Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

Overview

David Fleischer, MD, and Carina Venter, PhD, RD, discuss strategies for a proper diagnosis of food allergies in infants, specifically cow's milk allergy and its pathophysiology. Dr. Venter will review how to distinguish between IgE-mediated and non-IgE-mediated reactions to food. Dr. Fleischer will discuss current standard of care, including guided CMA elimination diet, while sharing his expert insights in the reintroduction of foods via oral immunotherapy. Dr. Venter will provide details about suitable and clinically recommended formulas. We will also discuss the latest insights into the mechanisms of allergy triggers, as they provide new research targets for allergy treatments. Our discussion also includes improving patient care as it advances beyond food-allergen avoidance.

Content Areas

- Discerning food allergy vs food intolerance
- Recognizing cow's milk allergy in infants
- IgE-mediated and non-IgE-mediated reactions to food
- Selecting the right infant formula for allergic patients
- Understanding oral immunotherapy
- Applying nutritional treatment strategies to mitigate food allergies

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.

Obtain your CE/CME credit at:
https://pnce.org/Cows-Milk-Allergy

Section

Learning Objectives

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

- Apply current standard of care for the diagnosis and management of cow's milk allergy in infants
- Link research targets to diagnosis and treatment of cow's milk allergy in infants
- Specify nutritional strategies to manage food allergy in infants

Faculty

David M. Fleischer, MD
Director, Allergy and Immunology Center
Associate Section Head
Children's Hospital Colorado
Aurora, Colorado

Carina Venter, PhD, RD
Assistant Professor, Pediatrics-Allergy
Children's Hospital Colorado
Aurora, Colorado

Accreditation and Certification

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Annenberg Center for Health Sciences at Eisenhower is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider number: 040207.

This program is accredited for 1.0 contact hour.
Program ID #5669-EM

Annenberg Center for Health Sciences is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

A maximum of 1.0 contact hour may be earned for successful completion of this activity.

Provider is approved by the California Board of Registered Nursing, Provider #13664, for 1.0 contact hour. To receive credit for education contact hours outside of the state of California, please check with your state board of registered nursing for reciprocity.

Annenberg Center for Health Sciences at Eisenhower is a Continuing Professional Education (CPE) Accredited Provider with the Commission on Dietetic Registration (CDR). Registered dietitians (RDs) and dietetic technicians, registered (DTRs) will receive 1.0 continuing professional education unit (CPEU) for completion of this program/material.
Provider number: AC857
Activity number: 149124

Disclosure Statement

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in health care and not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

David M. Fleischer, MD

Research Support	DBV Technologies- clinical area: Food allergy Aimmune Therapeutics- clinical area: Food allergy
Consultant	DBV- clinical area: Food allergy Aimmune- clinical area: Food allergy Kaleo- clinical area: Food allergy INSYS- clinical area: Food allergy Nestlé- clinical area: Food allergy
Speakers Bureau	Abbott- clinical area: Food allergy

Carina Venter, PhD, RD

Speakers Bureau	Danone- clinical area: Allergy and Immunology Abbott- clinical area: Allergy and Immunology

The faculty for this activity has disclosed that there will be no discussion about the use of products for non-FDA approved indications.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

Additional content planners

The following have no significant relationship to disclose:
Coy Flowers, MD (peer reviewer)
Victoria Anderson (medical writer)
Heather Jimenez, FNP (nurse reviewer)

Annenberg Center for Health Sciences

Charles Willis, Director of Continuing Education, consults for Pfizer, Inc; all other staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

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

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 July 1, 2019 and is eligible for credit through November 9, 2020.

Contact Information

For help or questions about this activity please contact Continuing Education:

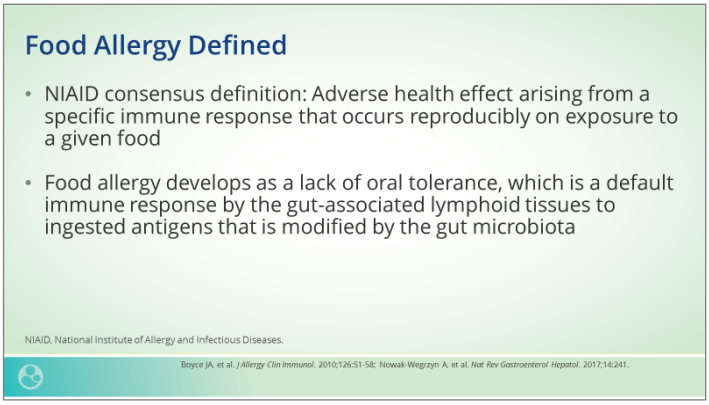
ce@annenberg.net

Editor's Note: This is a transcript of an audio webcast presented on November 5, 2018.

Module 1: Diagnosing and Managing Food Allergies in Infants

Dr. David Fleischer: In Module 1 we'll be looking at diagnosing and managing food allergies in infants. We'll look at the definition of a food allergy. Again, how to diagnosis it, specifically looking at IgE-mediated cow's milk allergy, prevalence of food allergies, strategies for proper diagnosis, and then again distinguish between IgE- and non-IgE-mediated reactions.

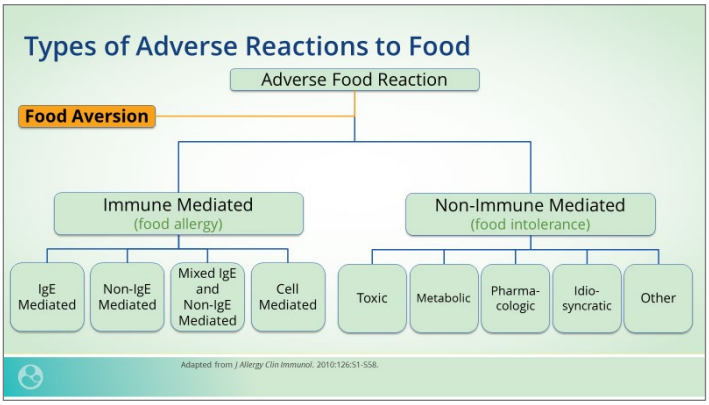
This is the NIAID [National Institute of Allergy and Infectious Diseases] consensus definition for a food allergy: It's an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food. It develops as a lack of oral tolerance, which is a more default immune response by the gut (looking at foods). And if they make more potentially dangerous antibodies to those with the IgE antibodies vs protective antibodies, [then] it can develop into an allergy.



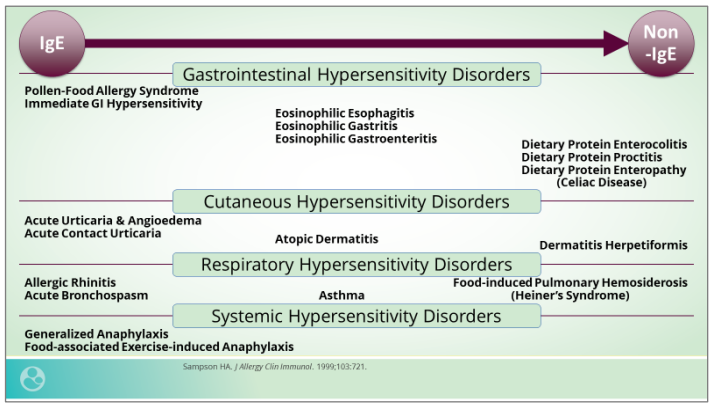
When we look at any reaction to a food, we basically call any bad outcome, or bad reaction to food, an adverse food reaction. To be IgE, or to be immune

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

mediated, it has to involve the immune system. And that's where it's either divided into IgE mediated, which again we'll be talking primarily about today, non-IgE mediated, [or] mixed disorders—and I'll show that on the next slide—or cell mediated. Non-immune-mediated reactions can be things like **food intolerance**, or lactose intolerance. Whereas [in] an example: you don't have the enzyme to break down the sugar in milk, but the protein that's in that milk, you can tolerate. Other reactions can be like food poisoning, pharmacologic reactions, and metabolic reactions, toxic reactions. If you have too much caffeine, you can have a toxic reaction to that. So, the other thing is **food aversion**. In some of these disorders, patients become quite averse to eating the food, so that's a subset within these types of allergies.



Again, here's the spectrum of food allergy from IgE mediated purely on the left, going to non-IgE mediated on the right. Our IgE mediated is all in the GI tract. A common one is pollen food-allergy syndrome, where you get some oral itching in your mouth when you eat certain fresh fruits and vegetables. You're actually allergic to more environmental allergens, but those proteins in the environmental allergens cross-react with certain foods, and you get itching in your mouth. When you cook those foods, those do not cause symptoms, usually. GI-mixed disorders, although we feel probably eosinophilic esophagitis and eosinophilic GI disease, is probably more non-IgE mediated at this point, is listed in the mixed disorders. And then non-IgE-mediated reactions—a typical one with respect to milk—is milk induced proctocolitis, where patients can get some blood in their stool when they ingest milk, and it usually goes away by age one.



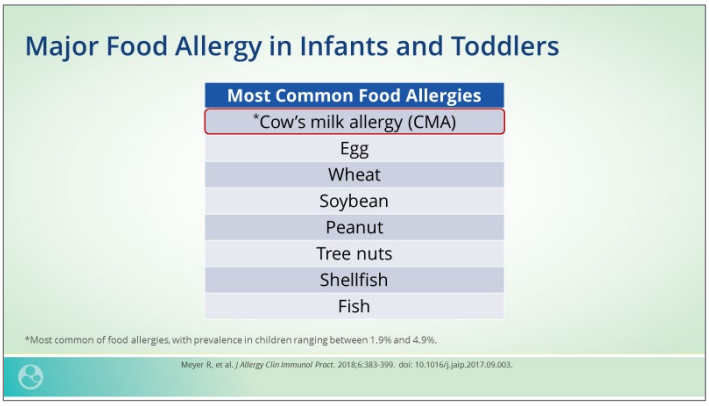
Cutaneous disorders in IgE mediated can present as urticaria and angioedema. More mixed disorders [include] atopic dermatitis. Respiratory reactions to food by themselves are quite rare. Again, these are usually symptoms of—and I'll show you in the next slide—that are usually typical based on what organ system you get symptoms from. And then, systemic hypersensitivity disorders are usually anaphylaxis, and generally those are just IgE mediated.

[Now we are] looking at prevalence of food allergy in infants and toddlers. Food allergies, at least in the US, affect about 4% to 8% of children under the age of 5 years. It's about 6 million children under age 18. About 40% of those have a history of severe reactions, and about a third of those patients have multiple food allergies, so not just one food allergy. Comparatively, it's roughly 3% to 4% in the general population in other developed countries. But, prevalence studies in the US have not been done based on food challenges. A true prevalence is often based more so, in these studies, based on telephone calls, or things like that, or surveys. We

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

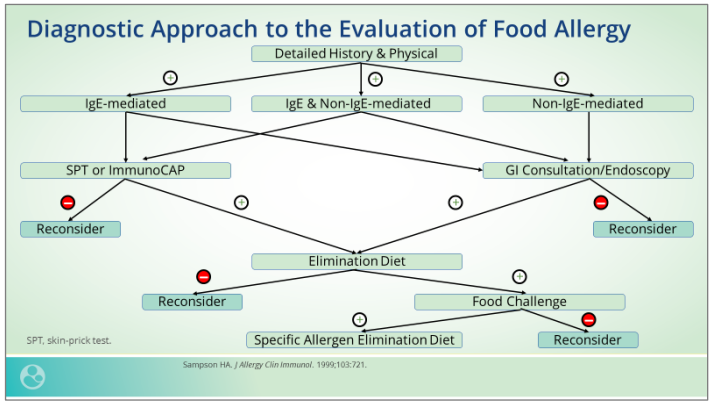
think prevalence is increasing. Again, having a true prevalence study where you do food challenges has not been done in the US. But, looking at peanut allergy, it's probably tripled over the past decade. Our focus, again [for this presentation], is going to be on cow's milk allergy, which is the most common allergen in infants with a prevalence of 2.5% under age 1 year.

Other common allergens include egg, wheat, soy, peanut, tree nuts, fish, and shellfish. And, with milk, it accounts for about 90% to 95% of IgE-mediated food allergy in children.



This is a little more complicated slide, and I'll go through it in not too much detail. The main points here are: What is going to guide you, whether you have a possible IgE-mediated reaction or not, is a detailed history; the clinical history is going to tell you which one it possibly is. [In a] physical exam, you'll find some things on patients that... If you're an atopic child, they have eczema, or other things that may lean you towards more IgE-mediated allergy. But again, the clinical history for both is most important. With IgE-mediated allergies on the left, we can use skin tests, we can use serum IgE testing. And then, if those are negative, we can consider doing the food challenge.

"A detailed clinical history is what guides you to determine whether you have an IgE-mediated reaction."



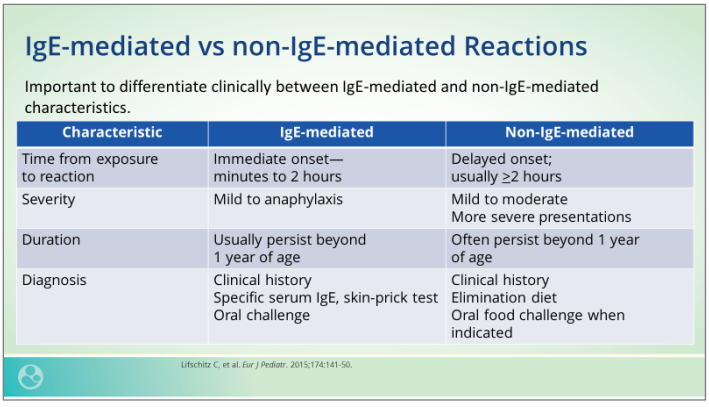
On the right, with the non-IgE-mediated reactions, again the clinical history is going to tell you whether it's non-IgE mediated or not. Some of those patients you may need to do—if you're looking at eosinophilic GI disease, GI disorders—an endoscopy, or have a consultation with a gastroenterologist. And sometimes you have to eliminate those foods and re-challenge those patients. Whereas we do food challenges primarily in patients with IgE-mediated allergy either to confirm they don't have the allergy or see if they've outgrown an already diagnosed allergy.

We're looking at IgE-mediated vs non-IgE-mediated reactions, and how to differentiate those based on timing of when you have the reaction, and when you eat the food, and [its] severity. So, [we are] looking at characteristics of time from exposure to reactions. In pretty much all IgE-mediated reactions, most of those reactions are going to happen within the first 15-30 minutes, but within the first 2 hours. There is a delayed IgE-mediated reaction that you can have to beef, although we won't go into detail with that. Non-IgE-mediated reactions typically are more delayed in onset, usually after more than 2

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

hours. The severity in both can be quite severe, so you can have mild reactions with IgE-mediated reactions, or you can have anaphylactic reactions. You can have mild to moderate, too, with non-IgE, but you can have more severe presentations, as well.

As far as duration of allergies, with IgE most of those go beyond year 1 of age. Some foods, like milk and egg, are usually outgrown; whereas, when you look at peanuts, tree nuts, and seafood, the vast majority of those are not outgrown and go on into adulthood. With non-IgE mediated, some persist beyond 1 year of age. Like I said, with milk-induced proctocolitis, those usually outgrow around 1 year of age. If you look at other milk-induced FPIES [Food Protein-Induced Enterocolitis Syndrome], or food protein-induced enterocolitis, most of those patients don't outgrow it until age 3 years. Again, what I said with diagnosis, the clinical history for both is going to drive you as to what you may think is IgE or not IgE, and what tests you may or may not do. Again, with IgE-mediated reactions, we can do skin tests, and we can do serum-IgE testing.



IgE-mediated vs non-IgE-mediated Reactions

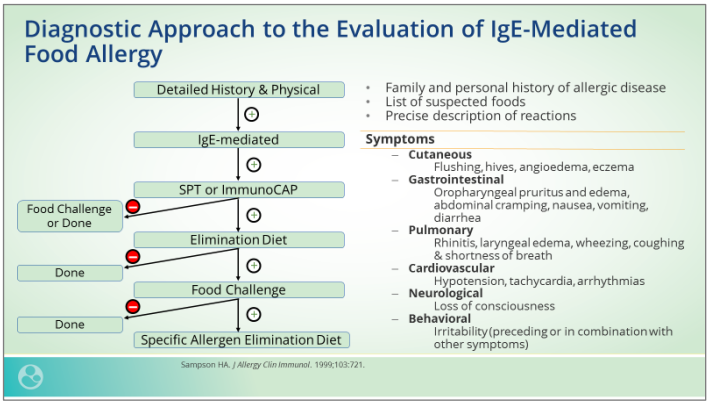
Important to differentiate clinically between IgE-mediated and non-IgE-mediated characteristics.

Characteristic	IgE-mediated	Non-IgE-mediated
Time from exposure to reaction	Immediate onset—minutes to 2 hours	Delayed onset; usually ≥2 hours
Severity	Mild to anaphylaxis	Mild to moderate More severe presentations
Duration	Usually persist beyond 1 year of age	Often persist beyond 1 year of age
Diagnosis	Clinical history Specific serum IgE, skin-prick test Oral challenge	Clinical history Elimination diet Oral food challenge when indicated

Lifschitz C, et al. *Eur J Pediatr.* 2015;174:141-50.

Food challenges are really a part of both, again, primarily to see if they've outgrown the allergy; sometimes, with more IgE mediated, we may use them to confirm, as well. Again, clinical history and an elimination diet are going to be the things with most non-IgE-mediated disorders testing; you can't use skin tests, and you can't use serum blood tests, because IgE tests... Again, because it's not IgE mediated.

When we look at the diagnostic approach to the evaluation of IgE-mediated allergy... again, I'll stress that detailed history is going to be very important. Some other things you'll find out from history is many of these patients have a family history of other allergic diseases, such as eczema, allergic rhinitis, or asthma. You want to get, [through] the history, the list of the suspected foods, and a precise description of the reaction. So, how much they ate, when they ate it, and how quickly after they ate the food did they have symptoms, and then what kind of symptoms they've had. Also, good things to ask are, have they eaten the food since then? Many patients, for example, with milk, they may have reacted to some form of raw milk, but have they eaten it in a baked good or something like that and not reacted? Those are important things to find out.

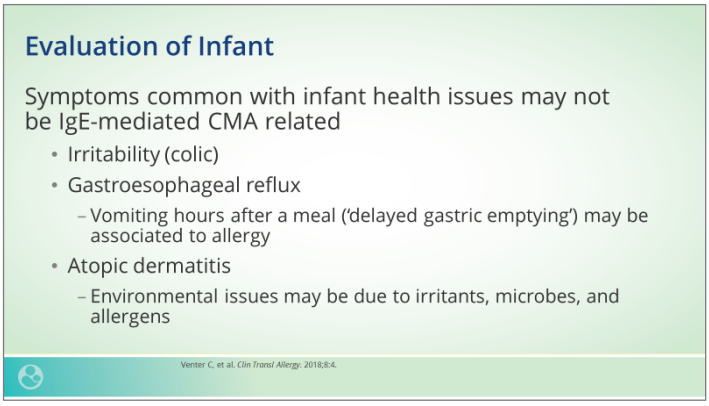


The symptoms that we'll see with IgE-mediated reactions, again, depend on what organ system you're looking at. The most common things we'll see, especially in infants, are hives, or urticaria. Patients can have some swelling or angioedema, eczema, as well. GI is something we'll also see quite commonly in reactions in infants under age 1, with vomiting. [In] pulmonary, you can get wheezing, but again wheezing is usually not isolated by itself;

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

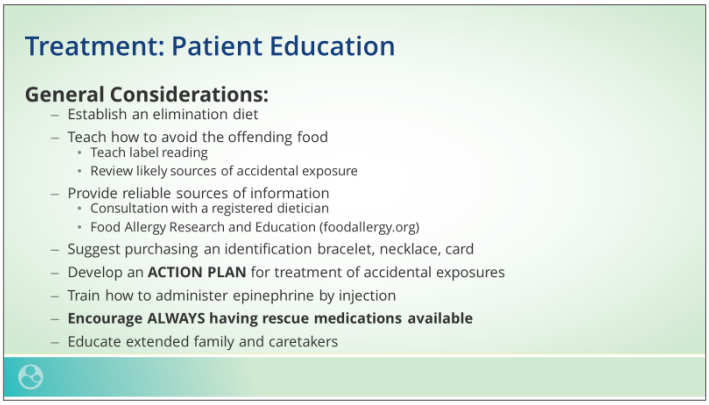
usually there's other organ systems involved, such as the skin. GI tract, you can have upper respiratory symptoms with congestion and runny nose, and you can get severe symptoms, obviously, with asthma and laryngeal edema. Cardiovascular symptoms: hypotension is less common in children, and more common in adults, but it can happen. Patients can have neurological symptoms, loss of consciousness. Something we'll see quite commonly in the food challenges we do,c are behavioral changes. So, when we're doing a food challenge in young infants, or young toddlers, who can't tell us how they're feeling, often they'll be playing with their parents, or playing with toys, and then suddenly they get very quiet, and go and sit in the parents' lap, and that's often the sign that they're not feeling well. So, that's what we mean by behavioral symptoms.

In the evaluation of an infant, again, the common symptoms, what we talked about with IgE mediated, there are symptoms you can have with cow's milk that may not be IgE-mediated reactions. So, you can have irritability, gastroesophageal reflux, and these are more common in the mild to moderate non-IgE-mediate cow's milk allergy. Reflux [for example], as I said, and, atopic dermatitis is usually a delayed reaction, as well, and it can also be due to environmental factors. Other things that can cause eczema flares in young kids and infants are when they get upset… they can have eczema flares. When they have infections or when they get vaccines, it can also cause… So, it doesn't mean that all these things are directly related to foods and not other things.



When we have a diagnosis of an IgE-mediated reaction, these are the things we will consider and talk to families about. Obviously, establishing an elimination diet is important. Teaching [parents and caregivers] how to do labeling reading. Another important thing that… We always try to have our patients at least meet with a dietitian, because it's not just avoiding the foods you can't eat, it's also making sure you are getting those nutrients that you do need in other forms, and the dietitians are very good about doing that.

Having reliable information. There are certain websites that can be helpful. Foodallergy.org is one that's monitored by allergists and other physicians, so that the documentation and information is up-to-date and accurate. Some patients will consider getting an identification bracelet.



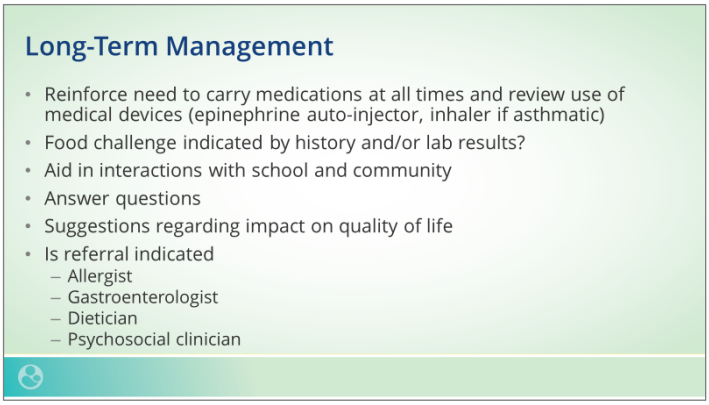
We definitely want them to have an action plan—an anaphylaxis action plan—so they know how to treat

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

reactions based on what symptoms they have. It [the information] reviews when you may use just an antihistamine and when you should use epinephrine.

Training how to use epinephrine is very important, because we can't predict necessarily the severity of reactions based on testing. And just because you haven't had a severe reaction before, anaphylaxis, does not mean you won't in the future, so we always want to be prepared and have epinephrine auto-injectors with patients. And then, always having them with them, as I said. And then, it's not just educating the parents, but if there are other caregivers, such as babysitters, nannies, grandparents, or siblings who are taking care of the child, we want to make sure to educate them, as well.

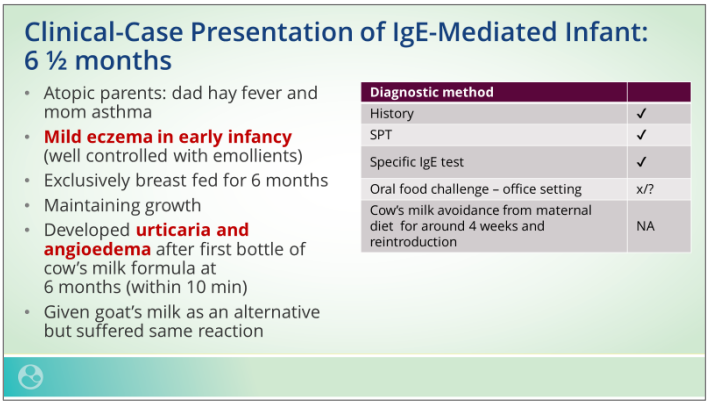
Long-term management. We usually see patients for food allergy at least once a year to update their medications, refill prescriptions, go over any new research that may be coming out, or new treatments that we'll talk about later in this talk. Looking at the results from those tests, we may order a food challenge. There may be things [to discuss] as kids go from preschool to elementary school. There are often questions about how to manage that. Answer all questions. Then, we always want to look at how food allergies are impacting the quality of life. We know food allergy, unfortunately, has impact not just on the patients, but on the whole family. Oftentimes, we're fortunate here that we do have not just dietitians, but we also have a psychosocial clinician, a psychologist, who helps with our patients, because again we want them to have a healthy level of anxiety with their food allergy. But oftentimes, unfortunately, that level of anxiety can be very high, to the point where it significantly impacts their quality of life.



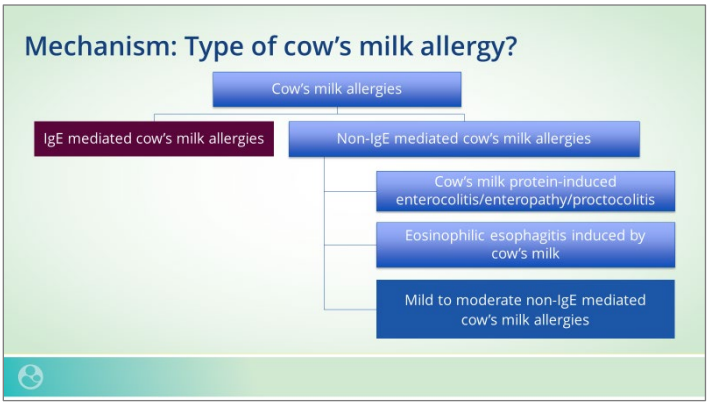
Now, we'll look at a clinical case of an IgE-mediated food allergy in an infant. This infant was 6½ months old. They have atopic parents: father has allergic rhinitis, and mom has asthma. Mild eczema in their early infancy that's controlled with moisturizers and bathing. Was breastfed for 6 months and doing well with maintaining growth and development. But, the first time this infant got a bottle of cow's milk formula at 6 months, within 10 minutes developed urticaria and angioedema. They tried giving goat's milk as an alternative but had the same reaction. And that's not uncommon, since goat's milk has about 90% cross-reactivity with cow's milk.

So, given the clinical history, it certainly sounds like IgE mediated, because of the timing of the reaction, how quickly the symptoms and the type of symptoms that developed within those 10 minutes. We can confirm that with skin tests, and we can also do a serum IgE test to help confirm the clinical history. At this point, a food challenge is likely not necessary. This infant has a clear history of symptoms acutely, and the type of symptoms that would be consistent with IgE-mediated allergy. We'd recommend cow's milk avoidance at this point.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

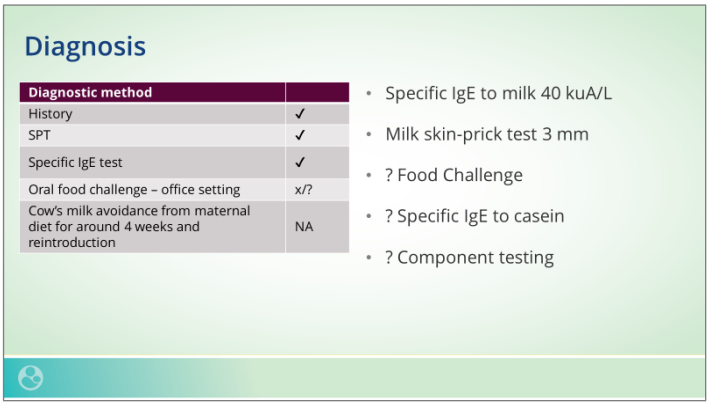


Again, we're looking at IgE-mediated cow's milk allergy in this infant. That will be the focus of the rest of the talk, as well. But, as you can see, other non-IgE-mediated cow's milk allergies can include the milk-induced proctocolitis I talked about. Enterocolitis, so food protein-induced enterocolitis, or FPIES. Eosinophilic esophagitis is often...milk is often a trigger for those patients. And then, the more mild-to-moderate non-IgE-mediated cow's milk allergies. The reflux and colic that I talked about earlier.



So, looking at what other tests we did with this infant, the specific IgE to milk was 40 kilo units/L. The blood tests go on a level from undetectable to greater than 100. The skin test was 3 mm, which is considered positive.

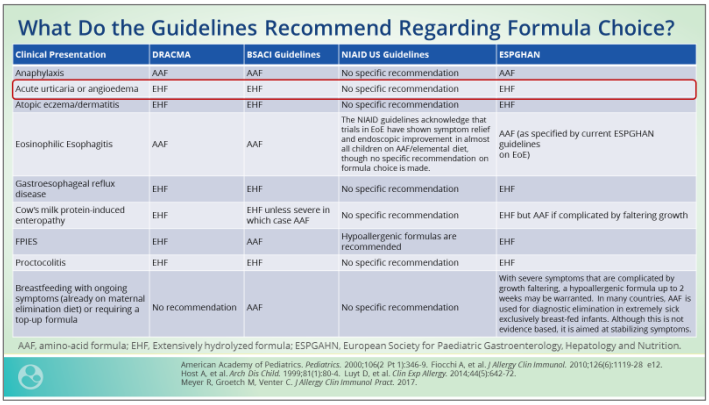
An important point here that neither the skin test nor the level of that blood test can predict what severity reaction a patient will have. The higher the skin test, or the larger the skin test, and the higher the blood test, the more likely that the patient is to react, but again, you can't predict severity. Again, I would not do a food challenge in this patient at this point. When the patient is older, probably between ages 1 and 2, I would consider doing a baked-milk challenge in our challenge unit. And, casein levels can sometimes help predict, if you'll pass the bake challenge or not, but we don't often do a lot of component testing early on.



So, what do you recommend for this infant as far as a formula choice, because mom has stopped breast feeding? Generally, with a more mild reaction of urticaria or angioedema, you can use an extensively hydrolyzed formula (EHF). Carina [Venter, PhD, RD] will talk about these more. In about 90% of patients with cow's milk allergy, they will tolerate an extensively hydrolyzed [formula]; but, in some patients, especially those who have had anaphylaxis, we'll often go right to an amino acid-based formula to remove any risk of reaction. Some families will do food challenges to the hydrolyzed formula, just to make sure they tolerate [it] before letting them introduce it at home.

With that, I will let Carina take over.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment



What Do the Guidelines Recommend Regarding Formula Choice?

Clinical Presentation	DRACMA	BSACI Guidelines	NIAID US Guidelines	ESPGHAN
Anaphylaxis	AAF	AAF	No specific recommendation	AAF
Acute urticaria or angioedema	EHF	EHF	No specific recommendation	EHF
Atopic eczema/dermatitis	EHF	EHF	No specific recommendation	EHF
Eosinophilic Esophagitis	AAF	AAF	The NIAID guidelines acknowledge that trials in EoE have shown symptom relief and endoscopic improvement in almost all children on AAF/elemental diet, though no specific recommendation on formula choice is made.	AAF (as specified by current ESPGHAN guidelines on EoE)
Gastroesophageal reflux disease	EHF	EHF	No specific recommendation	EHF
Cow's milk protein-induced enteropathy	EHF	EHF unless severe in which case AAF	No specific recommendation	EHF but AAF if complicated by faltering growth
FPIES	EHF	AAF	Hypoallergenic formulas are recommended	EHF
Proctocolitis	EHF	EHF	No specific recommendation	EHF
Breastfeeding with ongoing symptoms (already on maternal elimination diet) or requiring a top-up formula	No recommendation	AAF	No specific recommendation	With severe symptoms that are complicated by growth faltering, a hypoallergenic formula up to 2 weeks may be warranted. In many countries, AAF is used for diagnostic elimination in extremely sick exclusively breast-fed infants. Although this is not evidence based, it is aimed at stabilizing symptoms.

AAF, amino-acid formula; EHF, Extensively hydrolyzed formula; ESPGAHN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition.

American Academy of Pediatrics. *Pediatrics.* 2000;106(2 Pt 1):346-9. Fiocchi A, et al. *J Allergy Clin Immunol.* 2010;126(6):1119-28 e12. Host A, et al. *Arch Dis Child.* 1999;81(1):80-4. Luyt D, et al. *Clin Exp Allergy.* 2014;44(5):642-72. Meyer R, Groetch M, Venter C. *J Allergy Clin Immunol Pract.* 2017.

Immune Response

Microbiome

- Ensures integrity of the gut wall and regulation of the immune system
- Diverse microbiome associated with tolerance development
- The role of diet diversity in this is unclear

Yu W, et al. *Nat Rev Immunol.* 2016;16(12):751–765; Mazzocchi A, et al. *Nutrients.* 2017;9(8). pii: E850.

Module 2: Immunologic Research

Dr. Carina Venter: In Module 2 we will be discussing immunological research, as well as the microbiome. We will look at the science behind infant food allergies, particularly cow's milk allergy. We will discuss a little bit about the pathophysiology of cow's milk allergy, and then we will look at the immune response and microbiome, as well.

The more we learn about the microbiome and how it interacts with the immune system, the more we understand that you really cannot separate the microbiome from what we see immunologically in infants with food allergies, and particularly IgE-mediated cow's milk allergy. The microbiome is important, as it ensures the integrity of the gut wall. Because it stimulates the mucus reduction, it maintains the tight junctions, and it regulates the immune system. It is well described in the literature that a diverse gut microbiome is associated with increased reduction of the regulatory cytokines, particularly TGF-beta and IL-10.[1] Therefore, a diverse microbiome is assumed to be associated with tolerance development, but the role of diet diversity in diverse microbiome is still unclear.

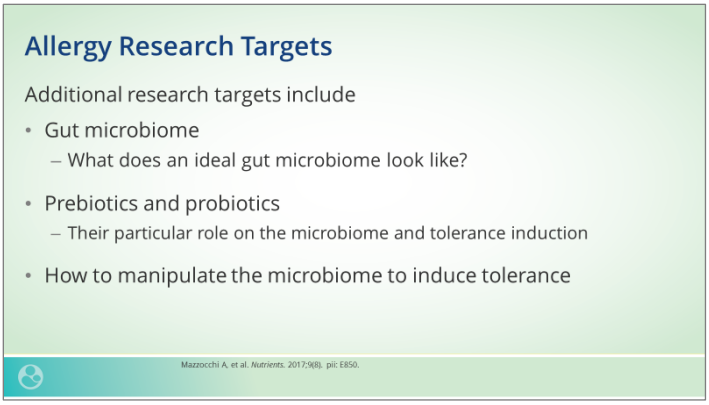
The only data where we directly look at is higher-diet-diversity intake vs lower-diversity intake, and its effect on the microbial diversity is data from an elderly home.

If technically you consider that increasing solid food introduction, or starting solid food introduction, in the infant's diet is a measure of diet diversity, then we do have data to show that as soon as we start introducing solids into an infant's diet, the diet will become much more diverse, and mainly microbiome that we see in early infancy in breastfed infants.

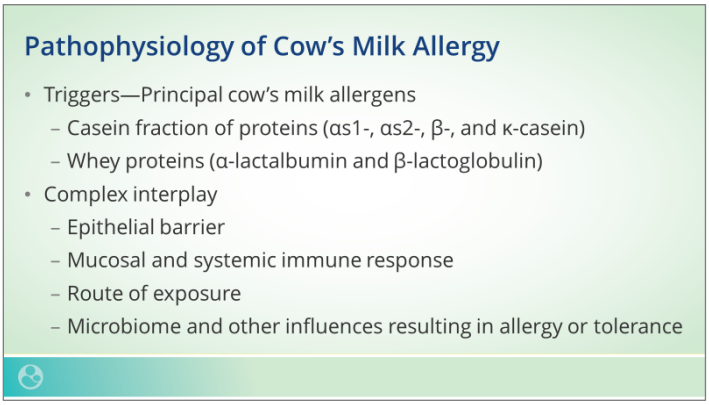
Additional research targeting cow's milk allergy at this point includes that we need to understand better what an ideal gut microbiome looks like. And even if it does exist, because it may be the gut microbiome, or an ideal gut microbiome may differ from person-to-person, and may also differ in terms of which disease we are trying to prevent. Development of prebiotics and probiotics... So, prebiotics are, of course, the good fiber that feed the probiotics, which are the beneficial bacteria in the microbiome; what their role is in terms of tolerance inductions and prevention of allergic disease, and whether pre and probiotics together, referred to as symbiotic, have a more potent effect on tolerance development and disease prevention. And then, we need to learn how to manipulate the microbiome to induce tolerance. In early life feeding

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

that may be the breast milk or breast feeding, it may be infant formula. And then, finally, the focus on how we best introduce solids into an infant's diet to induce tolerance in, for example, cow's milk allergic infants.

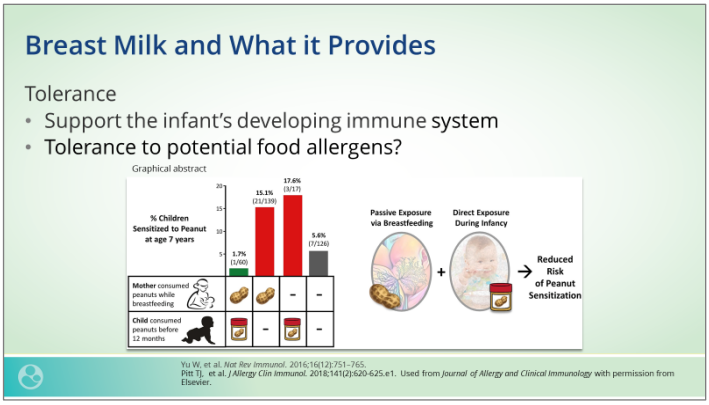


In terms of cow's milk, there's a large number of proteins in cow's milk, but the main ones involved in cow's milk allergy are the casein proteins, or casein fractions of protein, which is the α-, the β-, and the κ-casein. Quite interestingly, there's very little κ-casein left in cheese, because the rennet used in cheese making destroy the κ-casein. The whey proteins are referred to as α-lactalbumin, which we often find in large amount in cookies, especially commercially available cookies. And then β-lactoglobulin, which is one of the main triggers of cow's milk allergies in young infants.



It is particularly the infants who mainly sensitize to the β-lactoglobulin that develop tolerance to products containing baked cow's milk, such as cookies or muffins, and in some cases perhaps pancakes or waffles. I showed in the previous slide that there's a complex interplay between the microbiome [and the] epithelial barrier, which will determine how much protein is absorbed. So, we do know that when there's inflammation in the gut, which leads to more allergen exposure, or allergen absorption, we can get more severe symptoms in children sensitized, or clinically allergic, to a food.

There's a lot of discussion about the role of breast milk in prevention and tolerance development, and also what breast milk provides. There's a large number of immunomodulatory factors involved in breast milk. The one that's probably most studied is the human milk oligosaccharides, which some people may prefer to eat as prebiotics. So, we know breast milk has the potential to support the infants' developing immune system, but the other interesting component of breast milk is when a maternal ingestion of the allergen will lead to transfer of the allergen to the infant. We do know that in cow's milk consuming mothers, 95% will transfer some level of β-lactoglobulin to the infant.



In terms of peanut allergy and peanut transfer via breast milk, we have the studies published from the child-study group in Canada, where they showed that if you consume peanuts while breastfeeding, and you introduce peanuts early into the infants

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

diet, you have an additional beneficial effect on prevention of sensitization compared to when you just introduce peanut allergens early into the infant's life.[2] They did not look at the overlap effect. They did look at when the moms were eating peanuts while they were breast feeding, or the infants were introduced early, but they didn't have the power to look at whether this happened in combination. And so, other than focusing on the immunomodulatory components of breast milk, we need to learn a lot more about proteins excreted by breast milk to the infant, and what effect that may have on either tolerance development or disease induction.

Module 3: Nutritional Treatment Strategies

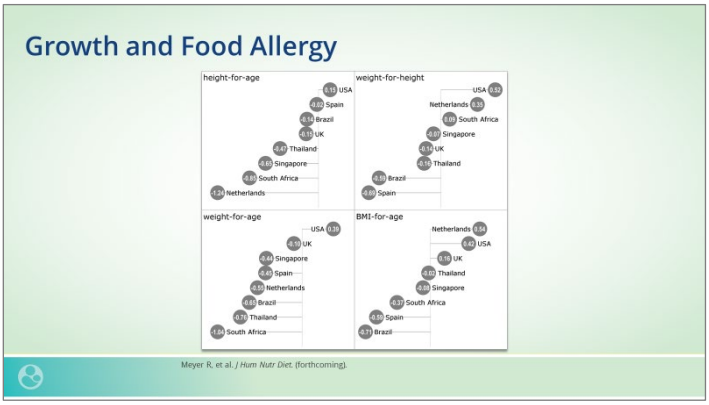
Dr. Carina Venter: So, that was the microbiome, and now we will look at nutritional treatment strategies for cow's milk allergy via looking at current standards of care, clinical recommendations, interventional therapies for the treatment of food allergy, which Doctor Fleischer will discuss. We will talk about suitable infant formulas, and then also mechanisms and triggers of allergy.

The current standard of care of IgE-mediated cow's milk allergy is that you have to avoid cow's milk. I think we've moved a long way away from recommending complete cow's milk avoidance in all infants at all times, because we're now beginning to understand that up to 70% to 75% of cow's milk allergic infants may become tolerant to baked milk before they develop tolerance to cow's milk, as it comes in a formula or available commercially.

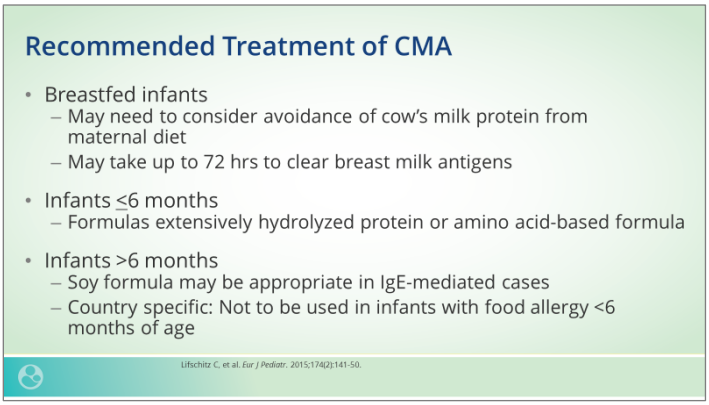
We also understand more and more that cow's milk allergy, in particular, can have an effect on growth. So, we need to monitor growth in terms of the weight, the length, and the head circumference. And, in terms of these 3 measures, I would definitely say that length is the most important aspect to monitor, because children with cow's milk allergy often start to stunt their growth before they actually start to lose weight.

This is data from a study I've conducted with Rosanne Meyer across 12 centers internationally. This study is in press in the *Journal of Human Nutrition and Dietetics*.[3] Very interestingly, if you look at the first part of the figure, in the Netherlands we found that children with food allergies were actually the shortest, or they have the lowest height-for-age, which is particularly interesting, as we know that the Dutch population is actually the tallest population in Europe. We also found differences in terms of weight-for-height across the different studies, and the different center studies; also, weight-for-age, and BMI-for-age. I think the message from this slide is you need to know your population; you need to know your patients; and you need to monitor them well, so you get a good understanding of the pitfalls in terms of growth you may have in your particular patient population.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment



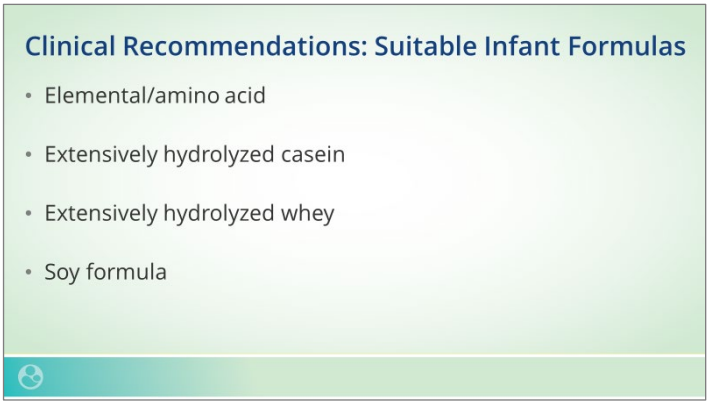
Then, in terms of breastfed infants, I think one of the questions I most often get is, should I tell the breast feeding moms to stop breast feeding? Never. Should I tell the breast feeding mom to avoid or to exclude cow's milk from her diet? There's a very simple answer. If the child only presented with symptoms of IgE-cow's milk allergy as soon as infant formula is introduced, or as soon as solid foods containing cow's milk is introduced, then you only need to change the formula, and avoid cow's milk from the infant's diet.



There's no need [for] the breast feeding mother to avoid cow's milk in her diet. However, if the symptoms occurred when mom was consuming cow's milk and exclusively breast feeding, then clearly there is a good reason for a period of avoidance from the maternal diet, to see if the infant's symptoms improve. It may take up to 72 hours to clear breast milk antigens. Interestingly, speaking...interesting to me, I was speaking all across the world the last few weeks, and in many centers, they tell mothers to stop breast feeding for 72 hours while they express, and try a hypoallergenic formula. After the 72 hours of excluding cow's milk, the mothers start breast feeding again. That would not be my personal practice, but it is interesting to note that this practice does occur in different areas of the world.

Infants under 6 months of age, we could use formula, such as extensively hydrolyzed protein, which could be whey or casein formula, or we could use amino acid-based formula. And, in infants over the age of 6 months, soy formulas could be used in IgE-mediated cow's milk allergic cases. This is very country-specific, particularly in the United Kingdom, the chief medical officer recommends that soy formula not be used as a first option of treatment for cow's milk allergy in infants under 6 months of age.

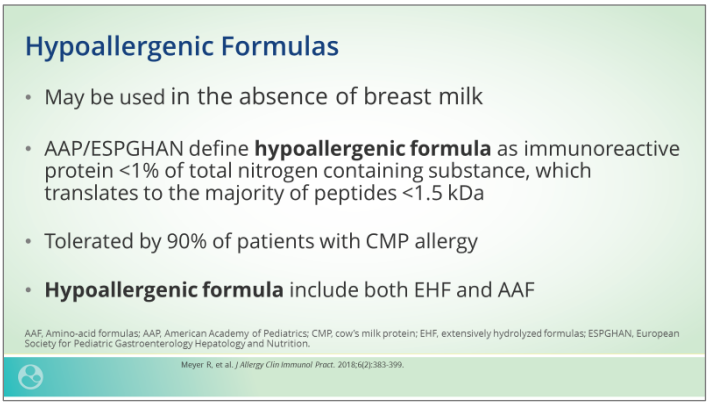
So, the 4 formulas that we can use would be elemental (or amino acid-based) formulas, extensively hydrolyzed casein or whey formulas, and then soy formula.



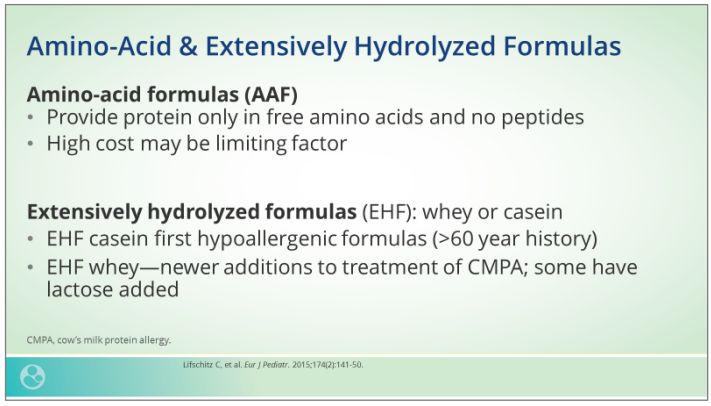
There are different definitions of hypoallergenic formulas. We have the American Academic of Pediatrics, and the European Society for Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines.[4] In essence, we say that we

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

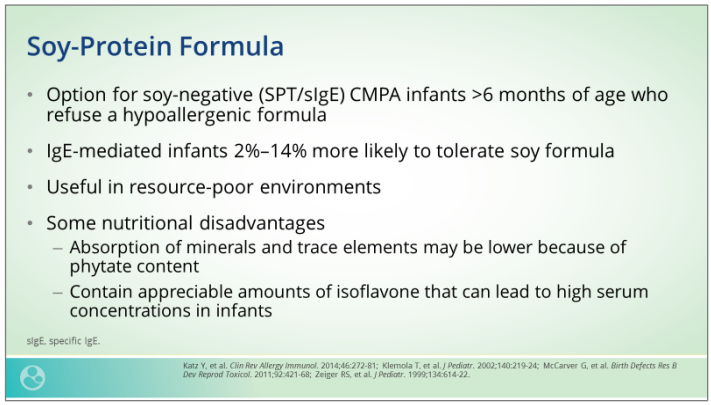
want the majority of the peptides to be smaller than 1.5 kilodalton (kDa). But, clinically the definition that matters most is whatever formula is used—and has the claim of being hypoallergenic—this formula should be tolerated by 90% of patients with cow's milk allergy. And so, hypoallergenic formulas, at this point in time, include both extensive and amino acid-based formula. But these definitions are being rewritten at present, and it would be interesting to see what 2019 will bring in terms of the definition of hypoallergenic formula.



So, [in] the amino acid-based formula, they have no peptides; they only have amino acids. The high cost of these may be a limiting factor in clinical use. In extensively hydrolyzed formulas, whey or casein, the casein formulas have been used for more than 60 years. More recently, we've seen the development of the whey formula. Some of them have lactose added, which was a concern in terms of the use in patients with secondary lactose deficiency, due to cow's milk allergy. But studies have now been conducted to show that the lactose added to the whey hydrolyzed are safely tolerated, even in children with diarrhea.



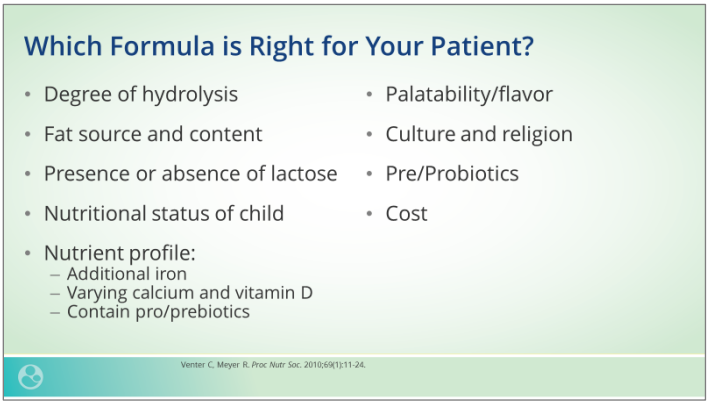
Soy-protein formulas, like I said, can be used in infants more than 6 months of age. About 2% to 14% [of infants] with IgE-mediated cow's milk allergy may not tolerate the soy formula. And then, some nutritional disadvantages include that it could affect absorption, and we are concerned about the isoflavone content. We're really concerned in terms of amount of isoflavone per kilo of body weight, which is why we have the 6 month cut-off age for safe use of soy formula.



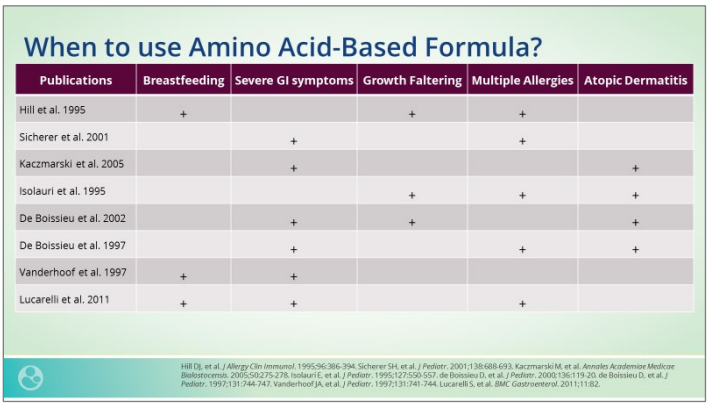
There are many factors we have to think about when we chose the right formula. We can think about the degree of hydrolysis. Some people find that MCTs [medium chain triglycerides] are important. We can look at the presence or absence of lactose; the nutritional status of the child. We look at the nutrient profile; the amount of iron, calcium, and vitamin D in formula; whether it contains pre or probiotics may be important to

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

some clinicians. Palatability, flavor, culture, and religion. Some of the formulas do contain pork enzymes. And then of course, cost.

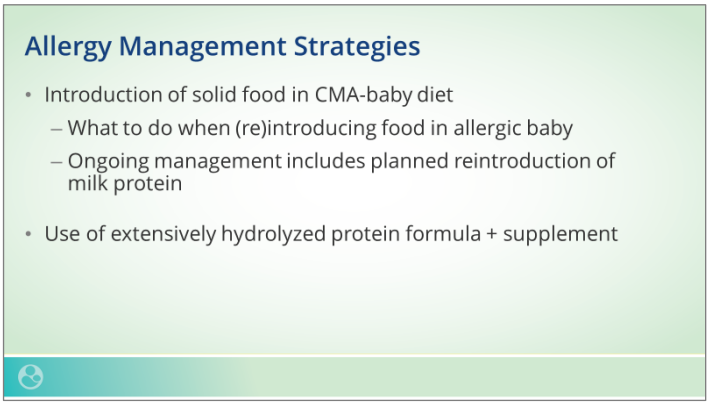


So, this is another paper I did with Rosanne Meyer and Marion Groetch. It was published in *Journal of Allergy and Clinical Immunology in Practice* this year.[5] We summarized all the available studies we could possibly find on using formula for the treatment of food allergy and cow's milk allergy. We found that amino acid-based formula, it indicated in infants where they reacted to cow's milk via breast milk, so those babies who have symptoms of IgE-mediated cow's milk allergy, while exclusively breastfed. It's not often seen, but it does exist.



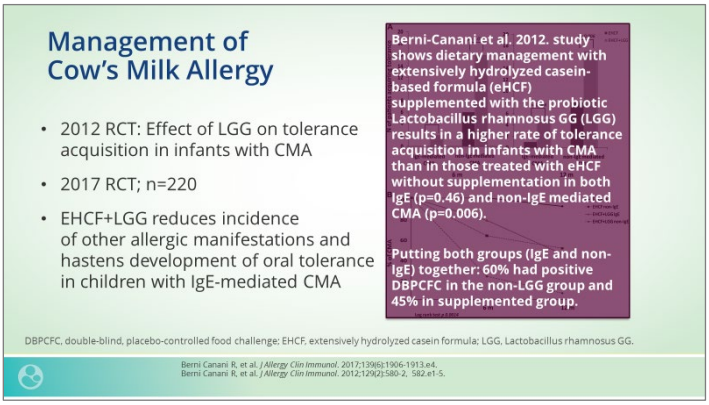
Those with severe gastrointestinal symptoms, those with growth faltering, or failure to thrive, those with multiple food allergies, and those with severe atopic dermatitis, particularly those who do not improve on optimal topical treatment—so, those are the 5 important points of [when] amino acid should be used. In conjunction to that, the sixth would be a history of anaphylaxis, as Dr. Fleisher already mentioned. All other infants could be placed on either an extensively hydrolyzed casein or whey formula; and, there's no way at this point in time to really recommend one above the other.

So, allergy management strategies. When we get to the introduction of solid foods, we need to give the mother advice on how to avoid cow's milk, [and] which other foods to introduce, and then, also possibly, when to reintroduce cow's milk into the infant's diet. We need to make sure we choose an appropriate formula. We may need an additional supplement, as well.



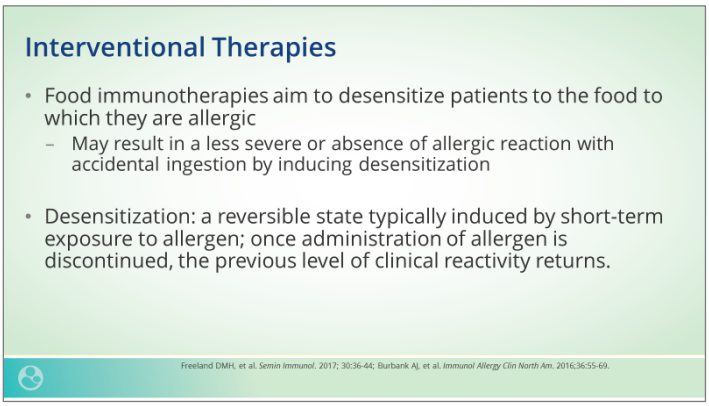
Then, there's one study where they looked at the tolerance development in cow's milk allergy.[6] So, in terms of cow's milk allergy, we have studies indicated that the microbiome, and the dependence of particular bacteria differ between kids who become sensitized or not. Those who develop clinical cow's milk allergy or not, and also those who are going to become tolerant quicker or not. And so, this is one study showing if we add lactobacillus GG to a hypoallergenic formula, that it actually does speed up or accelerate development of tolerance in both IgE- and non-IgE-mediated cow's milk allergy.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment



So, interventional therapies: I'm going to hand it over to Dr. Fleisher now.

Dr. David Fleischer: Thank you, Carina. Before I talk about the interventional therapies, I just want to preface this with [the caveat] that there's currently no FDA-approved treatment for food allergy at this point. So, the things that I'll talk about in the next few slides are not to be done at home with parents. These are things that, at this point, need to be done within an allergist's office. Small doses of any food to try to help desensitize the patient should not be done at home.

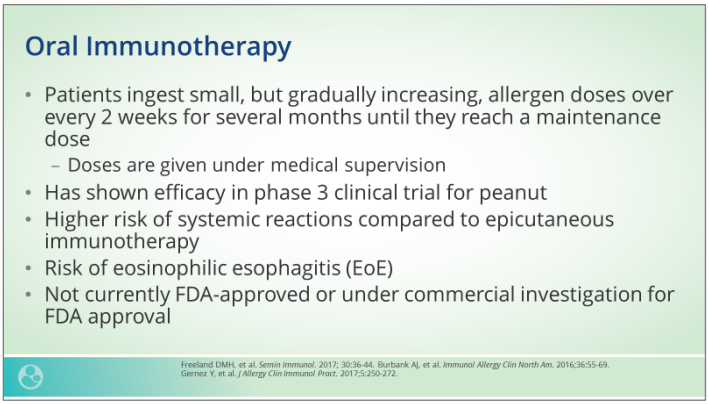


But, we're at a very exciting point in time now with food immunotherapies. Next year we will hopefully have several approved for the treatment of peanut allergy, and I'll talk about one that's getting closer with milk. But, the idea with food immunotherapies is to try to desensitize patients to the food to which they are allergic, which may result in either having a less-severe reaction, if they accidentally eat that food, or no reaction at all, by this mode of desensitization.

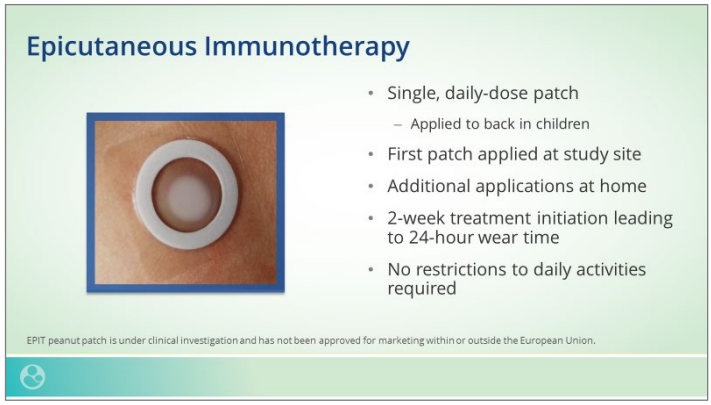
Desensitization means a reversible state that's typically induced by short-term exposure to the allergen. Unfortunately, once you stop that regular exposure to that allergen in a still-allergic patient with an IgE-mediated allergy to that food, usually that desensitization is lost, and can be lost as quickly as a week. So, it can happen quickly.

The 2 types of immunotherapy that are now being investigated, primarily, are oral immunotherapy, where you're giving patients small, but gradually increasing, usually every 2 weeks, of the foods, for several months until they reach what's called a maintenance dose. For example, with the peanut product now that's being developed, that's going from about a half a mg of protein of peanuts to getting about 300 mg, or about one peanut, a day. So again, as I stated before, these doses are given under medical supervision. This is not to be done at home. Again, it shows efficacy in a phase 3 clinical trial for peanut. There are higher risks of having reactions compared to the topical or epicutaneous immunotherapy I'll talk about next. Patients can get eosinophilic esophagitis induced by these therapies; it's a big concern with milk, because, again, milk is one of the biggest triggers with EoE, eosinophilic esophagitis. Again, there's nothing currently FDA approved or under commercial investigation for oral immunotherapy to milk, yet. There have been some clinical trials outside... inside US, and outside the US, which unfortunately had some more severe reactions to milk oral immunotherapy, so it may not actually be developed in the US.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

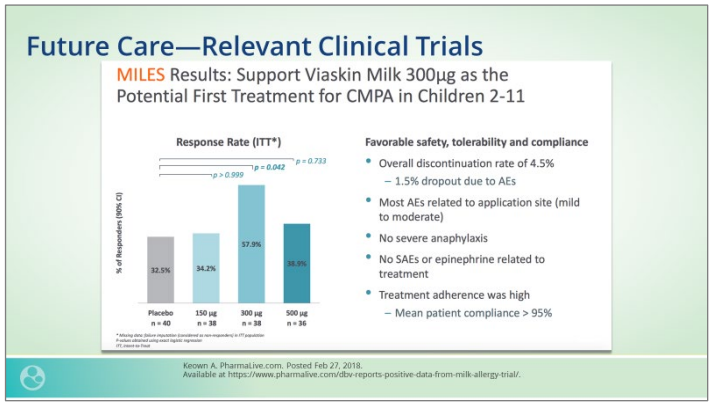


The epicutaneous, or what we call the patch, immunotherapy is what you see in the photo. It's a patch with the... There's a film in the middle, in that kind of opaque center is the protein that's electrostatically sprayed onto that film. You can do this with milk, you can do this with egg, and peanut, and those are the 3 foods that are being investigated right now in this therapy. It's a single-dose patch, unlike the oral immunotherapy, so there's no up-dosing every 2 weeks. Basically, the first patch is applied right now in clinical study sites for about 3 hours, and then at home over the coming 2 weeks you go to 24-hours a day. Again, that's at home, so a little more advantage in not having to come every 2 weeks to get up-dosed. There's no restrictions, as there can be with oral immunotherapy, for physical activity within certain hours of taking the oral dose. [They] are not the same here with epicutaneous, so it may be a little more convenient for patients than the oral immunotherapy.



This is a phase 2 clinical trial that's been done with the milk epicutaneous patch. So, next year hopefully they'll begin phase 3, what we call a pivotal trial, that will hopefully lead to FDA approval—we hope within the coming years.

This is the first potential treatment for cow's milk allergy, and this is in 2- to 11-year-olds. This study was done[7]... They looked at 3 different doses, which is often the case in the phase 2 trial where you're trying to find the one dose that works the best. As you can see in the figure, the response rate was highest in that 300-µg dose. About 58% of patients did respond to the lower and higher dose, but the response rate was better to the 300, and that's the dose, 300 µg, that will be used in the phase 3 trial, most likely.



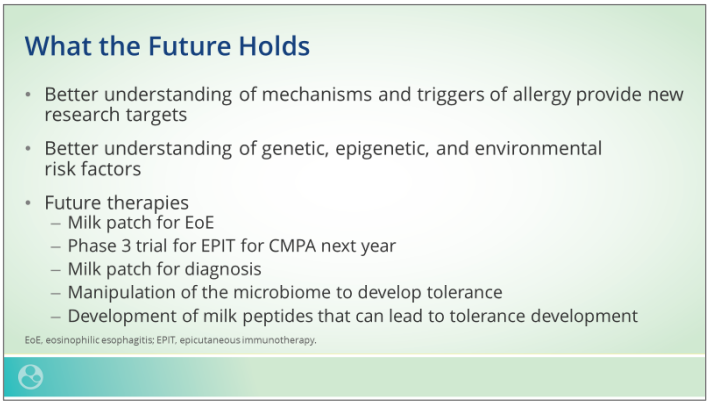
With the patch, safety and compliance are a little bit easier than the oral immunotherapy. Discontinuation rates are usually quite low, only

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

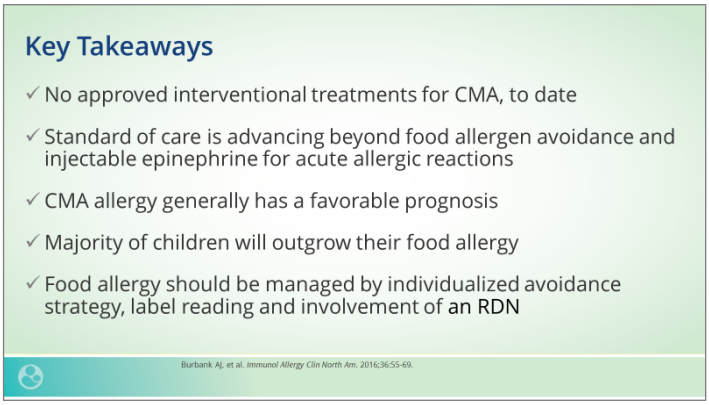
about 1% to 2% due to adverse events to the patch itself. The most common thing you'll see with these patients is topical skin reactions that are usually mild to moderate. There were no severe anaphylactic reactions in this phase 2 trial, and no serious adverse events or epinephrine used to treat any reactions to the patch. Again, since it's a little bit easier to use, compliance is quite high. So, hopefully this will go to phase 3 next year.

So, what does the future hold? A better understanding of mechanisms and triggers of allergy will provide new research targets. Those 2 types of therapy will likely be the first ones that may be approved. There will be others that will be investigated. As we learn more about food allergy and immunotherapy, there will be new waves of products coming out.

We hope to better understand some of the genetic, epigenetic, and environmental risk factors my colleague, Dr. Venter, is working on. Again, future therapies: the milk patch has been studied in a phase 1 pilot study to treat milk-induced eosinophilic esophagitis, so that's another exciting treatment, potentially, for milk. Again, there will be a phase 3 trial next year. Milk is also being looked at as a patch for diagnosis of non-IgE-mediated allergy. Carina also mentioned looking at the microbiome and how to manipulate that possibly to develop tolerance. And, there may be more peptides for milk developed that can lead to tolerance development, again, in the form of immunotherapy.



Key takeaways from today's presentation: there are no approved interventional treatments right now for cow's milk allergy. Within the next few years we hope to have those. Right now, the standard of care in treating an IgE-mediated allergy or a non-IgE is to avoid that food. With IgE-mediated food allergy, you need to have epinephrine auto-injectors available for possible acute reactions that are severe. Cow's milk allergy, in general though, has a favorable prognosis, it's more likely to be outgrown, as opposed to peanut or tree nuts, so most of them will outgrow it. We hope to accelerate that by some of the big milk challenges we do, as well. But food allergies should be managed by individual avoidance strategies, looking at label reading, and involvement of a dietician, [which] is really important. With that, we'll move on to questions.



Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

Question & Answer

Editor's Note: This is a transcript of audience questions together with faculty responses from the November 5 and 7, 2018, audio webcasts.

Which children are most at risk to develop cow's milk allergy?

Dr. Fleischer: I think family history certainly plays a role [in] how you define [it] with risk factors for peanut, milk, or egg. As far as high risk, there's been some controversy with respect to peanut, at least, but certainly family history of having allergic disease, so parents having 1 atopic disorder, such as asthma, eczema, or food allergy themselves puts that infant at higher risk, but the problem is we're seeing more, and more families don't have risk factors, as far as family history, that develop food allergies, and not just milk allergy. Eczema seems to be a risk factor for developing food allergy, so I think those are some of the risk factors.

But I still don't think we completely know all the risk factors, and that's some of the research Dr. Venter and others are doing, with respect to microbiome and other ways to possible prevent these from happening. Early introduction may be something that also may play a role in preventing the allergy. We had recommended, in the past, avoiding milk until age 1 year to try to prevent it from happening. Now, at least some observational data show, if you give it within the first few weeks of life, you may actually prevent it from happening. So, still a lot to learn, but we know some risk factors.

Has research shown an association between mother's use of antibiotics during pregnancy and the risk of cow's milk allergy in infancy?

Dr. Venter: There's research indicating that using antibiotics in pregnancy increases the child's risk for developing allergic disease, but not, as far as I know, cow's milk allergy, in particular. But, as I always say, antibiotics in pregnancy is only used when it's needed, so it's a difficult decision to make. But associations have been shown, in short.

Dr. Fleischer: And it may be effective on the microbiome, and other things.

Dr. Venter: Yes.

Dr. Fleischer: Right. So, I think there's ... The true randomized controlled trials of having antibiotics or not... We haven't had the data, but observational says it may have some affect.

Which clinical manifestation of an allergic reaction to cow's milk is most common?

Dr. Venter: I think it depends on where the prevalent studies are being conducted, because in Europe, for example, 80% of those kids with cow's milk allergy normally present with what we refer to as a mild-to-moderate non-IgE-mediated cow's milk allergy. Whereas, here in the United States, the focus is much more on management and diagnosis of IgE-mediated cow's milk allergy. Unfortunately, we do not have a good prevalence study comparing prevalence of all the different aspect of cow's milk allergy, so IgE, FPIES, EoE, and mild-to-moderate non-IgE cow's milk allergy in the States vs the European countries. I would say, from what we know at the moment, we see more IgE cow's milk allergy in the States, and more of the mild-to-moderate non-IgE cow's milk allergy in Europe with a clear increase in prevalence to cow's milk triggering FPIES and cow's milk triggering EoE.

How do you choose when to use skin prick testing vs ImmunoCAP testing?

Dr. Fleischer: It really depends on what's available to you. I mean, we as allergists can do skin testing, so we'll often do that because it gives us a quick answer, within 15 minutes of placing the allergen on the skin, to confirm a diagnosis. Most practitioners,

primary care providers, family practitioners, obviously don't have access to skin testing, and we don't want them doing skin testing, because it takes some training. That's when they can use a serum IgE test. If we have a patient who has severe eczema, or allergic disease, and they can't get off antihistamines, then we'll do a blood test. Most of the time, though, I would say we, as allergists, do the skin test first to confirm clinical history. And then, I will do an ImmunoCAP-IgE test to milk just to get an idea of what the level is, because that may help me decide when I'm going to do a baked-milk challenge, but also gives us a number that we can follow over time to see if they are outgrowing it, and when I would do a raw milk challenge.

How accurate are the skin prick tests?

Dr. Fleischer: If you have a clinical history that is consistent with an IgE-mediated reaction, and you get a positive test, that is much higher... They can still be false positive, especially without a clinical history, half the time. So, we generally recommend to not do a bunch of screening, either skin test or blood test, without the clinical history consistent with an IgE-mediated process. If you have a negative skin test, the negative predictive value is much higher, so about 95% certainty that it's not an allergy, at least IgE-mediated. But still, if you've got a clinical history with a negative skin test, those are the patients we would challenge under medical supervision—not recommended to do at home. So, it really depends on your clinical history, which is why I stress that so importantly, to get that before you start doing any tests.

If they're eating a food... Let's say you do a panel, primary care provider does a panel, because they just want milk, for example, but it also has egg and peanut. If they're eating egg and peanut, and those tests are positive, I wouldn't necessarily take those things out, because they're eating it, and tolerating it. That's probably more false positives.

Which clinical manifestations of an allergic reaction to cow's milk is most severe?

Dr. Fleischer: Obviously, anaphylaxis is the most severe IgE-mediated reaction you can have, that's a life-threatening reaction that obviously develops quickly. I'd say, though, with most infants, the first reactions that are usually happening are not anaphylactic in nature. Again, oftentimes you'll see urticaria or hives, and/or vomiting. But obviously, anaphylactic reactions can happen. That's the most severe form.

You can have severe non-IgE-mediated reactions, especially in patients who have FPIES, the vomiting, and diarrhea that can happen several hours after having cow's milk or soy. Those patients can get quite dehydrated pretty quickly, and need IV fluids, and lethargic from that. But IgE-mediated is the anaphylactic reaction. It's the one we most worry about. But again, just because you haven't had an anaphylactic reaction in the past does not mean you won't have one in the future. So, we always have patients prepared to treat anaphylactic reactions with medication.

Why is there such a delay in cow's milk allergy research?

Dr. Fleischer: I'm not sure there's a true delay. I think the problem is peanut allergy gets much more press, more than milk, but it's actually... If you looked at reactions and life-threatening reactions in the first several years of life, it's more common to have reactions to milk, but unfortunately what we hear more and more about is peanuts. So, that tends to be the one, I think, to have some bias in getting that treatment first. And especially because patients don't usually outgrow peanut allergy; only about 20% outgrow it. So, if most outgrow milk, and

70%, as Carina said, tolerate baked milk, the need for research there in some ways was sort of biased towards peanuts. I think, as we're seeing, there are teenagers and adults that go on into adulthood with milk and egg allergies, so it's important to try to get those patients treated, as well. I think it's catching up, but I think part of it's been that bias with peanut, and it's not outgrown usually.

Dr. Venter: That's technically true for the studies looking at treatment, but I think if we look at prevention and tolerance induction using the microbiome, then I think we're miles ahead with cow's milk allergy compared to our understanding of the microbiome of children with egg or peanut allergy, and how that may play a role in prevention and tolerance induction. So, I think the focus of the research, for all the reasons Dr. Fleisher just mentioned, have just been very different.

Dr. Fleischer: I think that's a good point. When you look at prevention of specific allergies, there's been 5 studies looking at egg, and there's been 1 looking at peanut. There's been 1 ... Milk is part of 1 trial, but that's something that hopefully will be studied, and there may be a trial in the future here in the US looking at it.

Does the research show an increase with infant use of PPI, or H2 blockers with cow's milk allergy?

Dr. Fleischer: There's some observational data to show that possibly the use of acid blockers could play a role; that you're not digesting those proteins if your acid is suppressed as well, so you're getting absorption of larger proteins, but there's been really no direct correlation that we can say for sure. The problem with observational studies are those PPIs and antacids—the H2 blockers are commonly used—that you get enough patients, and enough patients have milk allergy. That's the highest allergen prevalence in those first few years of life, that you can find association, but cause and effect I don't think is there.

What specific research targets reviewed have been linked to diagnosis and treatment of cow's milk allergy?

Dr. Venter: I think in terms of the diagnosis—I'll leave the treatment again to Dr. Fleisher—the whole issue of baked-milk challenges... and in terms of food, what actually is a baked-milk challenge? Is it a cookie, is it a muffin, how long does it have to be baked? How big does it have to be? Can we use a pancake and a waffle instead? As much as it may sound trivial, we have hours of discussion about how do we conduct these baked-milk challenges. There's some research coming out of Mount Sinai helping us decide whether we need to do specific IgE-casein to β-lactoglobulin [studies], and are there cut-off points that can help us decide when we need to do this baked-milk challenge. So, that's 1 aspect of the diagnosis I think we are learning more from, and on which the research is being focused. In terms of treatment...

Dr. Fleischer: Treatment, again, I think there's been some fear about doing milk oral immunotherapy. The trials have been more focused on peanut with oral immunotherapy. I think the patch, now that it's going to be going into phase 3 trials, and if the peanut patch gets approved next year, we're... (The submission for FDA approval was done a few weeks ago, so hopefully next year we'll know about that.) I think that will open the door for milk to get approved, as well.

Can milk fortifier added to human breast milk, and fed to the preterm infant, contribute to potential cow's milk allergy?

Dr. Venter: Well, I don't know if there are studies conducted. I must say I have, in clinical practice, seen a number of children who presented with

cow's milk allergy exactly at the point where the fortifier was added to the breast milk. I don't particularly want to say that was the trigger. I'm happy to say that was the time when they presented. But whether there have been well-conducted trials looking at human-milk fortifier vs cow's milk, or even other allergic outcomes, I'm not aware of those.

Dr. Fleischer: No, neither am I.

Which children are most at risk to develop CMA?

Dr. Fleischer: We know some risk factors based on some studies. For example, if a patient has moderate or severe atopic dermatitis or eczema, they can be at higher risk for developing milk or egg or peanut allergy. Family history likely plays some role, as well. It's based on some studies. So, if you've got a parent or a sibling who has an allergic disease, you may be at more risk for developing an allergic disease, which may include food allergy, as well. There are data when we look at the prevention of cow's milk allergy, as far as timing of introducing cow's milk.

In a couple of observational studies to the randomized control trials that are done with peanut and the early introduction of peanut vs delayed introduction, at least in 1 study, if milk was introduced within the first few weeks of life compared to later on, that introducing the first 2 weeks of life increases your risk of developing cow's milk allergy. We know some things, but again the quality of the data may not be the best, and the new observational data are there, so we still need to learn a lot more, but those are some basic ones.

Which critical manifestations of an allergic reaction to cow's milk is most common?

Dr. Venter: I think that really depends on where you practice and where the studies are conducted. In Europe, where there's a lot more emphasis on diagnosing children with mild-to-moderate non-IgE cow's milk allergy, that would make up to about 80% of children with cow's milk allergy. Here in the United States, where we focus more on IgE-mediated food allergy, the majority of our patients with cow's milk allergy have IgE-mediated disease. Unfortunately, we do not have any head-to-head studies comparing the different types of cow's milk allergy in Europe with the United States. But looking at the publications out there, I would say that is the case.

What specific research targets are reviewed and have been linked to diagnosis and treatment of cow's milk allergy?

Dr. Venter: In terms of research, I think one of the main things [our center] but also other centers are focused on is understanding tolerance development of baked-milk products better, because we know that about 75% of children with IgE-mediated cow's milk allergy will develop tolerance to baked-milk products. Then, there's the question: Does it have to be a muffin? Does it have to be an exact dose of cow's milk protein? How long does it have to be baked for? What temperature does it have to be? Then, also in terms of testing, should we just be doing specific IgE tests or skin prick tests? Or should we be looking at casein and β-lactoglobulin levels? Are there any particular cut-off points that would help us make the decision about going ahead with the food challenge?

I don't know if there's anything else that Dr. Fleischer wanted to add in terms of diagnosis.

Dr. Fleischer: In terms of diagnosis, the epicutaneous patch is being investigated to look at diagnosis of non-IgE-mediated milk allergy. That will be a study that will hopefully start later this year, or early next year. Right now, clinical history, as I talked about earlier in the talk, is the key for deciding whether you have IgE mediated or non-IgE

mediated, but this may be a confirmatory test to unlikely use the skin test or the blood test. For IgE mediated, this may be a test we can use to more definitively diagnose, if you've got non-IgE-mediated milk allergies.

Carina and I will, and some other centers will, be involved in that study, as well.

Based on which formula is right for your patient, how do you determine the best EHF casein or whey, and for which children?

Dr. Venter: As I've suggested in the presentation, there are particular groups of children who need to use amino acid-based formula. Once you've made the decision about using an extensively hydrolyzed formula, there's really no data to suggest whether casein formula is better than the whey hydrolysate. Peptide size really does not matter in terms of clinical tolerance. There were studies looking at clinical development, but haven't really found that those formulas with smaller peptide sizes are tolerated better than those with a larger proportion of larger peptides.

Clinically speaking, I'd say that many people like the evidence we currently have about probiotic use and tolerance development. So, that might prompt them towards a formula that contains a probiotic, for example lactobacillus GG, added to a formula. But also we have a problem with taste perceptions and acceptance of these formulas. Very often infants who have been breastfed for a long time and who like the sweet taste of breast milk may not tolerate a casein formula, or certain casein formulas, as well as the whey-based ones, which tend to have a sweeter taste. In those cases, it may be taste that swayed towards a whey formula, [as] opposed to certain types of casein-based formula.

Can DHA and milk-fat globule membrane be added to non-milk-based formulas for those with cow's milk protein allergy?

Dr. Venter: If we talk about non-milk-based formulas, I am definitely aware that DHA is added to the amino acid-based formulas and that itself even has been done about testing visual acuity, cognitive development in infants using the DHA formula. Yes. DHA definitely can be added. I'm not sure about the second component.

Can you explain the difference of skin prick tests and ImmunoCAP testing, or are they essentially the same?

Dr. Fleischer: They're looking for the same type of immune response: whether skin or blood tests, you're looking for an IgE response to a food, so they both look at that. The skin test is done in an allergist's office, so they're not done usually in primary care provider's office, pediatricians, other offices like that. It's something we use when we've got a clinical history that's consistent—like we talked about—in the case of an IgE-mediated reaction, we can do a confirmatory test in the office and have an answer within about 15 minutes of whether it's positive or negative.

Without a clinical history of reacting to a food, just doing a skin test can have a high false-positive rate of about 50%. If it's a negative test, then it has what we call a high negative predictive value, about 95% of not being the problem. Even if you have a negative skin test, or undetectable blood test, and you've got a clinical history that's consistent with an IgE-mediated reaction, the next step would be to do a food challenge, observe a food challenge. The blood test can be ordered by any medical provider, whether in practice or an academic center.

Those are more readily available to order, if a patient can't get off antihistamines, because you

need to be off antihistamines for skin testing. Sometimes we'll do blood tests; sometimes we'll do [these tests] as well, to monitor patients to see [if] they are in the process of outgrowing their allergy. Are their numbers coming down? Because skin tests can remain positive for many years even after you've outgrown an allergy. The blood tests in some ways help us predict when to do a food challenge or not. But they're both looking for the same response, again, ordering either one of them, should really only be done with a clinical history that you're consistent with an IgE-mediated process.

Do you have a recommendation for introduction of solid foods to children with a family history of cow's milk allergy, peanuts, or fish allergy?

Dr. Venter: Well, we have guidelines about the introduction of solid foods in children with peanut allergy, and we have suggested dosing, particularly in high-risk infants, of 2 g of peanut protein, which is if you use a kitchen teaspoon, just a heaped teaspoon of peanut butter, 3 times a week. But in terms of weaning infants with cow's milk allergy or for example fish allergy, there's no official guidance in which foods to introduce first. A common-sense approach would be that we will start with some grains. It could be baby rice, it could be fruits and vegetables. The WHO recommends we start with a grain-like baby rice. In Europe, the number-one weaning food is carrot puree. Again, here in the States, it could be either rice or an oat cereal that people start with. As the diversity of the food introduced in the diet increases, then we know there's no advice to delay the introduction of any allergens anymore.

In a milk-allergic child, once fruits, vegetables, and grains, and perhaps some meat, is introduced into the diet, then you can go ahead with egg, fish, even peanuts. I always suggest the use of red meat in weaning diets. It could be slow-cooked soft red meat, because we know that the majority of infants, particularly toddlers, in the US, are deficient in iron intake. That's one of the first weaning foods we recommend and is high in iron.

Then, the practical advice I normally give to patients is, if you are going to introduce an allergenic food, do it earlier in the day. If there are any symptoms, you can get to the hospital in daylight, and you don't have to be concerned in the middle of the night. And introduce 1 allergenic weaning food over a 3-day period, so you can make sure that the child is tolerating this allergen before you go to the next one. I think that's as good as it gets in terms of guidance at this point in time.

After elimination, at what point should food begin to be reintroduced, and is there a suggested order of food reintroduction?

Dr. Fleischer: If we're talking about IgE-mediated food allergies, like the infant that we discussed, you're not going to introduce it until you've done a food challenge, and whatever skin tests or blood tests or clinical history, suggesting they may pass a food challenge. I'm not sure about what the order of introduction [should be]. Most of the diets we do with non-IgE-mediated allergy, and Carina can talk more about that, is the general things are to take a food out, see if it improves whatever symptoms. The guidelines have been written, for example, with milk. She can comment on when to introduce it next. If you've got milk and egg and peanut allergy, when it's IgE mediated, it's really going to depend on the patient and their lab values when you're going to do a challenge. But those challenges are going to be done in an allergist's office as compared to some of the non-IgE mediated.

Dr. Venter: In the mild-to-moderate non-IgE-mediated infants (that excludes kids with FPIES and EOE), milk is commonly introduced at home in a process which we refer to as the **milk ladder**, which

starts with a biscuit or a cookie, depending on which term you prefer, followed by a muffin, then a pancake. Then, it depends in which country people live, but we would then step up to raw or baked cheese, which could be a pizza, if it's baked cheese, or just normal cheese, followed by yogurt, and then by milk, as we buy it commercially. These ladders, we try to adapt for each country to make sure the foods are culturally acceptable, and it is really in the kids with the mild-to-moderate non-IgE only, where we suggest the introductions are being done at home. Children with IgE-mediated cow's milk allergy, and particularly kids with FPIES, need to come into a hospital for an in-office challenge.

Do you maintain giving breast milk to babies while mothers start a bovine-free diet? How many days, minimum, of elimination diet is right to reintroduce breast milk?

Dr. Venter: If the question is whether we advise mothers to continue breastfeeding when we advise them to exclude cow's milk from their own diet, yes, that's our practice. There are some countries in the world where mothers are advised to stop breastfeeding, but continue to express, while an amino acid-based formula is tried for a period of 1 to 2 weeks. In our practice, we would suggest that mother takes cow's milk out of her diet and continues to breastfeed, because just having a child with cow's milk allergy who's reacting to the β-lactoglobulin mainly, that's passed by the breast milk, is no reason to discontinue breastfeeding.

What do you recommend for mothers who are breastfeeding, in terms of number of days to stop breastfeeding, while expressing milk and feeding a hydrolyzed formula or do you allow moms to continue to nurse their babies?

Dr. Venter: I allow them to continue to nurse the baby. Like I said, it takes about 72 hours for the breast milk to be clear of cow's milk proteins once the mother starts to avoid cow's milk. We don't recommend breastfeeding to be stopped for those 72 hours. We suggest to continue with breastfeeding.

Does consistent exposure to dairy products during childhood ensure dairy tolerance in adulthood?

Dr. Venter: I think that's a great question, but I don't think we have the answer. I must say I have never... When I was still practicing in the United Kingdom, my clinical caseload was predominantly adults. I often saw adults with new-onset fish or shellfish allergies, new-onset nut allergies, maybe people who have eaten seafoods or nuts their whole life and all of a sudden become allergic. I've never encountered new-onset cow's milk allergy in an adult, so I'm not sure if I have that answer.

Dr. Fleischer: For IgE-mediated allergy, it's not been reported to be tolerant to milk, and then suddenly become allergic, but as Carina said, there are nuts and seafood that patients can be tolerating for many, many years, and then in adulthood, for some reason, lose that tolerance, and we don't know why. When you use the word milk "tolerance" or "intolerance," there are patients who can be lactose intolerant, that's not a milk allergy. A patient can lose the ability to digest the sugar that's in milk, but not react to the protein, but that's again an intolerance. Allergy really has not been reported to come back in patients either who have outgrown it with milk, so they've had IgE-mediated allergy. It's not been reported to come back, because even if they don't like drinking a glass of milk or eating ice cream, milk is in so many foods that they're exposed to in another form. The recurrence comes back, but we really don't know why those adult patients lose and develop IgE-mediated allergy later on to the nuts and the seafood. It's something that really has not been investigated, I think, very well, yet.

Cow's Milk Allergy: Mechanisms, Diagnosis and Treatment

1. Mazzocchi A, Venter C, Maslin K, Agostoni C. The role of nutritional aspects in food allergy: Prevention and management. *Nutrients.* 2017;9(8). pii: E850. doi:10.3390/nu9080850

   Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. *Nat Rev Immunol.* 2016;16(12):751-765. doi:10.1038/nri.2016.111

2. Pitt TJ, Becker AB, Chan-Yeung M, et al. Reduced risk of peanut sensitization following exposure through breast-feeding and early peanut introduction. *J Allergy Clin Immunol.* 2018;141(2):620-625.e1. doi:10.1016/j.jaci.2017.06.024

3. Meyer R, et al. *J Hum Nutr Diet.* (forthcoming).

4. Meyer R, Groetch M, Venter C. When should infants with cow's milk protein allergy use an amino acid formula? A practical guide. *J Allergy Clin Immunol Pract.* 2018;6(2):383-399. doi:10.1016/j.jaip.2017.09.003

5. Meyer R, Groetch M, Venter C. When should infants with cow's milk protein allergy use an amino acid formula? A practical guide. *J Allergy Clin Immunol Pract.* 2018;6(2):383-399. doi:10.1016/j.jaip.2017.09.003

6. Berni Canani R, Di Costanzo M, Bedogni G, et al. Extensively hydrolyzed casein formula containing La ctobacillus rhamnosus GG reduces the occurrence o f other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. *J Allergy Clin Immunol.* 2017;139(6):1906-1913.e4. doi:10.1016/j.jaci.2016.10.050

   Berni Canani R, Nocerino R, Terrin G, et al. Effect of Lactobacillus GG on tolerance acquisition in infants with cow's milk allergy: a randomized trial. *J Allergy Clin Immunol.* 2012;129(2):580-2, 582.e1-5. doi:10.1016/j.jaci.2011.10.004

7. Keown A. DBV Reports Positive Data from Milk Allergy Trial. PharmaLive. Posted February 27, 2018. Available at https://www.pharmalive.com/dbv-reports-positive-data-from-milk-allergy-trial/.