Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

An Overview of Food Allergies in Children

Overview

Stanley Cohen, MD, introduces food allergies in infants and children, including the definition, prevalence, burden, and pathophysiology of food allergy. Dr. Cohen also reviews the differences between IgE- and non-IgE-mediated food allergies; the clinical signs and symptoms of food allergies; tolerance and intolerance; introduction of complementary foods; feeding considerations for children with and without allergies; and developing healthy feeding patterns.

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:

- Characterize the growing prevalence of food allergy among infants and children
- Differentiate IgE-mediated, NON-IgE-mediated, and MIXED IgE and NON-IgE-mediated reactions in pediatric patients.

Faculty

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Stanley A. Cohen, MD

Research Support	Takeda – clinical area: IBD Janssen – clinical area: IBD Medtronic – clinical area: capsule endoscopy AbbVie – clinical area: IBD AstraZeneca – clinical area: IBD QOL – clinical area: disaccharidase deficiencies
Consultant	Janssen – clinical area: IBD Medtronic – clinical area: capsule endoscopy AbbVie – clinical area: IBD AstraZeneca – clinical area: IBD QOL – clinical area: disaccharidase deficiencies Mead Johnson Nutrition – clinical area: infant and child nutrition
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The faculty for this activity has disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners

Stephanie Leonard, MD (peer reviewer)

Consultant	LabCorp – clinical area: food allergy diagnostics

The following have no significant relationship to disclose:

Erin Allen, MS, RD, LDN (RD reviewer)
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This activity is supported by an independent educational grant from **Mead Johnson Nutrition**.

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This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on August 2, 2019 and is eligible for credit through August 2, 2021.

Contact Information

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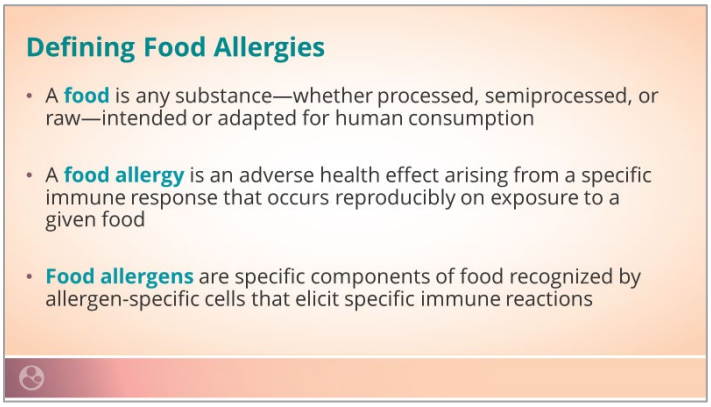
Editor's Note: This is a transcript of an audio webcast presented on July 9, 2019. It has been edited and condensed for clarity.

Dr. Stanley A. Cohen: We will now move on to the introduction to food allergies, covering the epidemiology, burden, and natural history of atopic disorders. In order to do so, we will first have to define our terms a bit.

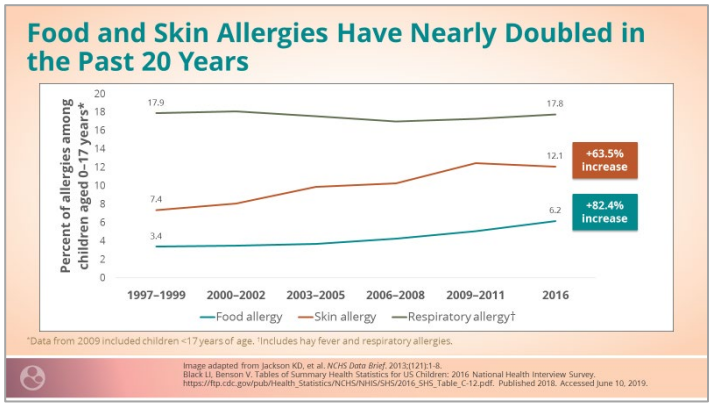
Since we put a lot of different things in our mouths, what we want to think about is that foods are any substance, whether processed, semi-processed, original, or raw, which is intended or adapted for human consumption. This is as opposed to all the other things that are orally ingested or placed in our mouths, including the food implements themselves.



Slide 1 – Defining Food Allergies

A food allergy is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. Food allergies, then, are the specific components of that food that are recognized by allergen-specific cells that then elicit specific immune responses.

If we recognize that allergies are a problem in children, what we also see is that respiratory allergies have remained steady in terms of their prevalence over the past 20 years. However, what we note is that there's a significant increase in both skin allergies and respiratory allergies, with food allergies nearly doubling over this period of time by nearly 82.4%.[1] It is also interesting to note that the prevalence of food allergy varies worldwide.[2] Food allergy is more prominent in some countries than it is in others. In part, that may be due to inadequate diagnosis, as there is not a lot of attention paid to allergies in certain parts of the world. But in fact, it may be also that there's just a global or regional variation in food allergy prevalence.



Slide 2 – Food and Skin Allergies Have Nearly Doubled in the Past 20 Years

An interesting study was done in Australia with 65,000 children at the time they entered school. Parent-reported nut allergy was [more than] twice as common in children of Asian descent that were born in Australia compared with children who were

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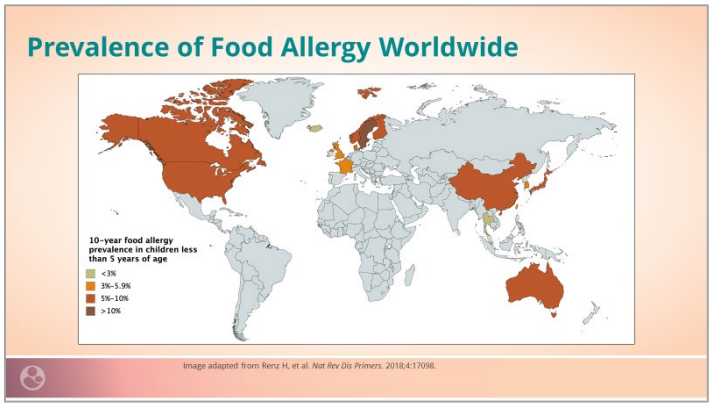
white and born in Australia; however, children born in Asia who then migrated to Australia in the first 5 years of life actually had a lower prevalence of allergies than children born in Australia.[3] The regional and migratory differences in food allergy prevalence give us the opportunity to start to develop a hypothesis of why food allergies may be on the rise in some parts of the world and not in others.

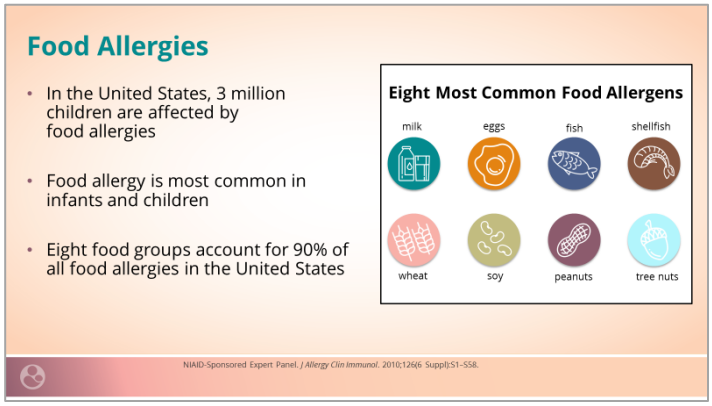


Slide 3 – Prevalence of Food Allergy Worldwide

The burden of allergic diseases is quite interesting, both on a societal basis as well as on an individual basis. If we look at how it affects society as a whole, up to 50 million Americans are affected by allergies. It's the sixth leading cause of chronic disease in the United States and appears to be on the rise. The impact on the health care system in the United States is $18 billion per year.[4] If we can improve prevention and diagnostic techniques, that may indeed have an impact on the prevalence and its associated costs, as well as its societal impact.

Slide 4 – Burden of Allergic Diseases

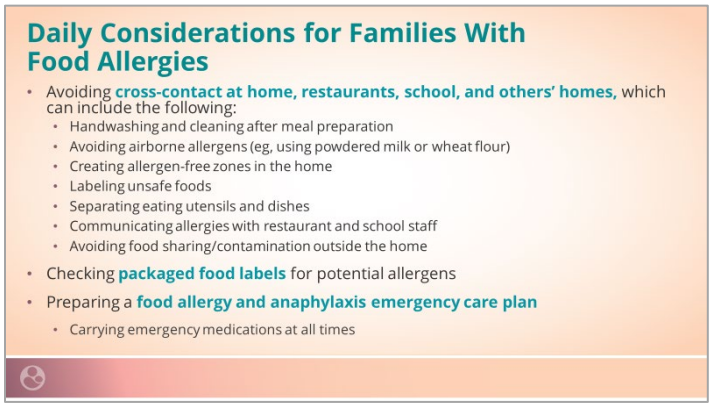
When we get specifically to food allergies, what we note is that 8 food groups account for 90% of all food allergies in the United States. Milk is far and away more common than the others, but allergies to eggs, fish, shellfish, wheat, soy, peanuts, and tree nuts also are exceedingly common. Food allergy is most common in infants and children, and a total of 3 million children are affected by food allergies.[5]



Slide 5 – Food Allergies

These food allergies not only have an impact on society as a whole, but also on individuals with allergy and their families. They have to avoid cross-contact at home, and then when they move from their home out into the community at restaurants, schools, and other homes, either in the family or at their friends'. Handwashing and cleaning before and after meal preparation become important. Avoiding airborne allergies has been something that we've recognized when we get on airplanes,

and somebody with a peanut allergy may need the airplane staff to change the snack that they produce and present.



Slide 6 – Daily Considerations for Families With Food Allergies

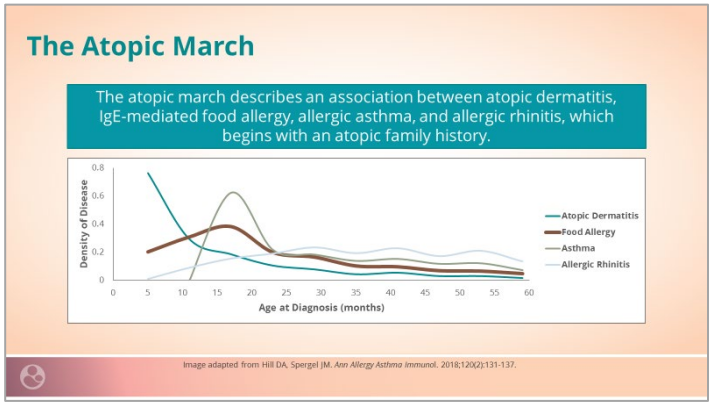
This also becomes important as children are in daycare centers and school, where powdered milk, peanuts, and wheat flour are also present and may affect what's being served. We want to create allergen-free zones in the home, and carefully label unsafe foods so that it's understood by all caregivers, as well as other children in the home. It's also important to separate the food utensils and dishes for the child who has allergies from the children who do not, and it's important that all of these considerations also be shared when the child goes to school and when the family goes out to restaurants. There are actually food cards that can be handed to waitstaff so that they know about that.

One of the biggest sources of concern is actually food sharing that occurs when the children go to school and one says, "I've got this sandwich, I've got that sandwich, you want to trade?" Cross-contact becomes a big issue, as all of those foods are then available in the school classroom, especially when foods are brought into the classrooms for birthday parties and other events.

It's important to check packaged food labels for potential allergens. And this often is a frightening event for families that are going to the grocery store, or when they're going out to restaurants and considering what's available for their child.

There also has to be a food allergy and anaphylaxis emergency care plan in place with emergency medicines available at all times for children who have food allergies.

The atopic march describes an association between allergies that present early in infancy and those that develop later. There is a postulated progression of disease in atopic infants and children, beginning with eczema and subsequently progressing to asthma and then allergic rhinoconjunctivitis. Eighty percent of children with specific food allergies had eczema in the first year of life: cow's milk allergy in 73%, egg allergy in 71%, and fish allergies in 51%. Asthma has a later onset, with only 42% of children with asthma evident in the first year, and 49% evident in the second year. In total, 92% of atopic children exhibit indications of allergies and asthma before 8 years of age, and rhinoconjunctivitis occurs even later, with only 59% having that condition at age 5 years.[6]



Slide 7 – The Atopic March

This is all seen clearly on the slide, with the evidence that food allergies generally occur simultaneously with eczema and, in most allergic children, proceed on to respiratory issues later.

If we look at just cow's milk allergy alone in infants, what you see is that at 5 years of age, 75% will also have other food allergies, 43% will have allergic

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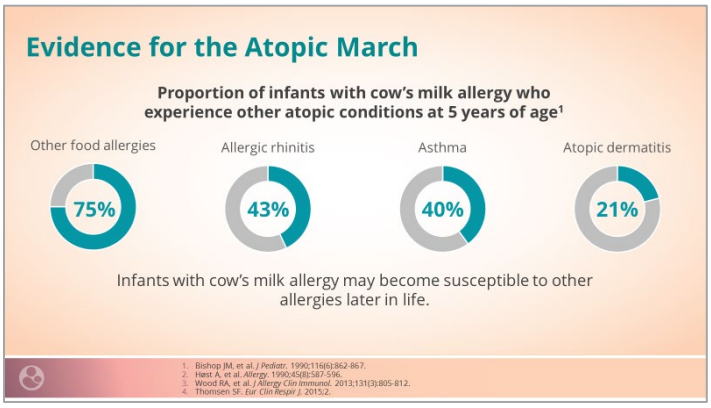
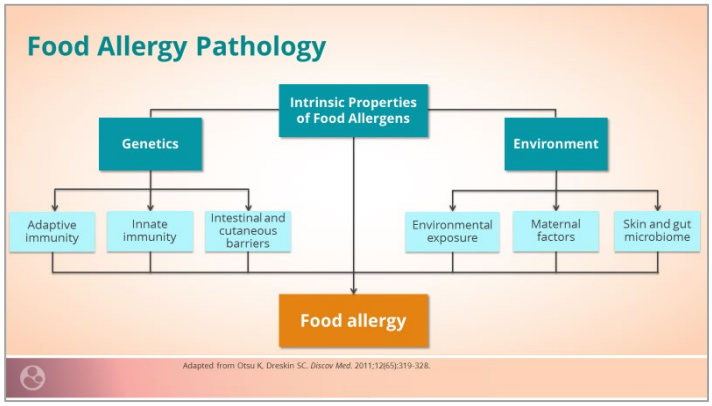
rhinitis, 40% will have asthma, and 21% will have atopic dermatitis by 5 years of age.[7]



Slide 8 – Evidence for the Atopic March

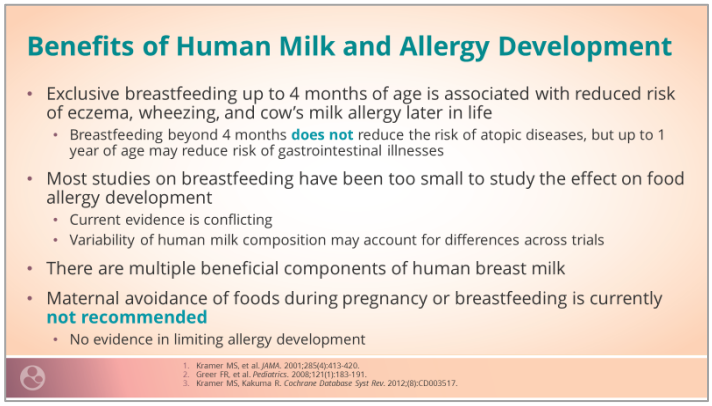
There seems to be a pathway that produces food allergy, but it's not simply the fact of having an exposure to the food allergy alone. There seems to be a significant genetic component that involves both the adaptive and innate immune systems for these children. And then the intestinal and cutaneous barriers that seem to allow penetration of the food allergen. What we know from Dr. Allen Walker's work, and others, is that this intestinal penetration seems to lessen by approximately 6 months of age, at which time there's more gut closure.[8]

Simultaneously, there are environmental factors that include environmental exposure to various allergens, maternal factors from the prenatal period through breastfeeding, and the skin and gut microbiome of the child. We do know that human milk seems to have a great impact on allergy development. Exclusive breastfeeding up to 4 months of age is associated with a reduced risk of eczema, wheezing, and cow's milk allergy later in life.[9]



Slide 9 – Food Allergy Pathology

Breast milk beyond 4 months of age does not reduce the risk of atopic diseases; however, breast milk has other factors that may help to reduce the risk of gastrointestinal illnesses up to 1 year of age. These include IgA that's transferred, lactoferrin, and various iron factors and other immunologic factors that seem to cross the breast milk.



Slide 10 – Benefits of Human Milk and Allergy Development

Most studies on breastfeeding have not been able to show the effect on food allergy development. Differences across studies may be attributable to small population sizes and a great deal of variation in human milk consumption and composition. There are also multiple beneficial components of human breast milk beyond just specific allergy components.

Maternal avoidance of foods, particularly during pregnancy and perhaps during breastfeeding, are

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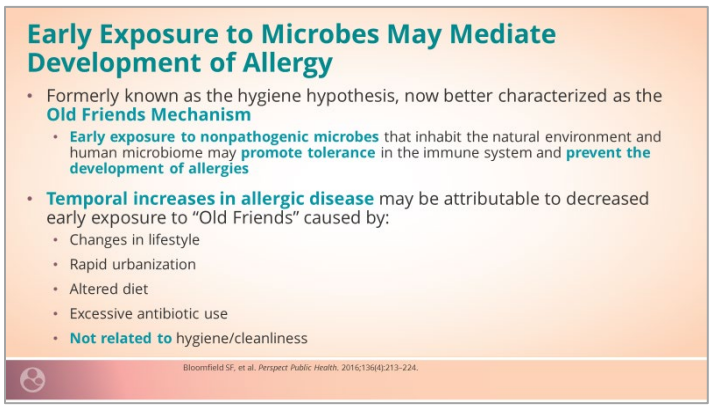
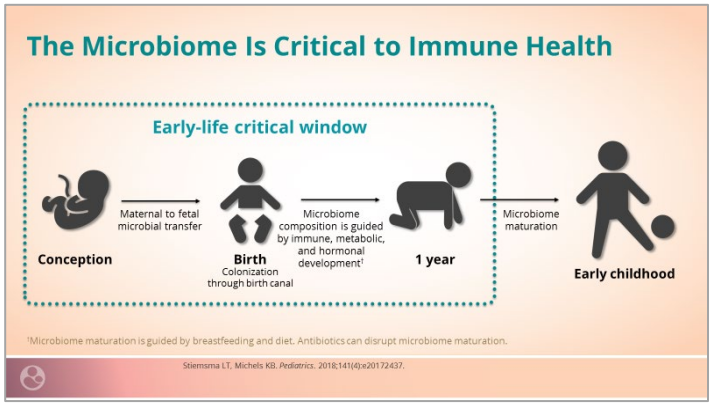
currently not recommended because there is no evidence that this limits allergy development.

At the same time, the microbes and the development of the microbiome may be very important in terms of exposure and subsequent allergy development. We formerly knew this as a hygiene hypothesis; although, it has nothing to do with actual hygiene or cleanliness. As a result, the term has now been better characterized as the Old Friends Mechanism. What that suggests is that early exposure to nonpathogenic microbes may promote tolerance in the immune system and prevent the development of allergies. The increase in allergies may specifically relate to changes in lifestyle, rapid urbanization, altered diet, excessive antibiotic use, and other pathogen exposures that occur early on that may develop tolerance or allergy production.



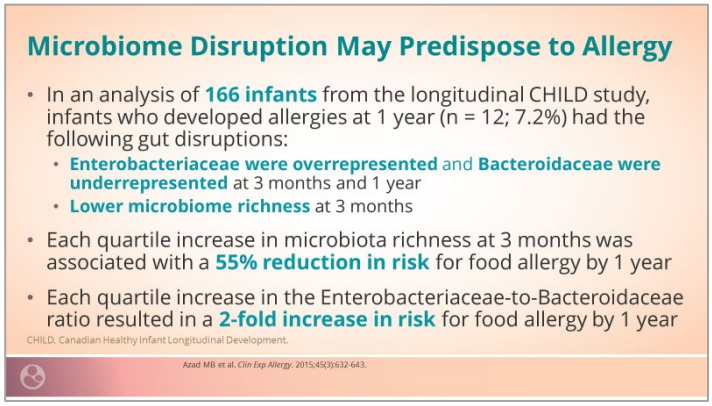
Slide 11 – Early Exposure to Microbes May Mediate Development of Allergy

Another way to look at this is that the microbiome, from its earliest time of development to early childhood, is critical in terms of allergy development. From conception until birth, we have the maternal-to-fetal microbial transfer. Then at birth there is colonization through the birth canal. The microbiome composition is then guided by breastfeeding and diet as well as immune, metabolic, and hormonal development. This, then, causes a microbiome maturation that is evident by early childhood.



Slide 12 – The Microbiome Is Critical to Immune Health

Simultaneously, microbiome disruption may predispose to allergy. In 2015, the longitudinal CHILD study evaluated 166 infants. Those infants who developed allergy at a year had the following gut disruptions: lower microbiome richness at 3 months of age, overrepresentation of Enterobacteriaceae, and underrepresentation of Bacteroidaceae at 3 months and 1 year of age in those who developed allergies.[10]



Slide 13 – Microbiome Disruption May Predispose to Allergy

It even gets more specific than that. For each quartile increase in the microbiota richness at 3 months of age, there was a 55% reduction in risk for food allergy at 1 year of age. Simultaneously, each quartile increase in the ratio of the Enterobacteriaceae-to-Bacteroidaceae ratio resulted in a 2-fold increase in risk for food allergy at 1 year of age.[10]

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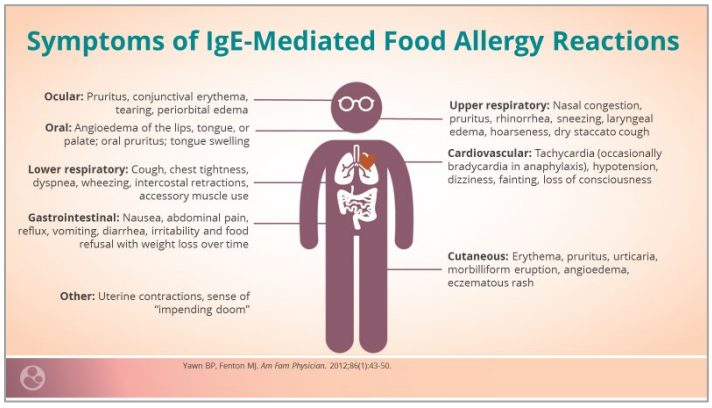
Food Allergy Characterization

When we characterize food allergies, it's important to note that not all allergies are IgE-mediated. There are in fact a great number of allergies that are non-IgE-mediated, or that are mixed-IgE and non-IgE-mediated food allergies. We will also talk about the clinical signs and symptoms as well as tolerance and intolerance, which really have different contextual meanings.

You've all seen the symptoms of IgE-mediated food allergies in various body systems. When we think about the eye, we think about the conjunctival erythema and tearing that is sometimes reported, and even periorbital edema can develop. In the upper respiratory tract, there's nasal congestion, frequent rhinorrhea, sneezing, laryngeal edema, and hoarseness that can be seen, along with a dry, staccato cough.



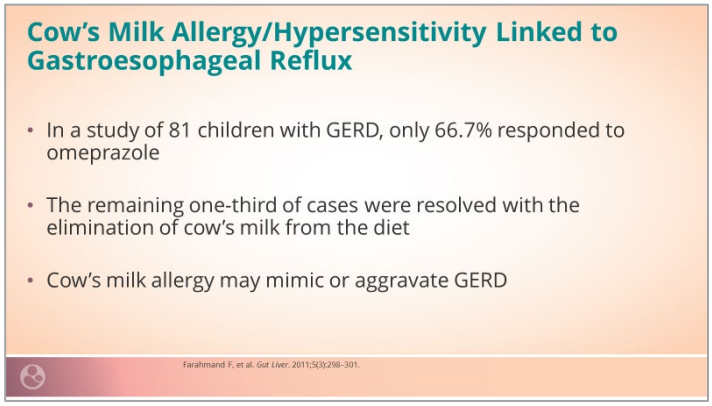
Slide 14 – Symptoms of IgE-Mediated Food Allergy Reactions

If we look even above that, at the oral area, we can see tongue swelling or angioedema of the lips, tongue, or palate. When we get down to the lower respiratory tract, we're looking at cough, chest tightness, wheezing, difficulty breathing, and even intercostal retractions.

The heart can be affected in terms of tachycardia and, occasionally, bradycardia in anaphylaxis. You may also see hypotension, dizziness, fainting, and loss of consciousness in some of the patients who have severe allergies with anaphylaxis.

Within the GI tract, which is my bailiwick, we see patients who come in with nausea, abdominal pain, reflux, vomiting, diarrhea, irritability, feeding refusal, and even weight loss over time. Skin manifestations include eczema, erythema, pruritus, urticaria, and angioedema as well as morbilliform eruptions, particularly on the face, torso, and upper extremities.

When one thinks about cow's milk allergy, it's also very interesting how often that is mistaken for or seems to aggravate gastroesophageal reflux. One particularly interesting study was performed in 81 children with reflux symptoms, where 66.7%—or two-thirds—responded to omeprazole. That means that one-third didn't respond to GERD treatment, but they did respond to elimination of cow's milk from the diet, suggesting that they truly had cow's milk allergies that either mimicked or aggravated reflux and reflux symptoms.



Slide 15 – Cow's Milk Allergy/Hypersensitivity Linked to Gastroesophageal Reflux

IgE-mediated allergies are often represented by a rapid onset, usually within minutes to 2 hours, after ingestion of even small amounts of food allergen. There was one patient of mine who came in to be tested for food allergy but didn't have to be. He actually crawled through a small puddle of spilled milk on the floor, licked his hand, and immediately

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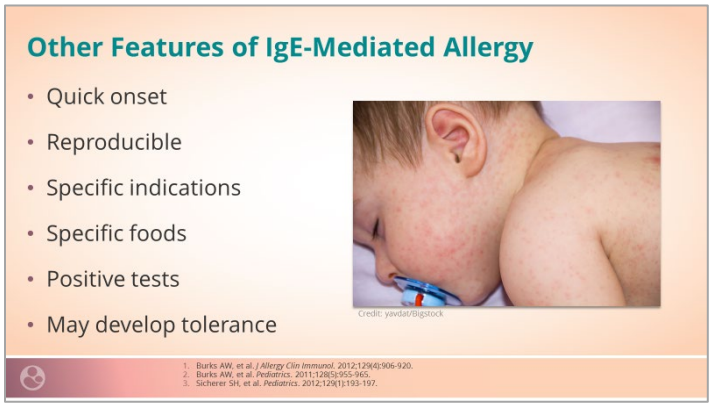
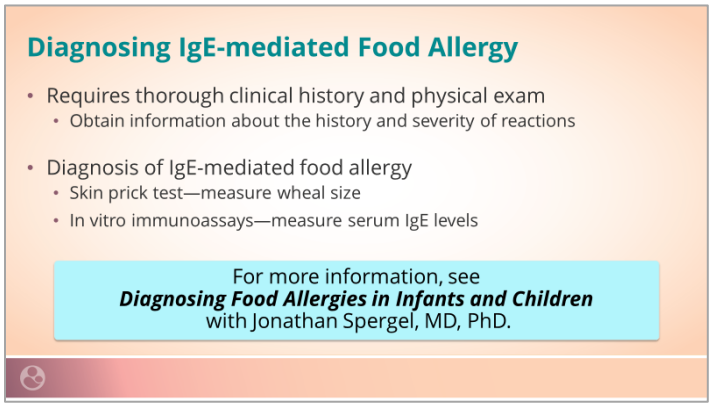
had symptoms of food allergy. This is a reproducible event, with often specific foods and specific reactions that are apparent. Usually, allergy tests are positive in many of the children, but negative tests can also be seen. Children with IgE-mediated allergies may develop tolerance over time.



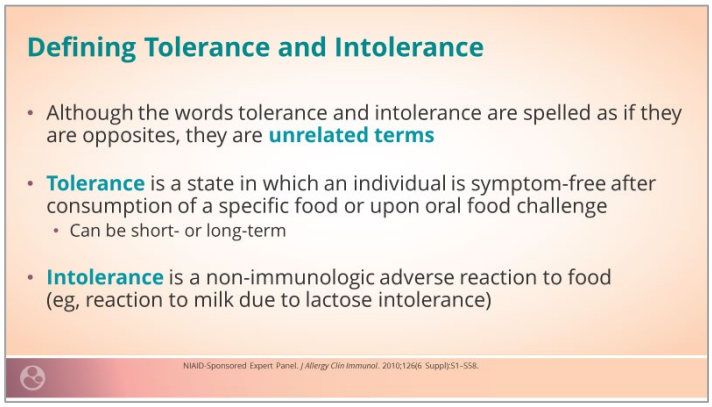
Slide 16 – Other Features of IgE-Mediated Allergy

To diagnose IgE-mediated food allergies, you can use skin prick testing to measure the wheal size or immunoassays to measure specific IgE levels. Additionally, there is a specific clinical history and physical exam that we want to go through. Dr. Jonathan Spergel is going to describe that in his talk on diagnosing food allergies in infants and children.



Slide 17 – Diagnosing IgE-mediated Food Allergy

In relationship to food allergies and food reactions, tolerance is very different than intolerance. They are actually unrelated terms. Tolerance is when an individual with allergies becomes symptom-free, even when he consumes a specific food or undergoes an oral food challenge in the office. Tolerance can be short-term or long-term.



Slide 18 – Defining Tolerance and Intolerance

Intolerance, on the other hand, is a non-immunologic adverse reaction to food. You can think of lactose intolerance as a reaction to milk that is non-allergenic but is instead induced by an inability to break down and digest lactose. Then, the resultant products go down through the intestine and cause bloating, diarrhea, gas, and discomfort—but not vomiting. If there's vomiting associated, we know that it's not lactose intolerance, and we want to think more about food allergy.

The natural history of food allergy is such that many children will outgrow allergies to milk, egg, soy, and wheat.[5] This could happen at any time from early childhood to the teenage years, and sometimes even into adulthood. It's important to note that higher levels of serum IgE at diagnosis are associated with a lower likelihood of developing tolerance later on. Tolerance usually, but not always, correlates with a decrease in serum IgE levels over time. It may not correlate with changes in the response to skin prick tests, but a reduction in the size of the wheal may be suggestive of tolerance development.

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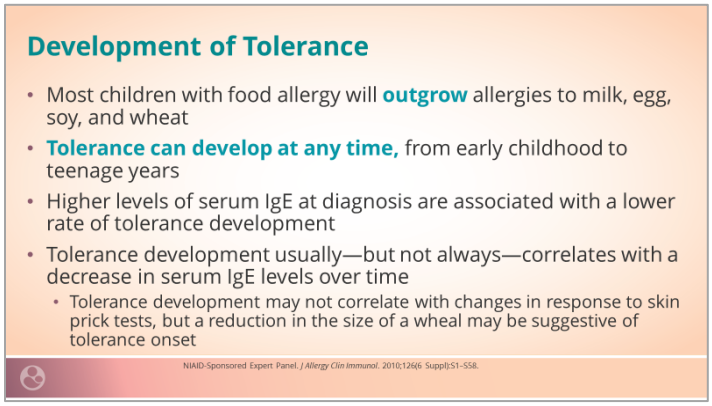
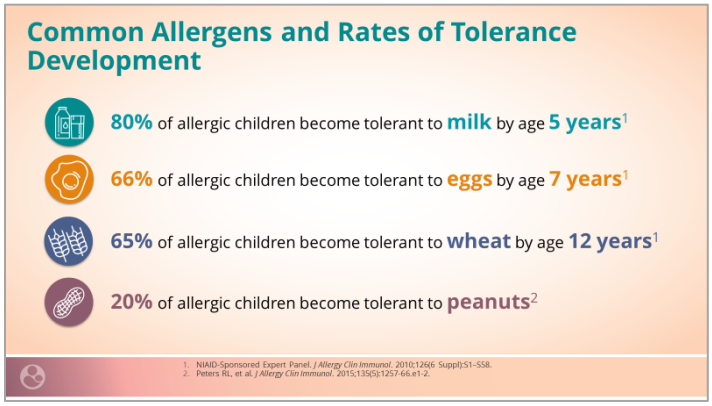


Slide 19 – Development of Tolerance

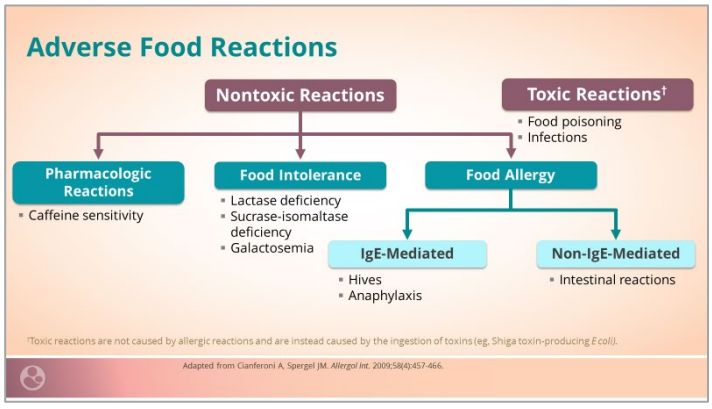
One of the things that parents want to know is how soon tolerance could occur. That's different for different foods. Eighty percent of allergic children become tolerant to milk by 5 years of age, whereas 66% of allergic children become tolerant to eggs by 7 years of age. In those who are allergic to wheat, 65% of allergic children become tolerant by age 12 years.[5] Yet, 20% or fewer allergic children become tolerant to peanuts at any time.[11]



Slide 20 – Common Allergens and Rates of Tolerance Development

When we're talking about food allergies, it helps to put the terminology into perspective. We hear about food poisonings and infections. Examples include *Salmonella* in peanut butter, *E. coli* in hamburger and meat products, *Isospora* occurred in berries, or *Cryptosporidium* in the water supply. These toxic reactions are obviously very different than the nontoxic reactions that occur, such as pharmacologic reactions like caffeine, which seems to bother many people. Caffeine reactions are dependent on concentration and timing, such as whether the caffeine is in tea or coffee and whether that's mitigated by other foods that are eaten at the same time.

Food intolerances like lactose intolerance are related to the disaccharidases that sit on the villi in the duodenum in the upper part of the jejunum. Lactase is the enzyme found there, and that can be destroyed, either from an infection or other disruption of the villi, such as with celiac disease. It can also be caused by a primary or hereditary lactose intolerance due to an inherited lactase deficiency. Sucrase-isomaltase deficiency is now being recognized as a cause of abdominal pain that presents similar to irritable bowel syndrome in adulthood and childhood. Galactosemia is something that presents in early infancy and is not truly a food intolerance but is instead a direct problem related to the enzymes that are in the liver. This presents with vomiting and jaundice in an infant who is exposed to lactose rapidly. Switching the formulas in these infants and switching the foods later simply result in resolution of these problems.



Slide 21 – Adverse Food Reactions

Food allergies, on the other hand, are not related to the volume of food ingested. Instead, food allergy can be caused by very small amounts of ingestion that can lead to IgE-mediated reactions, such as

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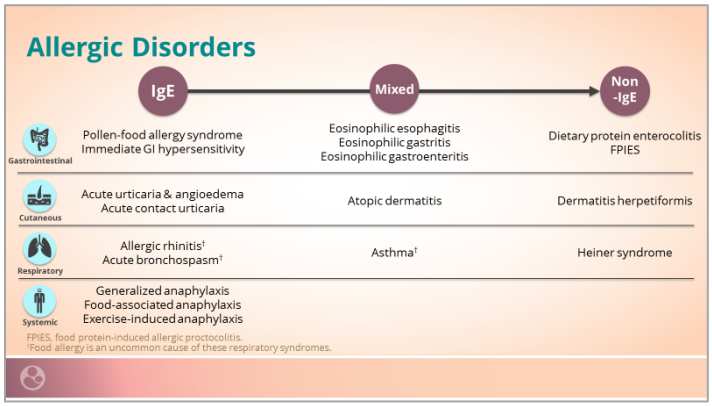
hives and anaphylaxis, or a non-IgE mediated intestinal reaction.

When we are then trying to differentiate allergic disorders in terms of IgE vs non-IgE, or mixed IgE and non-IgE related allergies, these can occur in various organ systems. Some of the most prominent are the respiratory system, skin, and GI tract. When we're thinking about IgE-mediated GI conditions, we're talking about a hypersensitivity that occurs right away with either milk or other allergenic food.



Non-IgE mediated responses can be to the same foods but present in a different way. There can be a direct reaction to milk in the intestine, causing dietary protein enterocolitis, or a much more extensive systemic response that occurs with food protein-induced enterocolitis syndrome (FPIES). There's a mixed combination that occurs with eosinophilic disorders in the esophagus, stomach, or both the stomach and intestine (esophagitis, gastritis, or gastroenteritis, respectively).

When we're looking at the skin, we can have angioedema or acute urticaria resulting from direct contact or from ingestion. There is dermatitis herpetiformis, which is a non-IgE mediated response that frequently occurs along with gluten-sensitivity in celiac disease. At the same time, there's also a mixed eczema or atopic dermatitis that can occur in the skin as well.

An IgE-mediated respiratory component is bronchospasm, and there's a mixed component there with asthma. A non-IgE mediated specific reaction is Heiner Syndrome. Additionally, there is a systemic IgE response that results in anaphylaxis that can be food, exercise, or generally induced.

Let's differentiate the IgE- and non-IgE-mediated reactions. It's important to do so in terms of presentation, prevalence, and clinic setting (either in the office or the hospital).

Comparison of IgE- and Non-IgE–mediated Food Allergies

	IgE-mediated food allergy	Mixed IgE or non-IgE–mediated food allergy
Prevalence in children	More common, about 6%	Rare, <1%
Typical organ systems involved in symptom presentation	Symptoms across broad range of organs, including oral, respiratory, cardiovascular, cutaneous, and gastrointestinal systems	Symptoms usually isolated to gastrointestinal system
Timing after oral intake	Usually seconds to minutes (within 2 hours)	Usually hours to days
Severity	May proceed to anaphylaxis	Variable, life-threatening is rare but can occur (eg, FPIES)
Pathogenesis	Type 1 immune hypersensitivity (IgE-mediated)	Cell-mediated immune hypersensitivity
Examples	Peanuts, tree nuts, seafood, milk	Eosinophilic esophagitis, food protein-induced enterocolitis syndrome

Ruffner MA, Spergel JM. *Ann Allergy Asthma Immunol.* 2016;117(5):452–454.
Wrobel JP et al. *Aust Fam Physician.* 2008;37(4):222-226.

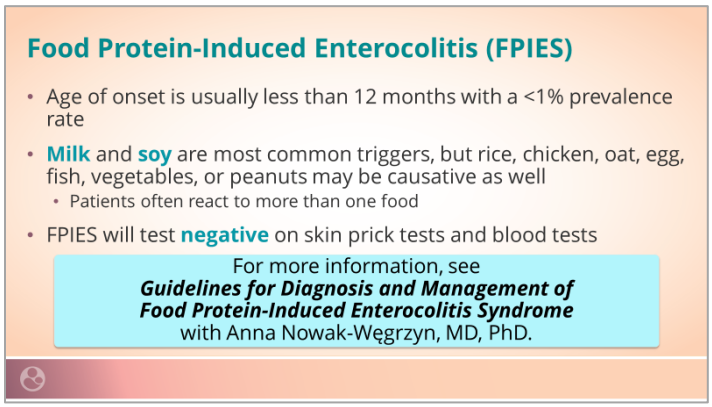
Slide 22 – Comparison of IgE- and Non-IgE-mediated Food Allergies

IgE-mediated food allergies are much more common, affecting approximately 3–6% of children, whereas mixed-IgE and non-IgE mediated food allergies or specific non-IgE-mediated food allergies are more rare, occurring in 0.4% to less than 1% of children.

A broad range of responses across organ systems occurs in the IgE-mediated food allergies. In contrast, the GI tract seems to be the predominant organ system that's involved in the mixed and non-IgE-mediated reactions; however, the skin can be affected as well, as we talked about with eczema and atopic dermatitis.

The timing after the meal is what often helps to differentiate between these conditions. In the IgE-mediated group, we're talking seconds to minutes, with all reactions occurring within 2 hours. However, in FPIES, we're looking at often minutes to

hours, and in eosinophilic esophagitis, it can be [in] days to months that we actually start to see the symptoms. The severity can be severe in both, but they're still somewhat different. Anaphylaxis in the IgE-mediated group is characterized by throat closing and difficulty breathing, whereas it's more of a shock state that can occur in severe FPIES. Most of the children don't have that degree of severity. However, because anaphylaxis in FPIES can progress to that degree, it is frightening, and something that often directs patients to the emergency room.

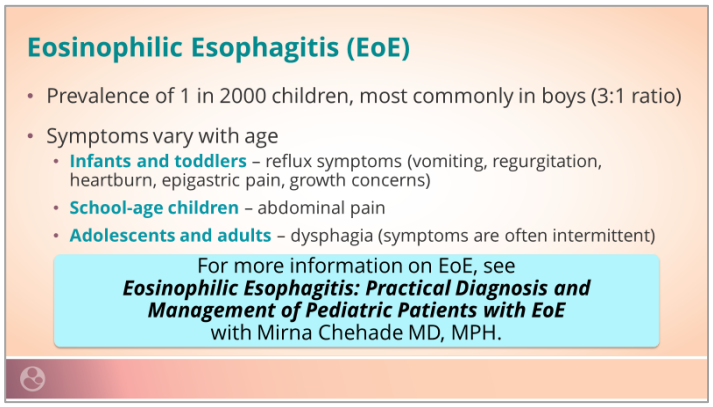


Slide 23 – Food Protein-Induced Enterocolitis (FPIES)

The mixed IgE- and non-IgE-mediated immune sensitivities are cell-mediated, whereas the IgE-mediation is through type 1 immune hypersensitivity, which is often simply called IgE-mediated immune response. Again, examples of IgE-mediated responses include reactions to certain foods like peanuts, tree nuts, seafood, milk, and soy. These things also cross over into eosinophilic esophagitis and food protein-induced enterocolitis.

Food protein-induced enterocolitis is exceedingly important and often under recognized. Dr. Anna Nowak-Węgrzyn is going to be speaking about specific guidelines for the diagnosis and management. I'll mention that FPIES usually occurs at less than 12 months of age, with less than 1% prevalence.[12] Milk and soy are the most common triggers, but grains, chicken, eggs, fish, vegetables, and peanuts can be causative as well, and often more than one food is involved. Children with FPIES will test negative on allergy tests that we use for IgE-mediated reactions.

Eosinophilic esophagitis also does not show up well on IgE testing and requires a specific kind of patch testing—if testing is done at all. The symptoms do vary with age, with infants and toddlers presenting with reflux, heartburn, epigastric pain, or growth concerns. They may not be growing—because the child is refusing feedings. They often aren't able to swallow, and they're vomiting. School-aged children will often complain of abdominal pain, and, as soon as they're able to describe it, dysphagia is reported when large boluses of food are consumed. Dr. Mirna Chehade is going to go over this in much more detail in her talk, with a practical discussion of diagnosis and management of EoE.



Slide 24 – Eosinophilic Esophagitis (EoE)

Food Allergy and Nutrition

Let's begin to look at a broader context of food allergy and how that's impacted by various points of nutrition. Historically, food allergy may not have been seen in infants because they required breastfeeding. The existence of mankind, in fact, required breastfeeding, as the ability to feed our young was important for mankind to exist. The benefits of breastfeeding are legion. They include optimal growth and neurodevelopment, decreased infections, ease of absorption and digestion, and

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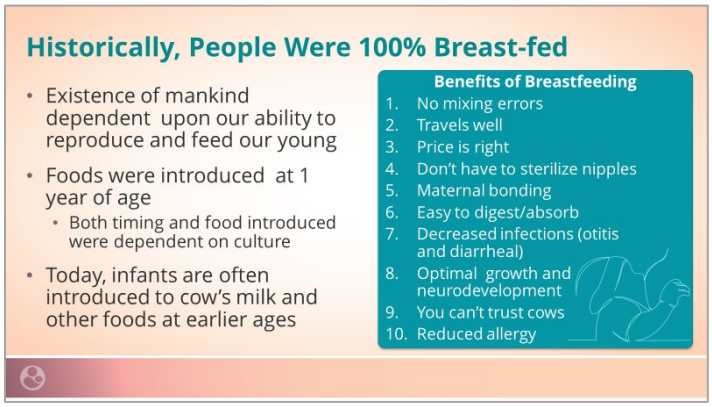
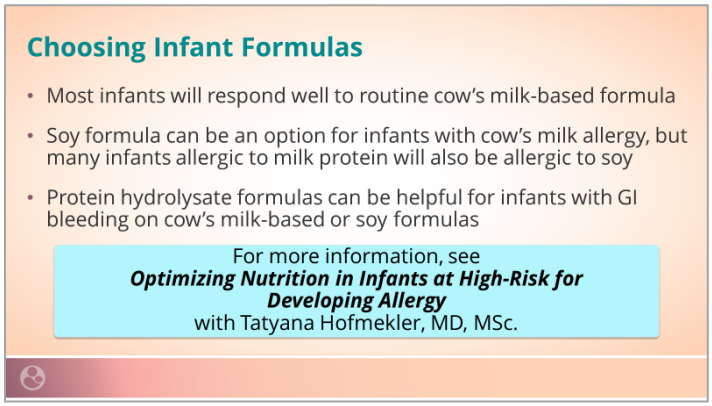
maternal bonding. And then there are other considerations that are humorous as well as important.



Slide 25 – Historically, People Were 100% Breast-fed

Foods in the ancient days weren't introduced until 1 year of age. Some of the first foods that were given to children were curds made using milk. Additionally, pap was introduced at approximately 1 year of age; however, that was dependent on the culture, as you'll see in just a bit. Today, we start to introduce cow's milk and foods at different ages, and that's being done earlier than it was historically.

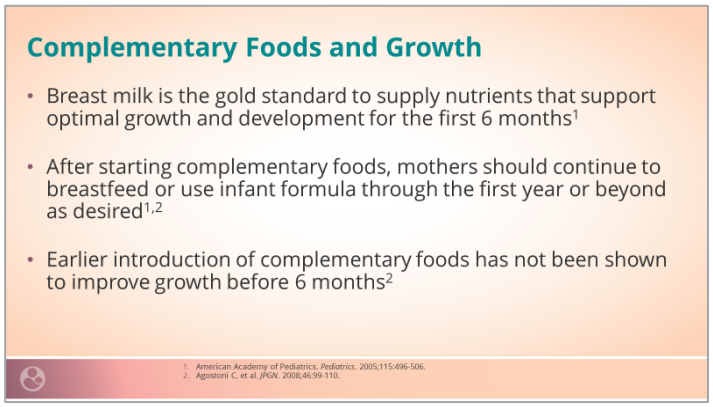
Dr. Tatyana Hofmekler is going to talk about how cow's milk has been adapted into formulas so that we can now feed our young when mothers are unable or unwilling to breastfeed and when a wet nurse is not available, or when we don't have milk banking that's available for preterm infants.



Slide 26 – Choosing Infant Formulas

Soy formula has, for a long time, been the primary option for infants with cow's milk allergies, but many infants are allergic to soy because of cross-reactivity with milk protein. Additionally, there are children with non-IgE-mediated milk protein intolerance that will be intolerant to soy as well. As a result, protein hydrolysates have been developed. These are formulas in which the milk is broken down by various means into peptide chains that can be helpful for infants with GI bleeding due to milk-induced allergies. These are even broken down further to amino acid formulas for certain infants.

Breast milk doesn't provide all the nutrients necessary for children past 6 months of age, but it is the gold standard for the first 6 months of life. After starting complementary foods, or infant foods, mothers should continue to breastfeed or use infant formula through the infant's first year, or beyond, depending on the desire of the mother.

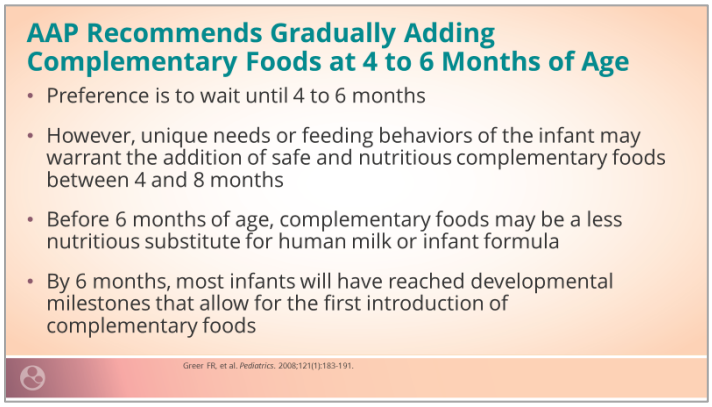


Slide 27 – Complementary Foods and Growth

Introduction of complementary foods before 6 months of age, however, has not been shown to improve growth. But recent data have shown that early introduction of some allergenic foods may lessen the development of allergies at later ages. The AAP has long recommended gradually adding complementary foods, but still using breast milk as the predominant source of calories and nutrition.

The preference is to wait until 4–6 months of age, but there are unique needs or feeding behaviors

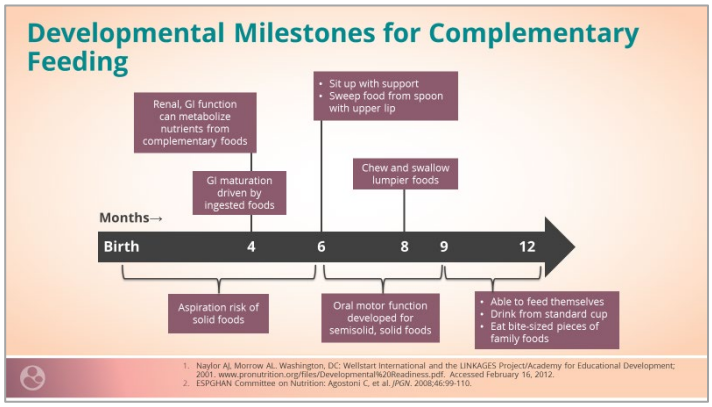
that may warrant the addition of safe and nutritious complementary foods between 4 and 8 months of age. Complementary foods may be a less-nutritious substitute for human milk for many infants, especially when they're used in abundance. By 6 months of age, most infants will have reached developmental milestones that allow for the first introduction of complementary foods.



Slide 28 – AAP Recommends Gradually Adding Complementary Foods at 4 to 6 Months of Age

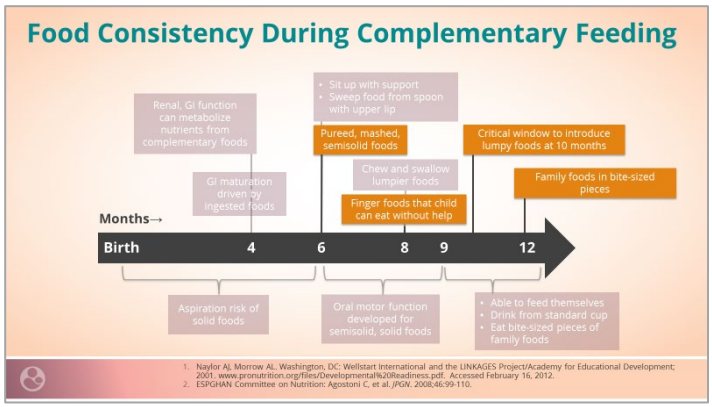
Here's why timing of [the] introduction of complementary foods is an important issue. One has to consider the developmental milestones that are important as to when foods should be introduced. Early on, there are aspiration risks to the introduction of complementary foods. In fact, infants have a protective mechanism called the tongue extrusion reflex, during which children stick out their tongue to try and prevent the introduction of foods. Moreover, infant renal function can be impaired by high protein loads, and GI function depends on the ability to break down, digest, and absorb the nutrients that are available.

Sitting up with support is another key indicator of readiness for feeding. We want to see that children are able to sweep the food from the spoon with their upper lip. Then, chewing becomes an essential factor, and being able to swallow and move the food to the back of their throat so that they can manipulate the food into a safe portion. This oral motor function is developed for semisolid, and then gradually for solid foods. Children are usually able to feed themselves by about 9 months of age. They are able to drink from a standard cup instead of from a bottle, and they're able to eat bite-sized pieces of family foods that do not contain either seeds or peels.



Slide 29 - Developmental Milestones for Complementary Feeding

With those developmental milestones recognized, it's possible to introduce pureed, mashed, and semisolid foods as early as 4–6 months of age, usually at about 4.5 months or so, once that tongue extrusion reflex abates. Finger foods can then be introduced when children can sit and eat without help and when they can use their pincer grasp to deliver the food from their plate to their mouths. Furthermore, there's a critical window that occurs by 10 months of age: lumpy solids with some consistency to them, rather than purees, should be introduced prior to that age.



Slide 30 – Food Consistency During Complementary Feeding

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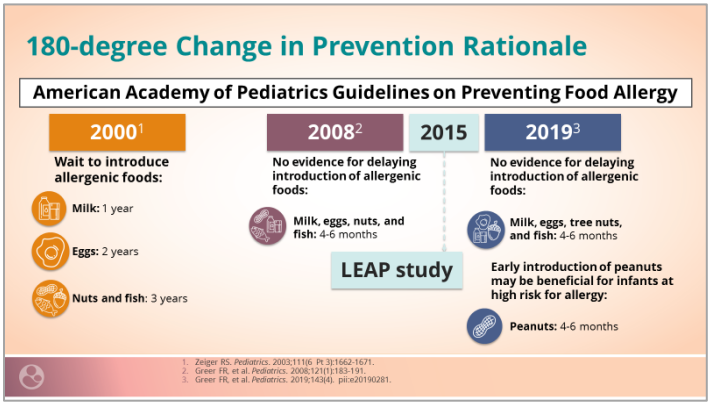
"Family foods" or "table foods" are foods that are in bite-sized portions that can be cut up and delivered to the child so that they can tolerate them well. There's now a move to what's called baby-led weaning, where children are able to hold the food themselves and start to introduce it to their own mouths with foods that are softer, and then gradually moving those up as they gain greater skill and facility in doing so.

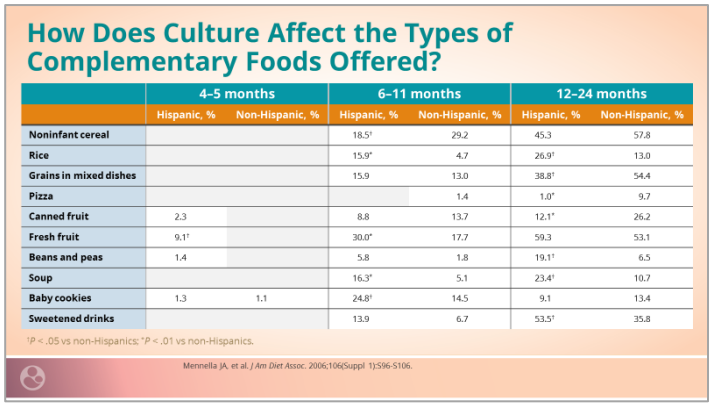
In terms of allergy prevention, all of these complementary feeding practices have led to a re-evaluation of food introduction based on feeding readiness. You may remember that as recently as 2000, milk was standardly introduced at approximately 1 year of age, with eggs, nuts, fish, and citrus foods often held to much later periods of time. However, by 2008, there was no evidence for delaying the introduction of allergenic foods beyond 6 months of age. This was led, in part, by recognizing that there was a lower prevalence of peanut allergy in Israel and China, where peanut products were introduced at younger ages.[9] This was then corroborated by a study called the LEAP study that has become very important in terms of our understanding, which Dr. Hugh Sampson and Marion Groetch are going to talk about later.[13]



Slide 31 – 180-degree Change in Prevention Rationale

As a result, the American Academy of Pediatrics has affirmed that there's no evidence for delaying introduction of allergenic foods beyond 4–6 months, and that the introduction of milk, eggs, tree nuts, and fish may be important at 4–6 months of age. In fact, introduction of peanuts at 4–6 months may be beneficial for infants at high risk for allergy when it's done in a safe and reliable context.[9]

What's interesting, as well, is that there's a very specific and significant cultural difference in the way that foods are introduced. For example, Hispanic infants and toddlers are more likely to be offered rice, fresh food, soups, beans and peas, and sweetened drinks, while non-Hispanic infants and toddlers are more likely to be offered noninfant cereals, grains and mixed dishes, peaches, and canned fruits during that same period of time.[14]

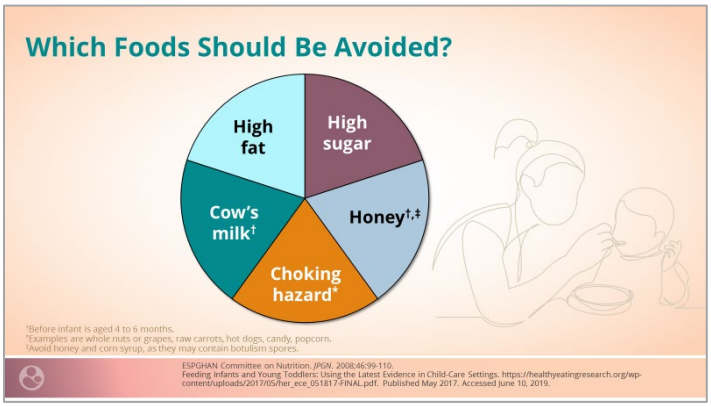


Slide 32 - How Does Culture Affect the Types of Complementary Foods Offered?

There are still foods that should be avoided. These include cow's milk. We start to feed yogurt and cheese early on and then gradually move up to cow's milk at an older age. That's in part because of the quantity of cow's milk that would otherwise be consumed, which might cause intestinal bleeding with an enterocolitis syndrome.

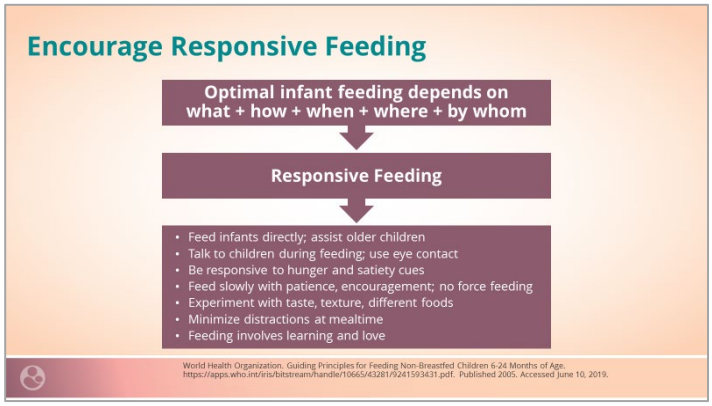
Choking hazards, as we earlier indicated, are very important. We certainly don't want that to be a problem. It's one of the reasons why puffs are often introduced as the first solid food, because they will usually melt in the mouth if they're not sufficiently chewed and swallowed. We certainly don't want to use honey before 1 year of age because of the

botulism spores that can be contained in honey and corn syrup. High fat and high sugar foods are not anything that we want to have in our diet, to prevent obesity.



Slide 33 – Which Foods Should Be Avoided?

All of this should be taken in context as we just talked about. We are trying to encourage a psychosocial impact, as well, for the child. The World Health Organization encourages what's known as "responsive feeding," which implies that there is an optimal infant feeding procedure that depends not only on what's introduced, but how it is done, when it's done, where it's done, and by whom. The intent is to feed infants directly, and that can be assisted by older children. We want to talk to the children during the feeding and use eye contact so that it's not just about shoveling the food in to get them to eat quickly, but rather to make feeding times engaging and loving. This is a nutrition moment as well as an interactive moment for infants. Responsive feeding also allows the parent or caregiver to be responsive to hunger and satiety cues. Hunger clues include leaning forward, opening the mouth, looking at the food, and even pointing to the parents' plates. Satiety clues include playing with the food or looking around the room.[15]



Slide 34 – Encourage Responsive Feeding

In order to be responsive, it's often necessary to feed with patience and encouragement, and without force. We want the child to be able to experiment with the taste and texture of different foods. It's of note that many children cannot really tell whether they like or dislike a food until they've had 15 tastes of that food. We want to minimize their distractions at mealtime, and again, we want to do this as a teaching moment with a great deal of love being expressed at the time.

Additionally, we want to take into account not only the parents' influences and the cultural influences but also the infant's innate preference for salt and sweet foods, as well as their dislike of sour and bitter foods. We want to continue to recognize that there's lots of flavor exposures that infants have had, both in utero and from breast milk or formula.

We should also recognize that there are a variety of foods that infants are offered, and that there's an innate fear of new foods in many children. There will be learned favorites as well as learned behaviors when foods are being brought to their mouths on a regular basis, or even when medicines are being brought to their mouths. Infants can have a feeding aversion because of all of these different experiences.

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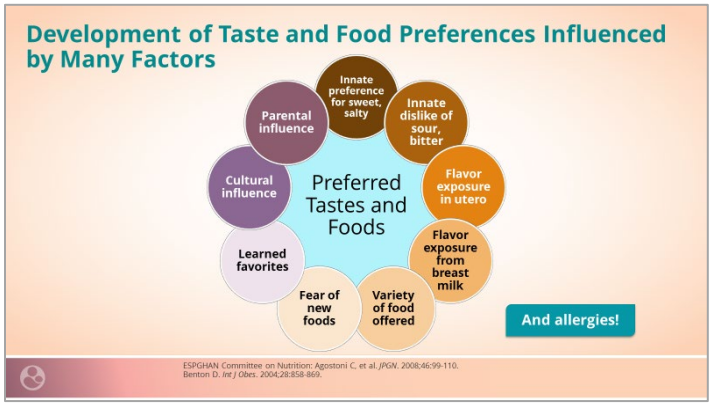
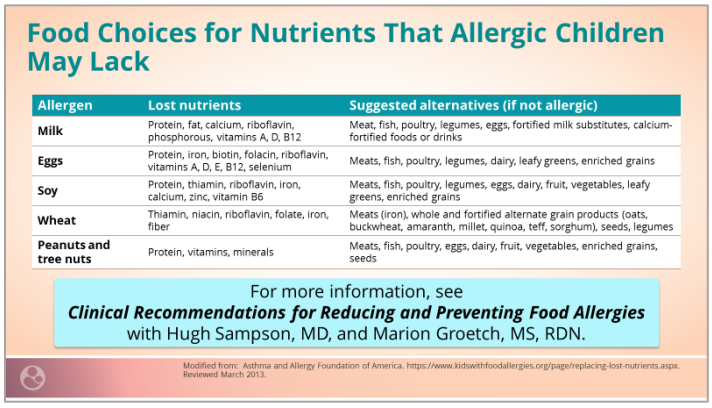


Slide 35 – Development of Taste and Food Preferences Influenced by Many Factors

We also have to recognize that as we reduce and avoid foods, nutrients can be deficient, and we have to get those nutrients in, in some way. Parents should consider suggested alternatives to different foods. Dr. Hugh Sampson and Marion Groetch are going to talk about this in more detail as they review about clinical recommendations for reducing and preventing food allergies.



Slide 36 – Food Choices for Nutrients That Allergic Children May Lack

If we talk about individual foods, we understand that milk, for example, is a main source of calcium and vitamin D, as well as other nutrients. Many of the proteins, fats, and calories in milk can be found in other foods, but in order to get calcium and Vitamin D, we often have to use fortified milk substitutes and calcium-fortified foods or drinks.

Eggs have biotin and choline in them as well as selenium. There are other nutrients, including vitamins, iron, and protein. These nutrients can be substituted with other foods as long as there are no other food allergies. Soy, wheat, peanuts, and tree nuts often present nutritional issues as well, with protein, vitamins, and minerals often requiring supplementation with other foods.

Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Cohen's responses from the July 22, 2019, audio webcast.

Can allergy symptoms include the urinary tract? For example, frequent bedwetting?

Dr. Cohen: We don't usually think so. Allergies don't present that way. They may present with a difference in terms of stooling, such as diarrhea, but it doesn't seem to have any impact on the bladder or the renal system.

If an individual has an IgE-mediated allergy that manifests with mild-to-moderate GI symptoms, and they choose to continue eating the food from time to time or have accidental exposures, is there a risk to their health long-term with this exposure?

Dr. Cohen: We don't fully understand that yet. We do know that if there's damage to the villi along the way, the patient is going to have continued damage as long as the food is in the diet, and this will not only cause problems with the villi and absorption, but it can also cause problems with the disaccharidases. If it's a respiratory allergy that's persisting, there may be some buildup in the tissues and thickening in the lungs, and that can be a problem for the patient.

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How common is it for children to have both IgE and non-IgE-mediated allergies? Does the presence of both types of allergies increase the risk for anaphylaxis?

Dr. Cohen: The presence of anaphylaxis is really an IGE-mediated phenomenon. The mixed and non-IgE-mediated situations really don't cause anaphylaxis themselves. Although with FPIES, you can get a non-IgE-mediated shock-like state that can be an emergency.

In terms of how common they are—still relatively uncommon. As we indicated before, allergies to IgE are usually in less than 6% of the population, and non-IgE-mediated allergies are usually in less than 1% of the population.

Have there been any studies on possible connection with non or mixed IgE-mediated conditions and learning disabilities or other milestones?

Not that I'm aware of. I think that it does raise that concern, but I don't think that anything has been established.

Can food allergies affect behavior in children?

Foods, in general, can affect behavior in children. We know that from sweets, caffeine, and even lassitude that comes from overeating. Food allergies themselves can cause irritability and can cause discomfort that can manifest in not feeling well, but there's no specific or direct reaction.

How does gluten intolerance fit within this discussion of food allergies?

Gluten intolerance raises a whole other range of topics. If you think about gluten intolerance, it can be mistaken for wheat allergy, which is an IgE-mediated event. With celiac disease, gluten exposure causes an autoimmune phenomenon where there is change in the tight junctions between the cells, which can cause this whole plethora of symptoms both in the GI tract and otherwise, in terms of fertility and skin reactions.

On the other hand, gluten intolerance that is not celiac-related is still something that we're trying to understand, and we haven't yet understood it fully. It may be that it's not truly gluten that the kids are reacting to, but the fructans that are actually found in wheat along with gluten.

Is a patient with celiac disease at higher risk for FPIES? Is there any link?

FPIES is something that occurs much earlier. Gluten intolerance doesn't usually show up until kids are older. Because of the time of exposure, most wheat products are held until closer to 6 or 8 months, whereas FPIES often will present even earlier than that.

There does not seem to be any direct association that I or anybody else is aware of.

What can you recommend for infants that are allergic to both soy and cow's milk?

There are some good alternatives in terms of milks; they're not true milks because they're vegetable-based, and milk by itself is a mammalian product.

Goat's milk is not a good choice because goat's milk and cow's milk have a great deal of cross-reactivity. The better choices are oat milk and pea protein milk. And then the ones that we need to be aware of, in a very different way, are almond milk and all the nut milks; they have almost no protein compared to the 8 g of protein in a glass of cow's milk or even oat milk. But nut milks have only 1 g of protein—or none at all, in the case of coconut milk. Furthermore, nut milks only have approximately 30 calories compared with cow's milk, which has 120–160 calories.

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Abbreviations

AAP	American Academy of Pediatrics	**GI**	gastrointestinal
EoE	eosinophilic esophagitis	**IgA**	immunoglobulin A
FPIES	food protein-induced enterocolitis syndrome	**IgE**	immunoglobulin E
GERD	gastroesophageal reflux disease		

1. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. *NCHS Data Brief*. 2013;(121):1-8.

2. Renz H, Allen KJ, Sicherer SH, et al. Food allergy. *Nat Rev Dis Primers*. 2018;4:17098. doi: 10.1038/nrdp.2017.98

3. Panjari M, Koplin JJ, Dharmage SC, et al. Nut allergy prevalence and differences between Asian-born children and Australian-born children of Asian descent: a state-wide survey of children at primary school entry in Victoria, Australia. *Clin Exp Allergy*. 2016;46(4):602-609. doi:10.1111/cea.12699

4. Centers for Disease Control and Prevention (CDC). Allergies. https://www.cdc.gov/healthcommunication/ToolsTemplates/EntertainmentEd/Tips/Allergies.html. Reviewed September 15, 2017. Accessed August 14, 2019.

5. 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

6. Cantani A. The growing genetic links and the early onset of atopic diseases in children stress the unique role of the atopic march: a meta-analysis. *J Investig Allergol Clin Immunol*. 1999;9(5):314-320.

7. Bishop JM, Hill DJ, Hosking CS. Natural history of cow milk allergy: clinical outcome. *J Pediatr*. 1990;116(6):862-867.

8. Walker AW. The principle of handling intestinal antigens. In: Branski D, Dinari G, Rozen P, Walker-Smith JA, eds. *Pediatric Gastroenterology. Aspects of Immunology and Infections.* Basel: Karger; 1986:10-13.

9. 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

10. 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):632-43. doi:10.1111/cea.12487

11. Peters RL, Allen KJ, Dharmage SC, et al; HealthNuts Study. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment. *J Allergy Clin Immunol*. 2015;135(5):1257-66.e1-2. doi:10.1016/j.jaci.2015.01.002

12. Ruffner MA, Spergel JM. Non-IgE-mediated food allergy syndromes. *Ann Allergy Asthma Immunol*. 2016;117(5):452–454. doi:10.1016/j.anai.2016.04.014

13. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy [published correction appears in *N Engl J Med*. 2016;375(4):398]. *N Engl J Med*. 2015;372(9):803–813. doi:10.1056/NEJMoa1414850

14. Mennella JA, Ziegler P, Briefel R, Novak T. Feeding infants and toddlers study: the types of foods fed to Hispanic infants to toddlers. *J Am Diet Assoc*. 2006;106 (Suppl 1):S96-S106.

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15. World Health Organization. Guiding Principles for Feeding Non-Breastfed Children 6-24 Months of Age. https://apps.who.int/iris/bitstream/handle/10665/43281/9241593431.pdf. Published 2005. Accessed August 14, 2019.