them, and in certain situations, that's very beneficial. These can be the patients that, for example, may have surgical short gut syndrome or parts of the bowel were removed, or these may be patients that have some underlying malabsorption process or a deficiency in their bile acids, as may be the case in patients that have underlying liver disease. Those patients probably benefit from the hydrolysate formulas that also have higher amounts of MCT oil.

For the other kids with normal growth in whom we're generally giving hydrolysate formulas for the purpose of an allergy, deciding among formulas probably should rely more so on taste and

consistencies. You'll find that some formulas are thinner than others, or maybe taste different from one to another, and so taste will probably also [weigh] heavily into that decision as well. Still, in some cases it is worth considering not just that it's a casein hydrolysate but also how much MCT oil is in those formulas.

In addition to Tier 3 protein hydrolysate or protein for amino acid elemental formulas, are there additional nutritional strategies you recommend for managing food allergy in children?

Dr. Hofmekler: The great overarching theme should be that early exposure is a good thing. Exposing our children and infants to "allergenic" foods at an early age, between 6 and 9 months of age, is probably a good thing.¹⁵ That will include things like peanuts, and if you don't have a concern for a milk protein allergy, you can expose them to milk. So honestly, early exposure to the "allergenic" foods is a good thing. That's probably the best thing that we can do to avoid allergies later on.

When infants or children are doing well on a cow's milk formula alternative, like soy or partial hydrolysate, how do you make the decision about whether and when to switch back to cow's milk formula?

Dr. Hofmekler: I think a lot of it depends on how sick the child was when the decision was made to switch from a cow's milk-based formula. If a child was quite ill and maybe was having growth issues, was very irritable, and was having blood in the stools, then it might be reasonable to wait a little bit longer and do very slow transitions.

In general, the majority of kids [outgrow cow's milk allergy]. [At 9 months of age] is generally the point where I start to have the discussion with families about whether or not we need to start retesting

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them, whether the allergy is still there. Generally, because most 9-months-old are exposed to table foods, a good way to do that would be to try milk exposure through table foods. That might mean you expose the child to some yogurt to see if the symptoms that were happening early on in infancy are happening again. If they seem to do fine with either the soft cheese or the yogurt, you can probably switch them to regular cow's milk-based formula at that point. However, if the kid was really ill early on, you may be a little bit more cautious.

Nevertheless, 9 months is a good point of trying to make that decision. There's definitely some families that may be okay with introducing those allergenic table foods to the infant's diet earlier on, and that may be okay. Or if they want to transition off of the hydrolysate or soy formula at 1 year of age, that's probably okay too as long as they're being exposed to the cow's milk protein in infancy.

If a patient with suspected cow's milk protein allergy may not tolerate soy formula, do you recommend a trial of soy formula or moving straight to partially hydrolyzed formula?

Dr. Hofmekler: If we're dealing with a milk protein intolerance, and they seem to not be doing well with a soy formula, then yes, a protein hydrolysate formula would be the appropriate next step. Or, if you feel like the child is quite ill, it's also reasonable to just skip entirely over the soy formula and go to the protein hydrolysate formula as well.

If the mother has an IgE-mediated food allergy, does breastfeeding still provide protection for that allergy or can it increase the risk for a child to develop the same IgE-mediated allergy?

Dr. Hofmekler: I don't know of a specific study that answers that question, but we do know that breast milk is protective, so it is still safe and recommended. Whether or not the breast milk ends up protecting the infant from the allergy is probably unknown. Genetics probably play a significant role in that situation, meaning that infant's genetics probably play a bigger role in influencing the child's risk for allergies, but it's still beneficial to breastfeed. She's not going to increase the risk of allergy by breastfeeding, and there are so many benefits of breastfeeding. So we should continue to encourage moms in these situations to breastfeed when possible.

Abbreviations

ARA	arachidonic acid	GI	gastrointestinal
CDC	Centers for Disease Control and Prevention	IgE	immunoglobulin E
DHA	docosahexaenoic acid	MCT	medium-chain triglyceride
EPA	eicosapentaenoic acid	TGFβ	transforming growth factor beta
FPIES	food protein-induced enterocolitis syndrome	WHO	World Health Organization

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1. National Center for Health Statistics: WHO Growth Charts. Data table for length-for-age and weight-for-age charts. Centers for Disease Control and Prevention website.
https://www.cdc.gov/growthcharts/who/boys_length_weight.htm. Updated September 9, 2010. Accessed August 9, 2019.
2. Otten JS, Pizzi Hellwig J, Meyers LD. Institute of Medicine of the National Academics. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. National Agriculture Library.
https://www.nal.usda.gov/sites/default/files/fnic_upload/DRIEssentialGuideNutReq.pdf. Updated 2006. Accessed August 9, 2019.
3. Nutrition: Breastfeeding. World Health Organization website.
https://www.who.int/nutrition/topics/exclusive_breastfeeding/en/. Accessed August 9, 2019.
4. Andreas NJ, Kampmann B, Mehring Le-Doare K. Human breast milk: a review on its composition and bioactivity. *Early Hum Dev*. 2015;91(11):629-635.
5. Abrahamsson TR, Jakobsson HE, Andersson AF, Björkstén B, Engstrand L, Jenmalm MC. Low diversity of the gut microbiota in infants with atopic eczema. *J Allergy Clin Immunol*. 2012;129(2):434-440. doi:10.1016/j.jaci.2011.10.025
6. Azad MB, Konya T, Guttman DS, et al; CHILD Study Investigators. Infant gut microbiota and food sensitization: associations in the first year of life. *Clin Exp Allergy*. 2015;45(3):632-643. doi:10.1111/cea.12487
7. Greer FR, Sicherer SH, Burks AW; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Timing of Introduction of Complementary Foods, and Hydrolyzed Formulas. *Pediatrics*. 2008;121(1):183-191. doi:10.1542/peds.2007-3022
8. Cohen S, Crane K. Formula algorithm for infants on Georgia WIC. Georgia Department of Health website.
https://dph.georgia.gov/sites/dph.georgia.gov/files/WIC_Resources/Nutrition_Unit/Special_Formula/2017%20Infant%20Algorithm%20and%20Resource%20Guide.pdf. Updated 2017. Accessed August 12, 2019.
9. Rossen LM, Simon AE, Herrick KA. Types of infant formulas consumed in the United States. *Clin Pediatr (Phila)*. 2016;55(3):278-285.
10. Green Corkins K, Shurley T. What's in the bottle? A review of infant formulas. *Nutr Clin Pract*. 2016;31(6):723-729. doi:10.1177/0884533616669362
11. Rossen LM, Simon AE, Herrick KA. Types of infant formulas consumed in the United States. *Clin Pediatr (Phila)*. 2016;55(3):278-285.
12. McCarver G, et al. NTP-CERHR expert panel report on the developmental toxicity of soy infant formula. *Birth Defects Res B Dev Reprod Toxicol*. 2011;92:421-468. doi:10.1002/bdrb.20314
13. Bhatia J, Greer F; American Academy of Pediatrics Committee on Nutrition. Use of soy protein-based formulas in infant feeding. *Pediatrics*. 2008;121(5):1062-1068. doi:10.1542/peds.2008-05641
14. Loss G, Apprigh S, Waser M, et al; GABRIELA study group. The protective effect of farm milk consumption on childhood asthma and atopy: the GABRIELA study. *J Allergy Clin Immunol*. 2011;128(4):766-773.e4. doi:10.1016/j.jaci.2011.07.048
15. Boyce JA, Assa'ad A, Burks AW et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-S58. doi:10.1016/j.jaci.2010.10.007
16. Fiocchi A, Burks W, Bahna SL, et al. Clinical Use of Probiotics in Pediatric Allergy (CUPPA): A World Allergy Organization Position Paper. *World Allergy Organ J*. 2012;5(11):148-167.
17. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol*. 1997;99(2):179-185. doi: 10.1016/s0091-6749(97)70093-9