Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

MONOGRAPH

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Overview

Experts in pediatric allergy and immunology share their insights reviewing clinical presentation and essential diagnosis criteria and histological features of severe food allergy, specifically cow's milk allergy (CMA), Food Protein-Induced Enterocolitis Syndrome (FPIES), and Eosinophilic Esophagitis (EoE). Faculty discuss common food triggers and what distinguishes these disorders from other major IgE-mediated and non-IgE-mediated food allergies. They also review how to administer an oral food challenge for patients with suspected food allergies and how to apply long-term nutritional and medical strategies using current guidelines for pediatric patients with severe food reactions.

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.

Section

Learning Objectives

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

- Develop clinical nutritional strategies to mitigate severe food allergy, specifically cow's milk allergy, in infants
- Recognize the clinical presentation of immunoglobulin E (IgE) and non-IgE-mediated food allergy, such as FPIES and EoE
- Facilitate shared decision making with families managing children with severe food allergy

Faculty

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Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

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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

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

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Speakers Bureau	Abbott- clinical area: Food allergy

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Consultant	Merck- clinical area of sublingual immunotherapy for dust mites ALK-Abelló- clinical area of data monitoring committee- clinical area for sublingual immunotherapy for dust mites
Advisory Board	Gerber Nutritional Institute- clinical area of solid foods for prevention of food allergy

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

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Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Diagnosing and Managing Food Allergies in Infants

David Fleischer, MD, director of the Allergy and Immunology Center and associate section head at Children's Hospital Colorado, and **Carina Venter, PhD, RD,** assistant professor of pediatrics-allergy at Children's Hospital Colorado, review strategies for a proper diagnosis of food allergies in infants, specifically the pathophysiology of cow's milk allergy. Dr. Fleischer discusses how to distinguish between IgE-mediated and non-IgE-mediated reactions to food, while Dr. Venter reviews solid food introduction and the role of breast milk in prevention and tolerance development. Dr. Venter also provides details about suitable and clinically recommended formulas. Dr. Fleischer continues the discussion with interventional therapies and what the future holds for research targets with a better understanding of mechanisms and triggers of allergy.

Dr. David Fleischer shares the National Institute of Allergy and Infectious Diseases consensus definition for a food allergy, stating it is an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.[1] It develops as a lack of oral tolerance, which is a default immune response by the gut. If the individual makes more dangerous antibodies to those with the IgE antibodies vs protective antibodies, an allergy can develop.

Any bad reaction to food is called an adverse food reaction. To be IgE, or immune mediated, it must involve the immune system, and is either IgE mediated, non-IgE mediated, mixed disorders, or cell mediated.

Non-immune-mediated reactions can be food intolerance, or lactose intolerance, where you don't have the enzyme to break down the sugar in milk, for example, but you can tolerate the protein in milk. Other reactions include food poisoning, pharmacologic reactions, metabolic reactions, and toxic reactions. The other condition is food aversion. In some of these disorders, patients become quite averse to eating the food, so it is a subset within these types of allergies.

The spectrum of food allergy is from purely IgE mediated to non-IgE mediated (see **Figure 1**). IgE mediated is in the gastrointestinal (GI) tract. A common condition is pollen food-allergy syndrome, which results in oral itching from eating certain fresh fruits and vegetables. The allergy is to environmental allergens; the proteins in the environmental allergens cross-react with certain foods, resulting in itching in the mouth. When cooked, these foods do not usually cause symptoms.

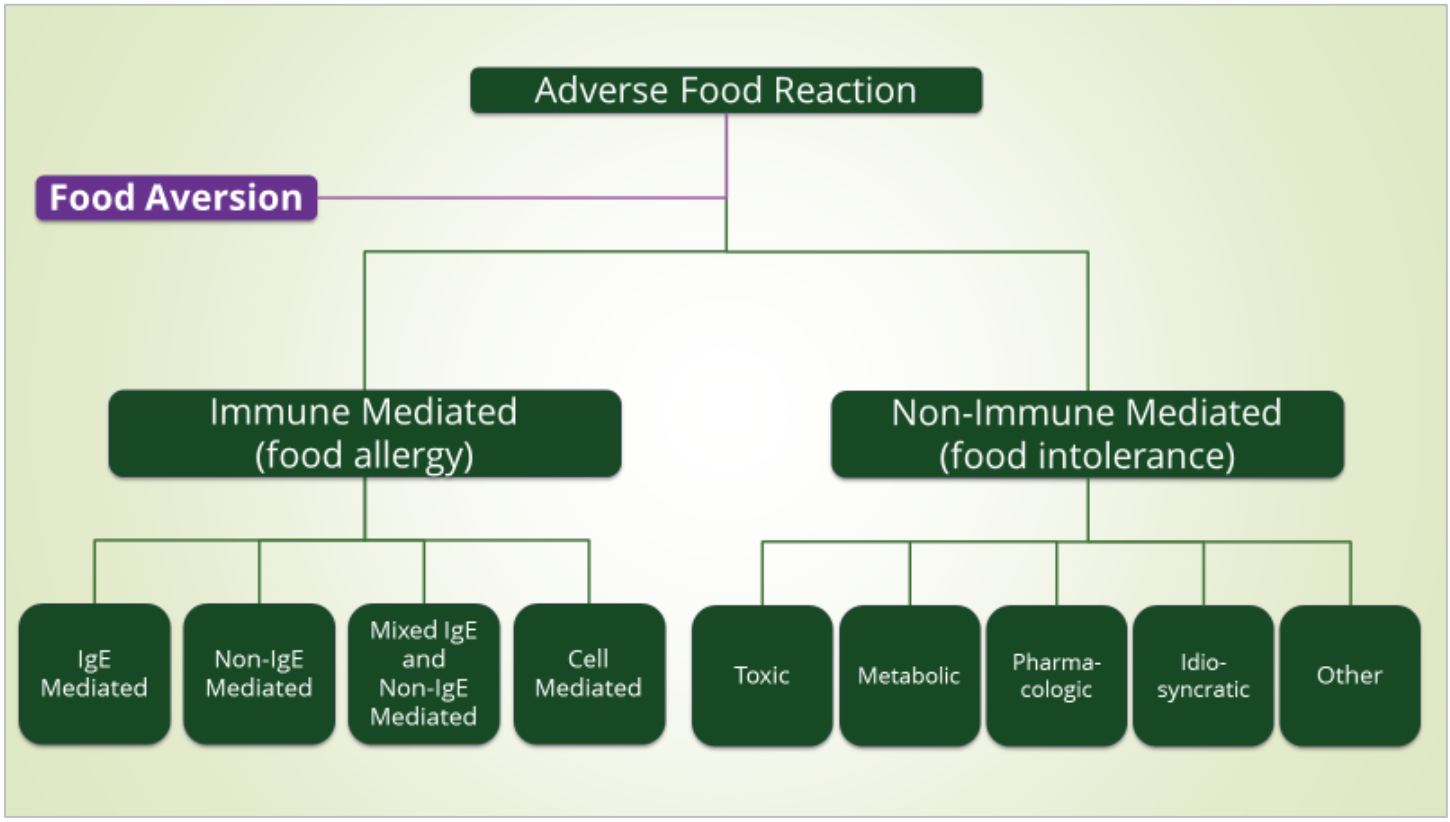


Figure 1–Types of Adverse Reactions to Food

Although we feel eosinophilic esophagitis (EoE), discussed later by Dr. Chehade, and eosinophilic GI disease, are more non-IgE mediated, we consider these mixed disorders. Non-IgE-mediated reactions also include milk-induced proctocolitis, in which patients can have blood in their stool upon ingesting milk. This condition, however, usually goes away by age 1.

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. Symptoms are based on the organ system in which symptoms appear. Systemic hypersensitivity disorders are usually anaphylaxis, and those are IgE mediated.

When looking at prevalence in infants and toddlers, food allergies—at least in the US—affect 4% to 8% of children under the age of 5 years, which is about 6 million children under age 18. About 40% of those have a history of severe reactions, and a third of those patients have multiple food allergies.[2] Comparatively, it is 3% to 4% in the general population in other developed countries.

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Prevalence studies in the US have not been done based on food challenges; however, we think prevalence is increasing. Peanut allergy, for example, has probably tripled over the past decade. Cow's milk allergy 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. Milk accounts for about 90% to 95% of IgE-mediated food allergy in children.[3]

Taking a detailed clinical history is the guide to determining a possible IgE-mediated reaction or not. In a physical exam, physical symptoms may indicate more IgE-mediated allergy. With IgE-mediated allergies, we can use skin tests or serum IgE testing. If those are negative, we consider doing the food challenge.

With the non-IgE-mediated reactions, the clinical history will tell you whether it's non-IgE mediated or not (see **Figure 2**). If you are looking at eosinophilic GI disease, you will have an endoscopy or a consultation with a gastroenterologist. Sometimes you may have to eliminate certain foods and re-challenge patients. Food challenges are done 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.

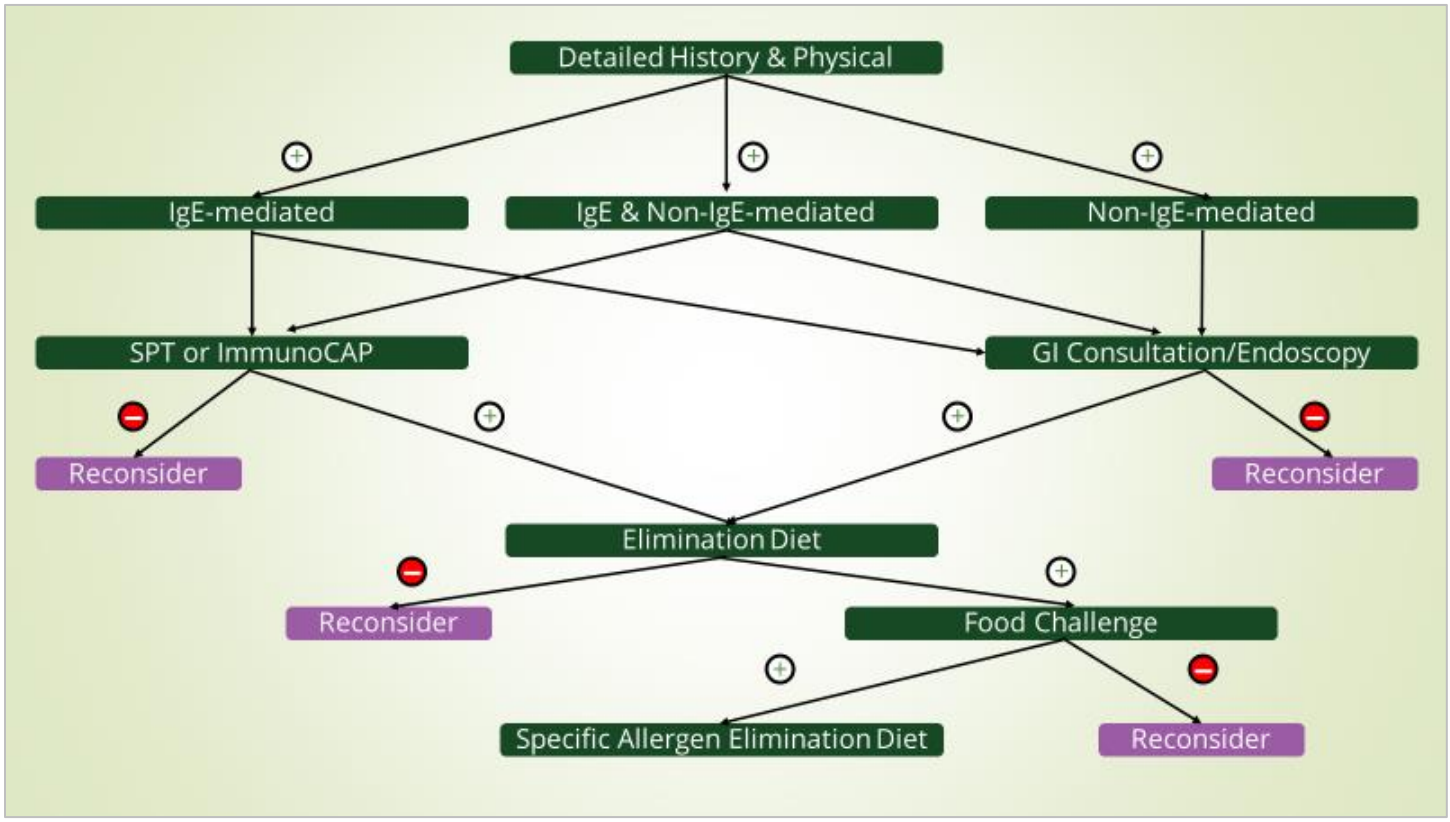


Figure 2–Diagnostic Approach to the Evaluation of Food Allergy

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

When looking at IgE-mediated vs non-IgE-mediated reactions, we look at characteristics of time from exposure to reactions. In almost all IgE-mediated reactions, most happen within the first 15 to 30 minutes, and usually within the first 2 hours. Non-IgE-mediated reactions are typically more delayed in onset, usually after 2 hours.[4] Both can be quite severe and can range from mild to moderate reactions to anaphylactic reactions.

As far as duration of allergies, most IgE mediated reactions last beyond 1 year of age. Some foods, like milk and egg, are usually outgrown; whereas, peanuts, tree nuts, and seafood can go on into adulthood. With non-IgE mediated, some can also persist beyond 1 year of age.

Other milk-induced conditions, such as Food Protein-Induced Enterocolitis Syndrome (FPIES), which Dr. Nowak-Węgrzyn covers in detail, are not outgrown by most patients until age 3. Again, the clinical history drives what is IgE or non-IgE, and what tests you may or may not do.

Food challenges are a part of both, to see if the patient has outgrown the allergy; and food challenges can be used with IgE mediated to confirm allergies.

In the diagnostic approach to the evaluation of IgE-mediated allergy, a detailed history is very important. Many patients have a family history of other allergic diseases, such as eczema, allergic rhinitis, or asthma. It is also important to review the list of suspected foods, with a precise description of any reactions. For example, ask how much they ate, when they ate it, and how quickly after they ate the food did symptoms appear, and then what kind of symptoms were experienced. Also, ask if they have eaten the food since?

The most common symptoms, especially in infants, are hives, or urticaria. Patients can have swelling or angioedema, eczema, as well. GI symptoms are quite common in reactions in infants under age 1, with vomiting. Pulmonary symptoms may include wheezing, but wheezing is usually not isolated; usually, other organ systems are involved, such as the skin. You can have upper respiratory symptoms with congestion and runny nose, and severe symptoms, with asthma and laryngeal edema. Cardiovascular symptoms, such as hypotension are more common in adults than children. Patients can have neurological symptoms, such as loss of consciousness.

You should be aware of behavioral changes, which are common in food challenges. For example, when doing a food challenge in young infants or toddlers who can't say how they're feeling, often they will be playing, and then suddenly get very quiet and sit in the parents' lap, indicating they're not feeling well.

In the evaluation of an infant, symptoms with cow's milk that may not be IgE-mediated reactions include irritability and gastroesophageal reflux. These are more common in the mild-to-moderate non-IgE-mediated cow's milk allergy. Reflux and atopic dermatitis are usually a delayed reaction and can be due to environmental factors.[5]

When we have a diagnosis of an IgE-mediated reaction, we need to consider and talk with families about an elimination diet. We teach parents and caregivers the importance of reading labels. We always try to have our patients meet with a dietitian, because it's not just avoiding foods, it's also making sure the patient is getting the right nutrients.

Certain websites can be helpful and provide reliable information, such as Foodallergy.org, which is monitored by allergists and other physicians, to ensure the documentation and information is up-to-date and accurate.

Patients and parents need an action plan—an anaphylaxis action plan—so they know how to treat reactions based on symptoms and to understand when to use an antihistamine and epinephrine. Training how to use epinephrine is very important. We can't predict the severity of reactions based on testing, and you always need to be prepared and have epinephrine auto-injectors with patients. It's not just educating the parents, but also caregivers, such as babysitters, grandparents, or siblings who are taking care of the child.

Long-term management. We usually see patients for food allergy once a year to update their medications, refill prescriptions, review new research or new treatments. Looking at results from tests, we may order a food challenge. There may be things to discuss as kids go from preschool to elementary school. We want to look at how food allergies are impacting the quality of life. Food allergy, unfortunately, impacts not just the patients, but the whole family. Oftentimes, psychosocial clinician or a psychologist can help patients and parents, so they have a healthy level of anxiety with their food allergy.

We're looking at IgE-mediated cow's milk allergy as the focus of this portion of the discussion, but other non-IgE-mediated cow's milk allergies can include the milk-induced proctocolitis, enterocolitis, or FPIES, as noted previously (see **Figure 3**). In EoE milk is often a trigger. In the more mild-to-moderate non-IgE-mediated cow's milk allergies, reflux and colic are common.

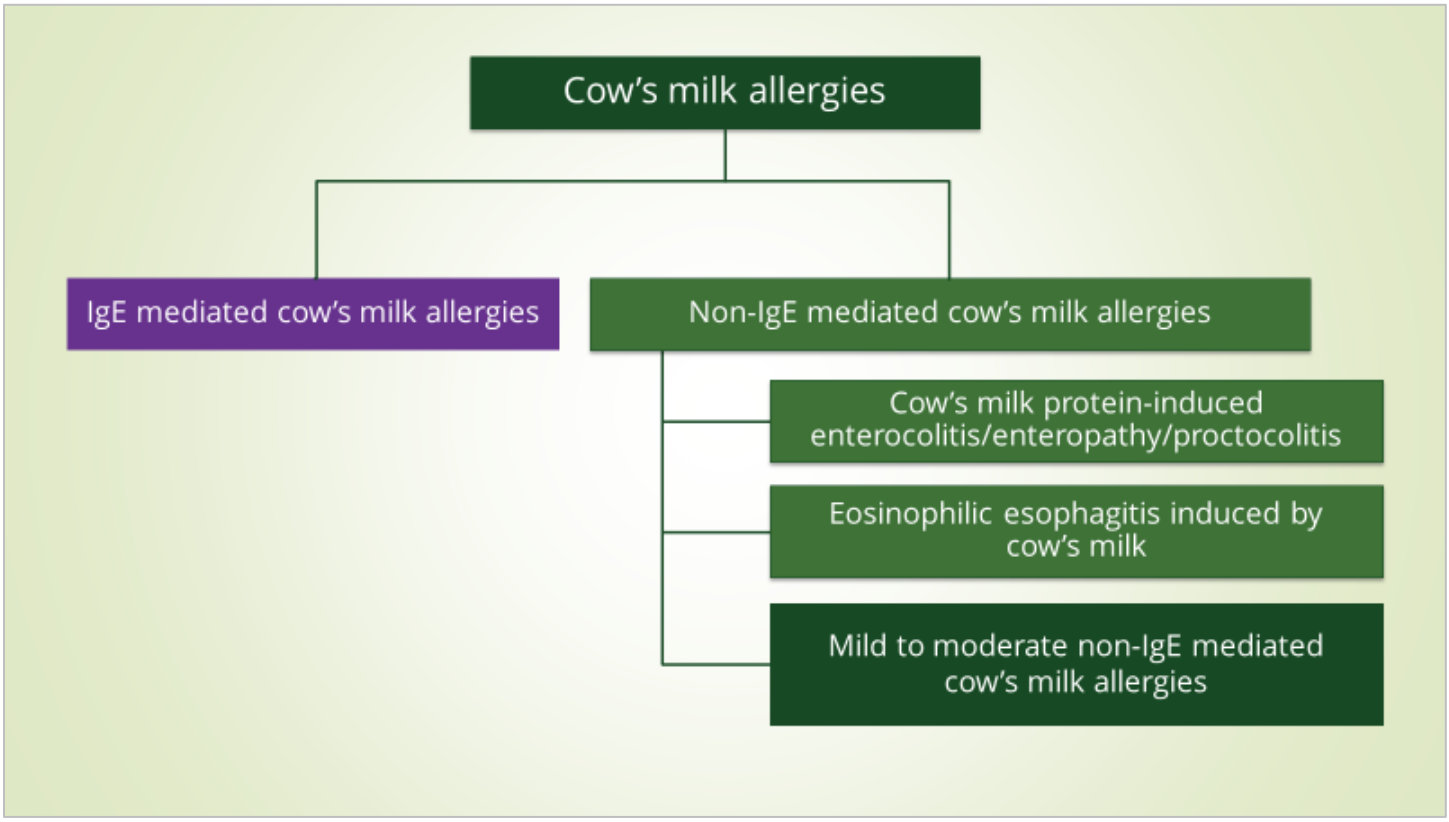


Figure 3–Mechanism: Type of cow's milk allergy?

Remember, neither the skin test nor the level of that blood test can predict the severity of the 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 the patient is to react, but you can't predict severity.

· Return to Index ·

Immunologic Research

Dr. Carina Venter, states that the more we learn about the microbiome and how it interacts with the immune system, the more we understand we cannot separate the microbiome from what we see immunologically in infants with food allergies, and particularly IgE-mediated cow's milk allergy.

The microbiome 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.[6] A diverse microbiome is assumed to be associated with tolerance development; however, the role of diet diversity in diverse microbiome is still unclear.

If you consider increasing or starting solid food introduction in an infant's diet as a measure of diet diversity, data show as soon as we start introducing solids into an infant's diet, the diet becomes much more diverse, and will include microbiome we see in early infancy in breastfed infants. Additional research targeting cow's milk allergy suggests we need a better understanding of what an ideal gut microbiome looks like, which 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 Prebiotics are the good fiber that feed probiotics, which are beneficial bacteria in the microbiome. Studies continue to determine 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. We need to learn how to manipulate the microbiome to induce tolerance. We also need to understand how we can best introduce solids into an infant's diet to induce tolerance in, for example, cow's milk allergic infants.

There are a large number of proteins in cow's milk, but those involved in cow's milk allergy are casein proteins, or casein fractions of protein, which include the α-, the β-, and the κ-casein, and β-lactoglobulin, which is one of the main triggers of cow's milk allergies in young infants (see **Figure 4**). Infants who sensitize to the β-lactoglobulin develop a tolerance to products containing baked cow's milk, such as cookies or muffins.

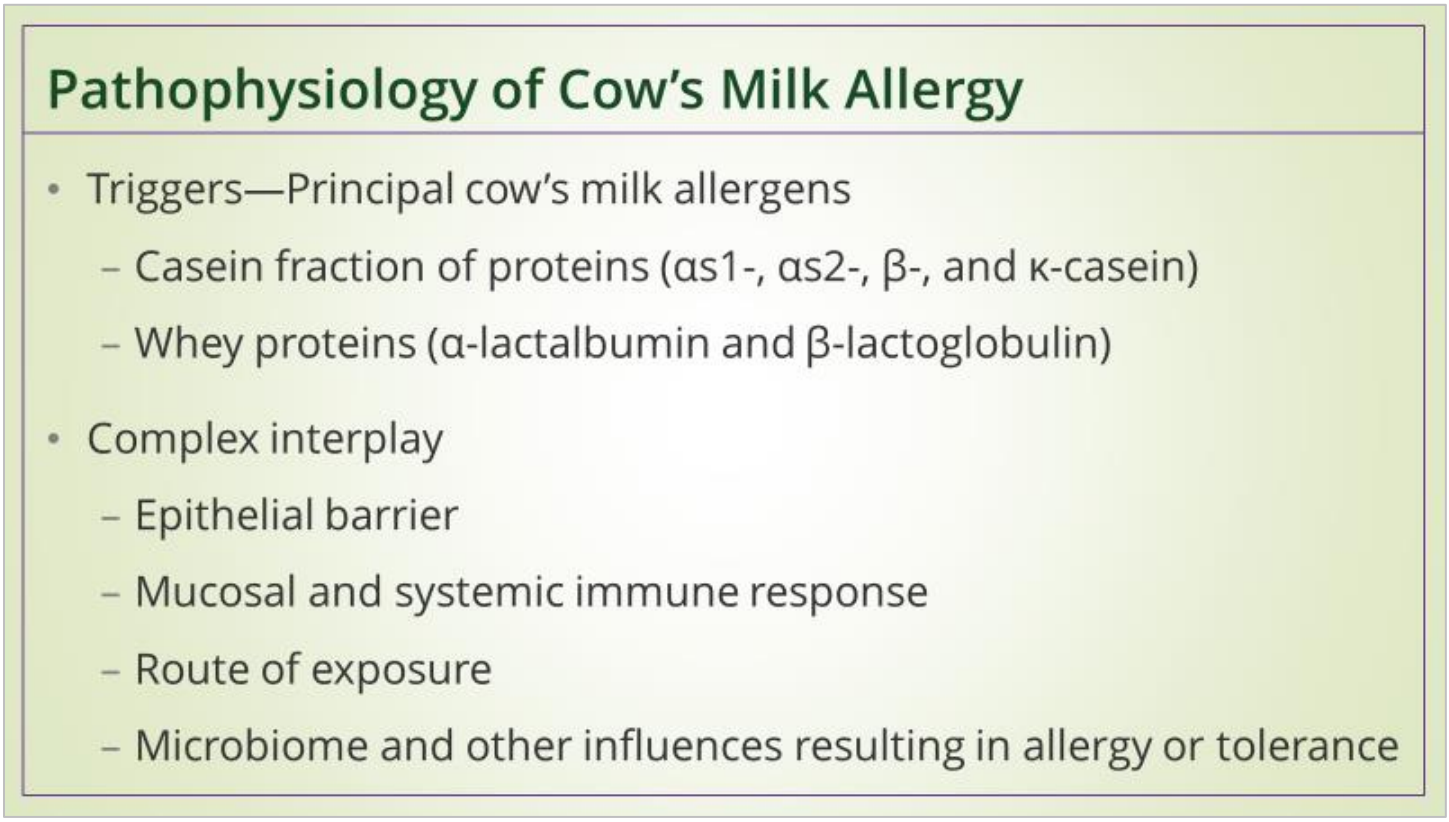


Figure 4–Pathophysiology of Cow's Milk Allergy

There is a complex interplay between the microbiome and the epithelial barrier, which determines how much protein is absorbed. Inflammation in the gut leads to more allergen exposure or absorption. More severe symptoms can result 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, as there's a large number of immunomodulatory factors in breast milk, with human-milk oligosaccharides studied the most. Breast milk has the potential to support the infants' developing immune system, but an interesting component of breast milk occurs when a maternal ingestion of the allergen leads to transfer of the allergen to the infant (see **Figure 5**). We do know that in cow's-milk-consuming mothers, 95% will transfer some level of β-lactoglobulin to the infant.[7]

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

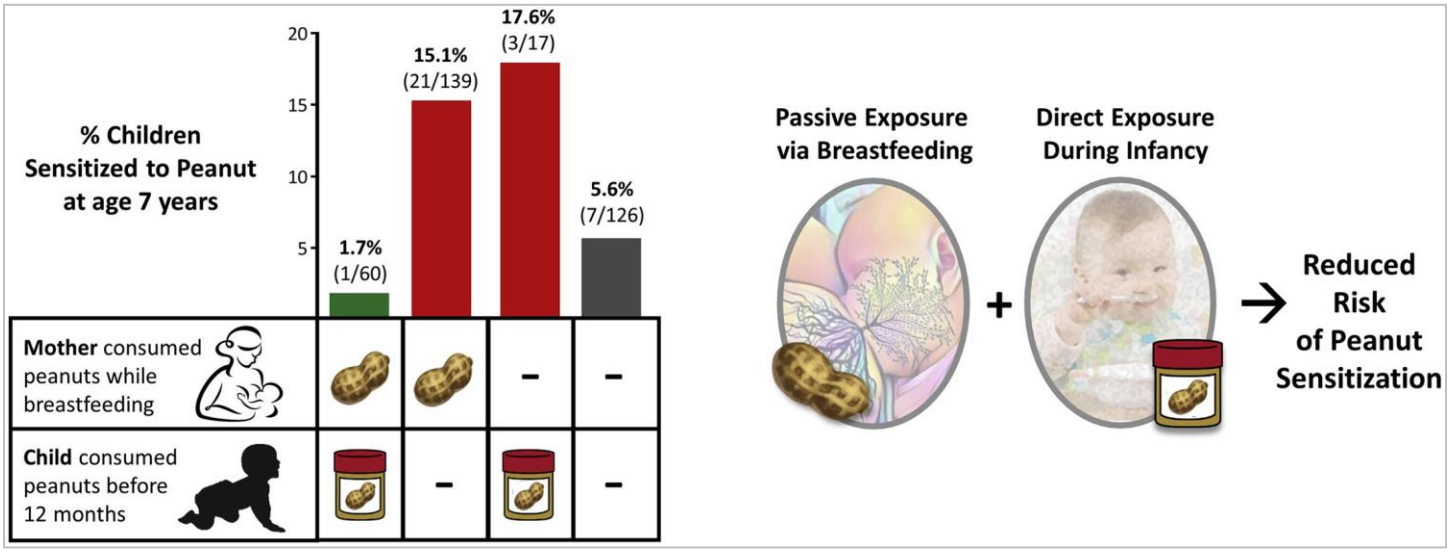


Figure 5–Breast Milk and What it Provides

In addition to focusing on the immunomodulatory components of breast milk, we need to learn more about proteins excreted by breast milk to the infant, and what effect that may have on either tolerance development or disease induction.

· Return to Index ·

Nutritional Treatment Strategies

The current standard of care of IgE-mediated cow's milk allergy is to avoid cow's milk. We've moved a long way away from recommending complete cow's milk avoidance in all infants at all times, because we're beginning to understand that 70% to 75% of cow's milk allergic infants may become tolerant to baked milk before they develop tolerance to cow's milk. We also understand that cow's milk allergy can have an effect on growth. We need to monitor growth in terms of weight, length, and head circumference. Length is the most important aspect to monitor, because children with cow's milk allergy often stunt their growth before they start to lose weight.[8]

In terms of breastfed infants, one question most often asked is should I tell the breastfeeding moms to stop breastfeeding? Never. Should I tell the breastfeeding mom to avoid or exclude cow's milk from her diet? There's a very simple answer. If the child only presents with symptoms of IgE-cow's milk allergy when infant formula is introduced, or as soon as solid foods containing cow's milk is introduced, you only need to change the formula and avoid cow's milk from the infant's diet. There's no need for the breastfeeding mother to avoid cow's milk in her diet. If the symptoms occurred, however, when Mom was consuming

cow's milk and exclusively breastfeeding, then there is 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.[9]

Infants under 6 months of age can use extensively hydrolyzed protein formula, which could be whey or casein formula, or we could use amino acid-based formula. In infants older than 6 months, soy formulas could be used in IgE-mediated cow's milk allergic cases (see **Figure 6**).

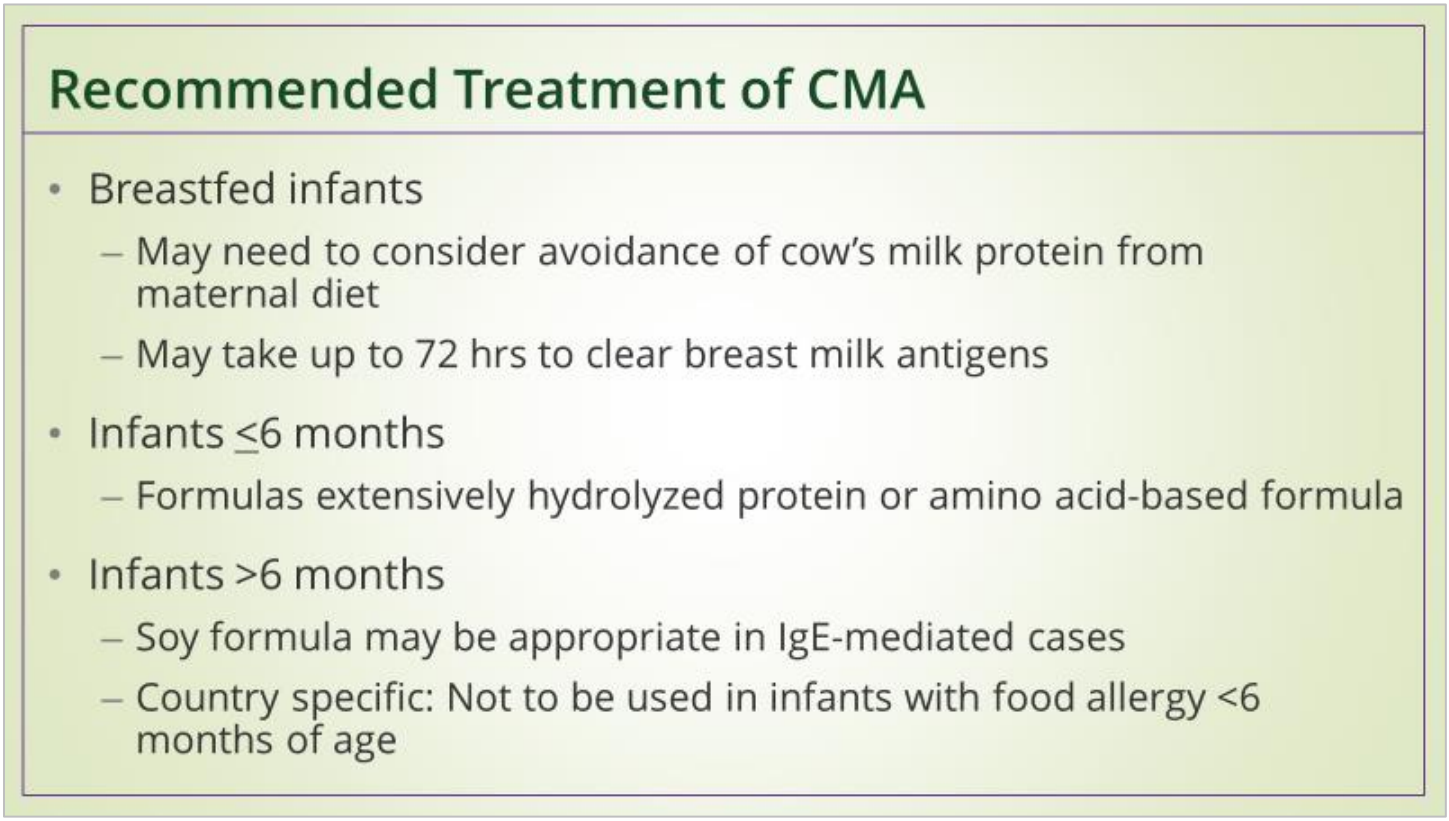


Figure 6–Recommended Treatment of CMA

The 4 formulas we can use include elemental (or amino acid-based) formulas, extensively hydrolyzed casein or whey formulas, and then soy formula.

There are different definitions of hypoallergenic formulas based on the American Academic of Pediatrics and the European Society for Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines[3]. In essence, we want the majority of the peptides to be smaller than 1.5 kilodalton (kDa). The definition that matters most clinically is the formula used—and has the claim of being hypoallergenic; this formula should be tolerated by 90% of patients with cow's milk allergy. Hypoallergenic formulas, at this point in time, include both extensive and amino acid-based formula. These definitions are being rewritten, and it will be interesting to see what 2019 brings in terms of the definition of hypoallergenic formula.

The amino acid-based formula 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 have lactose added, which was a concern in the use of patients with secondary lactose deficiency due to cow's milk allergy. Studies show, however, the lactose added to the whey hydrolyzed are safely tolerated, even in children with diarrhea.

Soy-protein formulas can be used in infants more than 6 months of age. About 2% to 14% with IgE-mediated cow's milk allergy may not tolerate the soy formula. Nutritional disadvantages noted is it could affect absorption, and we are concerned about the isoflavone content, in terms of the amount of isoflavone per kilo of body weight, which is why there is a 6-month cut-off age for safe use of soy formula.[10111213]

There are many factors to think about when choosing the right formula (see **Table 1**): the degree of hydrolysis; medium chain triglycerides (MCTs); the presence or absence of lactose; the nutritional status of the child; the nutrient profile; the amount of iron, calcium, and vitamin D in formula; whether it contains pre or probiotics; palatability, flavor, culture, and religion.[14] Some of the formulas do contain pork enzymes; and, of course, cost.

Table 1– 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.

In a recent paper published in the *Journal of Allergy and Clinical Immunology: In Practice* (2018),[3] all the available studies on using formula for the treatment of food allergy and cow's milk allergy were summarized. Amino acid-based formula is best used in infants with severe gastrointestinal symptoms, as well as in those with growth faltering or failure to thrive, with multiple food allergies, and with severe atopic dermatitis, as well as infants with a history of anaphylaxis. All other infants could be placed on either an extensively hydrolyzed casein or whey formula. There's no way to recommend one above the other.

Allergy management strategies. With the introduction of solid foods, instruction is needed on how to avoid cow's milk, and which other foods to introduce, and when to potentially reintroduce cow's milk into the infant's diet. An appropriate formula needs to be chosen, and potentially with a supplement.

A 2012 Berni Canani et al study looked at the development of tolerance in cow's milk allergy[15]. The study indicates microbiome differ between kids who become sensitized or not, those who develop clinical cow's milk allergy or not, and those who become tolerant quicker or not. A 2017 Berni Canani et al study showed adding lactobacillus GG to a hypoallergenic formula, accelerates development of tolerance in both IgE- and non-IgE-mediated cow's milk allergy.[15]

· Return to Index ·

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Interventional therapies

Dr. Fleischer continues the discussion with interventional therapies. Currently, there is no FDA-approved treatment for food allergy. Please note the information that follows is not to be done at home, but rather in an allergist's office. Even small doses of food to desensitize the patient should not be done at home.

Food immunotherapies try to desensitize patients to the food to which they are allergic, which may result in either having a less-severe reaction or no reaction at all.[16] Desensitization means a reversible state that's typically induced by short-term exposure to the allergen. Once you stop 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.[17, 18]

The 2 types of immunotherapy being investigated are oral immunotherapy, where you give patients small but gradually increasing (usually every 2 weeks) foods, for several months until they reach a maintenance dose. **These doses are given under medical supervision. This is not to be done at home.** Patients can experience EoE, induced by these therapies; it's a big concern with milk—one of the biggest triggers of EoE.

Ongoing clinical trials include epicutaneous therapy, or what we call the patch, immunotherapy (see **Figure 7**).

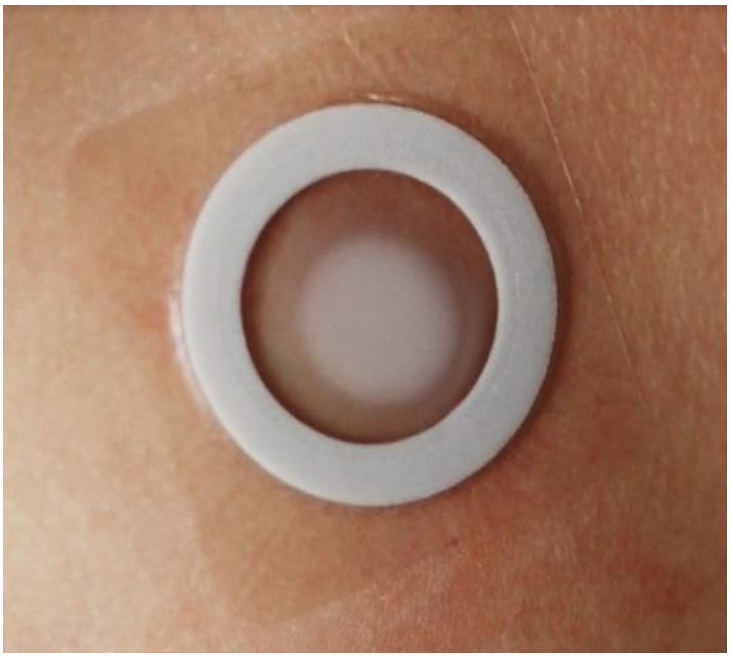


Figure 7–Epicutaneous Immunotherapy (daily-dose patch)

There is a film in the middle, and the opaque center is the protein that is electrostatically sprayed onto that film. Milk, egg, and peanut are the 3 foods being investigated in this therapy. It's a single-dose patch, so there's no up-dosing every 2 weeks, unlike the oral immunotherapy. The first patch is applied in clinical study sites for 3 hours, and then at home over the coming 2 weeks, 24-hours a day. Because it is applied at home, the advantage is not having to come every 2 weeks to get up-dosed. There are no restrictions for physical activity, like there can be with oral immunotherapy within certain hours of taking the oral dose. It may be more convenient for patients than the oral immunotherapy.

The phase 2 clinical trial was done with the milk epicutaneous patch. Hopefully, phase 3 will begin and lead to FDA approval—within the coming years. This is the first potential treatment for cow's milk allergy, and is specific to 2–11-year olds.[19]

With the patch, safety and compliance are a bit easier than the oral immunotherapy. Discontinuation rates are quite low, about 1% to 2%. The most common adverse event is topical skin reactions, which are usually mild to moderate.

What does the future hold? A better understanding of mechanisms and triggers of allergy will provide new research targets. As we learn more about food allergy and immunotherapy, there will be new waves of products.

We hope to better understand some of the genetic, epigenetic, and environmental risk factors. The milk patch has been studied in a phase 1 pilot study to treat milk-induced EoE. 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. We also discussed the microbiome and how to manipulate it to develop tolerance. There may be more peptides for milk developed that can lead to tolerance development in the form of immunotherapy.

There are currently no approved interventional treatments for cow's milk allergy; however, we hope to have them within the next few years. The current standard of care 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 and severe reactions. Cow's milk allergy has a favorable prognosis; it's more likely to be outgrown, as opposed to peanut or tree nuts. Food allergies should be managed by individual avoidance strategies, label reading, and with the involvement of a dietitian.

· Return to Index ·

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Defining FPIES

Anna Nowak-Węgrzyn, MD, PhD, professor of pediatrics and director of clinical research at Jaffe Food Allergy Institute, Division of Allergy and Immunology and Department of Pediatrics at Icahn School of Medicine at Mount Sinai, provides her expertise, first by defining what Food Protein-Induced Enterocolitis Syndrome, known as FPIES, is: a non-IgE, cell-mediated food allergy, which manifests as delayed, repetitive projectile vomiting after ingestion of food. It may be accompanied by diarrhea, and it occurs primarily in infants and young children.[20] This is one of several immunologic reactions to dietary food proteins.

FPIES is the most severe non-IgE-mediated food allergy because it can lead to shock and dehydration. In a chronic form, it can result in failure to thrive.[21] Currently, we don't have a good understanding of the pathophysiology of FPIES and awareness of FPIES remains low, with patients frequently misdiagnosed, resulting in a delayed diagnosis.

The classification of food allergy is based on IgE antibody involvement in pathophysiology. IgE-mediated food allergies manifest in the most severe form as anaphylaxis, which can be life threatening.

There is a category of non-IgE mediated, presumably T-cell mediated disorders, which include FPIES. There is also a group of mixed pathophysiology disorders represented by eosinophilic gastroenteropathies, as well as atopic dermatitis.

FPIES's prevalence is not well described. Until recently, it was believed that FPIES is a rare food allergy; however, recent studies indicate it may be more common than previously appreciated.[22, 23, 24]

The onset of FPIES typically occurs during the first year of life, and symptoms usually appear in an acute form, 1 to 4 hours after ingestion (which is substantially delayed compared to the immediate food-allergic reactions), with resolution of symptoms within 24 hours. FPIES manifests as projectile, repetitive emesis, which can occur 20 to 30 times in severe cases.

In younger infants with a more severe reaction, diarrhea usually starts 6 to 8 hours later. Children are pale, lethargic, and may develop dehydration; and, in 15% of the cases, they become hypovolemic. **The most common triggers for acute FPIES in the US are cow's milk, soy, rice, oat, as well as vegetables.**

In contrast, chronic FPIES occurs when symptoms develop over a period of days to weeks, and resolution may take days to weeks. **Chronic FPIES** has been described in young infants who are fed continuously with milk, cow's milk, or soy-based formulas. The onset of chronic FPIES is within 1 to 3 months of life. The

symptoms may take days or weeks to resolve. The most common manifestation is watery diarrhea, rarely containing mucous or blood in stools, accompanied by emesis, initially intermittent, but progressively worsens over the course of days to weeks.

This chronic condition can escalate quickly. Patients develop low albumen and total protein and fail to thrive. These infants are not growing and ultimately become dehydrated. When admitted to the hospital, they are dehydrated, with metabolic acidosis. They frequently have hypovolemic shock. Methemoglobinemia can also be observed. Some of those children require total parenteral nutrition (TPN). This is a serious condition.

It is important to understand **FPIES is a self-limiting food allergy of childhood, with a very favorable prognosis.** Based on experience, there are no long-term consequences. Most infants outgrow FPIES by age 3 or 5. Those with a more persistent form or phenotype can have symptoms until later years, but the majority will be FPIES-free by age 5.

Most patients with FPIES are IgE negative by skin or serologic testing, but in phenotype atypical FPIES, there can be positive skin testing or blood testing for the food triggering FPIES, which can be associated with a more protracted phenotype. Patients who develop specific IgE to the FPIES trigger tend to have a more persistent disease.

This overview is based on the *First International Consensus Guidelines for the Diagnosis and Management of FPIES,* published in the *Journal of Allergy and Clinical Immunology,* April 2017.[25] This was an initiative within the American Academy of Allergy, Asthma & Immunology, written with combined global expertise. The complete guidelines are open access and available through the International FPIES Association on **fpies.org**.[26] The guidelines provide recommendations regarding epidemiology and diagnosis, as well as the features of the phenotypes. They spell out specific diagnostic criteria for acute and chronic FPIES, and provide practical guidance on managing FPIES for acute emergencies, as well as long-term.

The clinical phenotype of FPIES, as noted in **Table 2**, is dependent on the amount, dose, and frequency of food allergen ingestion. Phenotyping patients provides guidance for diagnosis and management.

Table 2–FPIES Clinical Phenotypes

Phenotypes influenced by		
Age of onset	early (<9 months)	late (>9 months)
Severity	mild-to-moderate	severe
Timing and duration of symptoms	acute (symptoms resolve in 24 hrs)	chronic (resolution may take days to weeks)
Associated IgE-mediated food allergy	IgE negative	IgE positive

In **acute FPIES**, 2 phenotypes can occur in the same patient, depending on the age and the frequency of ingestion. If chronic FPIES is suspected, the reintroduction of the food trigger should be performed under physician supervision, not at home—as the reactions can be quite severe.

Once feeding with the offending food is discontinued, the infants with FPIES recover. The most common form or phenotype of FPIES is acute FPIES, so by 24 hours, the child is back to normal health (see **Table 3**).

Table 3– FPIES Phenotypes (continued)

Acute	Chronic
Ingestion following a period of avoidance (at least several days)	Young infants fed continuously with milk or soy formulas
Onset of emesis: 1–4 hours	Watery diarrhea
Lethargy, limpness (“septic appearance”)	Mucous, blood in stools
15% go into shock	Intermittent emesis
15% with methemoglobulinemia	Low albumin and total protein
6–8 hours later: diarrhea	Failure to thrive, poor growth
Onset: usually under 12 months; Fish/Shellfish: children, adults	Onset: first 1–3 months of life
Symptoms resolve within 24 hrs	Symptoms resolve within days–weeks, may require TPN
Cow’s milk, soy, rice, oat, vegetables	Cow’s milk, soy

· Return to Index ·

Diagnosis and Management of FPIES

Misdiagnosis in FPIES is common and can delay a diagnosis for months. The most common FPIES masqueraders include infectious diseases, such as acute viral gastroenteritis and sepsis. Anaphylactic reactions should be included in differential diagnosis, especially with reactions that occur within 1 to 2 hours.

Chronic non-IgE-mediated food allergic disorders, like eosinophilic esophagitis (EoE), food protein-induced allergic proctocolitis (FPIAP), and enteropathy are also differential, however, patients usually present with more chronic symptoms waxing and waning, but not progressively worsening. In severe cases, infants with FPIES present with distended abdomen, and are suspected of having intestinal obstruction.

It is not easy to diagnose FPIES with the first reaction because of extensive differential diagnosis. When the baby presents ashen, pale, and lethargic, every physician in the emergency department will consider sepsis, and will also think about serious obstructive GI problems or metabolic diseases. One of the conditions in the differential is necrotizing enterocolitis (NEC), which can occur in full-term infants and have a very dramatic course. Allergic vs non-allergic conditions also have to be included in the differential.[27]

We also want to compare FPIES to other non-IgE-mediated food allergies as noted in **Table 4**. Food protein-induced allergic enterocolitis and enteropathy (FPE) could be a serious reaction—as a patient can become dehydrated. Enteropathy manifests with chronic diarrhea, malabsorption, low weight gain, but there's no acute symptoms upon food ingestion. In contrast, food protein-induced allergic proctocolitis (FPIAP) is a benign condition;[28] the baby is thriving and appearing well. There are no acute symptoms upon food ingestion, whether this is direct feeding or exposure to food proteins through the maternal diet in the breast milk. Because allergic proctocolitis is common, it is equally common in formula-fed as breastfed babies. FPIES is uncommon in exclusively breastfed infants.

Table 4– Distinguishing FPIES, FPIAP, and FPE

	Main clinical features
FPIES	Delayed repetitive vomiting, pallor, lethargy
FPIAP	Benign blood in stool, baby thriving Average age at onset lower: 2 months vs 4-6 months in FPIES, no acute symptoms upon food ingestion
FPE	Chronic diarrhea, malabsorption, low weight gain, no acute symptoms upon food ingestion

FPIES is a diagnosis of exclusions. There are no diagnostic test or biomarkers, and **the clinician needs to recognize a pattern of symptoms**. It is difficult to diagnose, because there are no typical allergic symptoms we associate with food allergy— those infants have no urticaria, no itching, no coughing, nor wheezing. The onset is delayed, between 1 to 4 hours, typically 2 hours after food ingestion. This is substantially later than IgE-mediated food allergies, which usually start within minutes, or up to an hour.

Food triggers, such as cow's milk and soy, are common food allergens in classic food allergy, as we will discuss later, but rice, oats, sweet potato, and other vegetables are considered hypoallergenic for IgE-mediated food allergy. They show up as the most common solid food triggers for infants with FPIES.

If there is uncertainty, an **oral food challenge can be conducted to confirm the diagnosis**. This is the only available diagnostic test. Because there are no biomarkers, clinicians need to be familiar with the typical features: timing and onset of symptoms, with improvement, which follows withdrawal of suspected causal protein. A physician-supervised oral food challenge is necessary to evaluate for FPIES resolution.

The food challenges done by the physicians (who are familiar with food allergy) differ from typical food challenges for the IgE-mediated food allergy; the protocols are available for specific procedures for the physicians (see **Figure 8**). We do not recommend introduction of foods at home nor to perform home food challenges because of the potential for severe reactions. Because of dehydration and the inability to predict if the child is already outgrowing this condition, we recommend intravenous fluid be available for rehydration, if needed. In milder reactions, it's reasonable to attempt oral rehydration (breastfeeding or with clear fluids), but there should be at least a reasonable period between the episodes of vomiting and when the child is not lethargic or unresponsive. If those features are present or the child keeps vomiting, then take those children to the emergency room.[25]

Food challenges for FPIES should be done at centers with expertise in managing food allergy and conducting oral food challenges. The timing of the food challenge for resolution evaluation is usually between 1 and 2 years, or longer from the most recent reaction. When to perform a food challenge for evaluation for resolution is a very individualized decision.

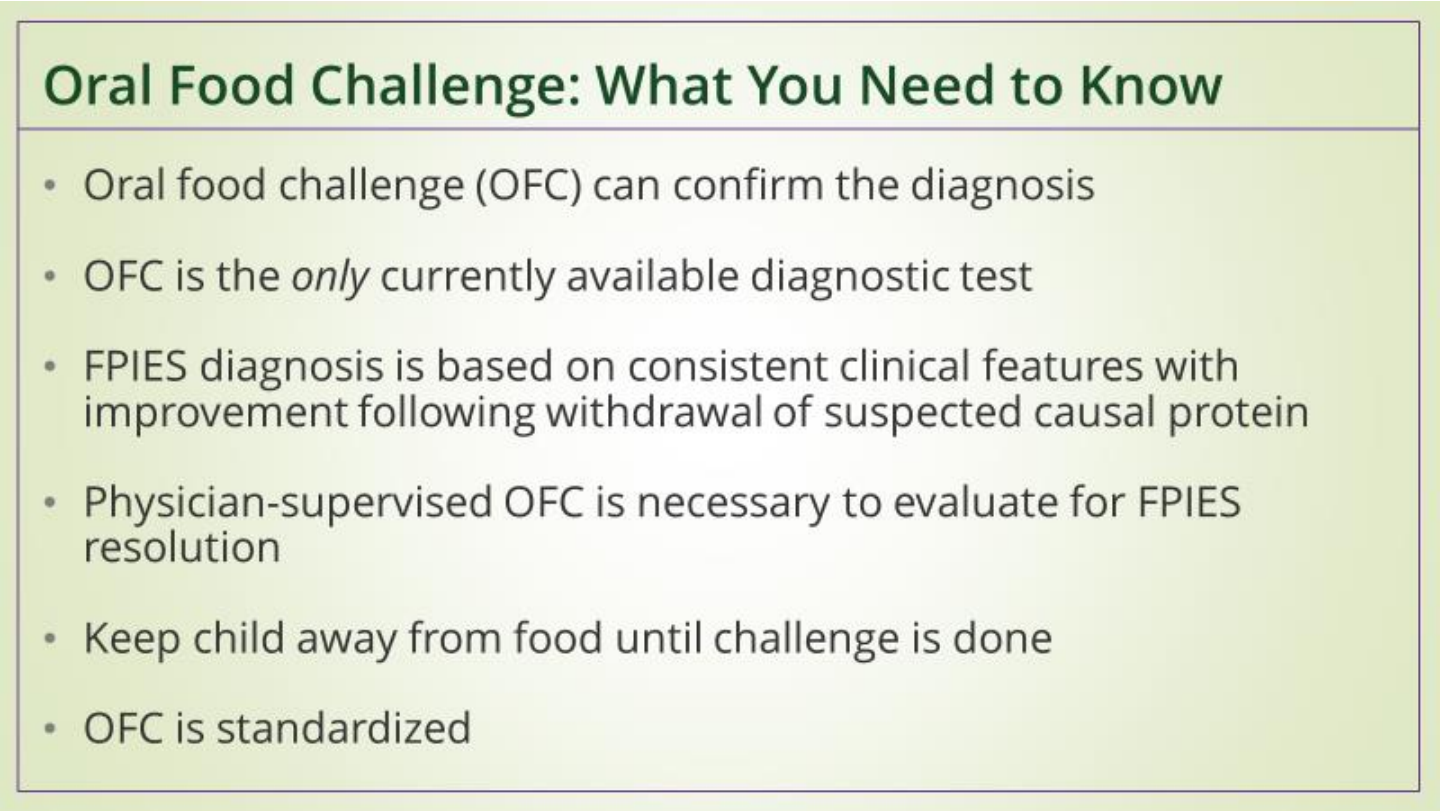


Figure 8–Oral Food Challenge: What You Need to Know

· Return to Index ·

FPIES Management Strategies

The current standard of care of food allergies is eliminating the offending food from the diet, which eliminates or reduces the risks of symptoms. However, it is associated with a nutritional deficiency in the long term. The guidelines recommend involving a nutritionist in the management to avoid unnecessary restrictions.

Accidental reactions can happen. Patients must be prepared. Because the recognition of FPIES is still not great, **we recommend written emergency treatment plans**. Go to the emergency room; call 911; and in a severe reaction, the child will need fluids to recover.

In mild reactions, such as vomiting—1 or up to 3 times—without lethargy or pallor, home management can be attempted unless this child has a severe reaction. In which case, go to the emergency room; call 911, because those reactions may be difficult to manage. **Every patient should have an individualized allergy action plan for FPIES.** We are sharing a letter that can be provided to the emergency room (see **Figure 9**), explaining what FPIES is, how it differs from classic food allergy, and suggesting treatments.

Because FPIES has a different pathophysiology than IgE-mediated food allergies, antihistamines and epinephrine are not usually helpful for FPIES reaction. A child experiencing an acute reaction should be evaluated for dehydration; the best treatment is rehydration, accomplished quickly with intravenous fluids.

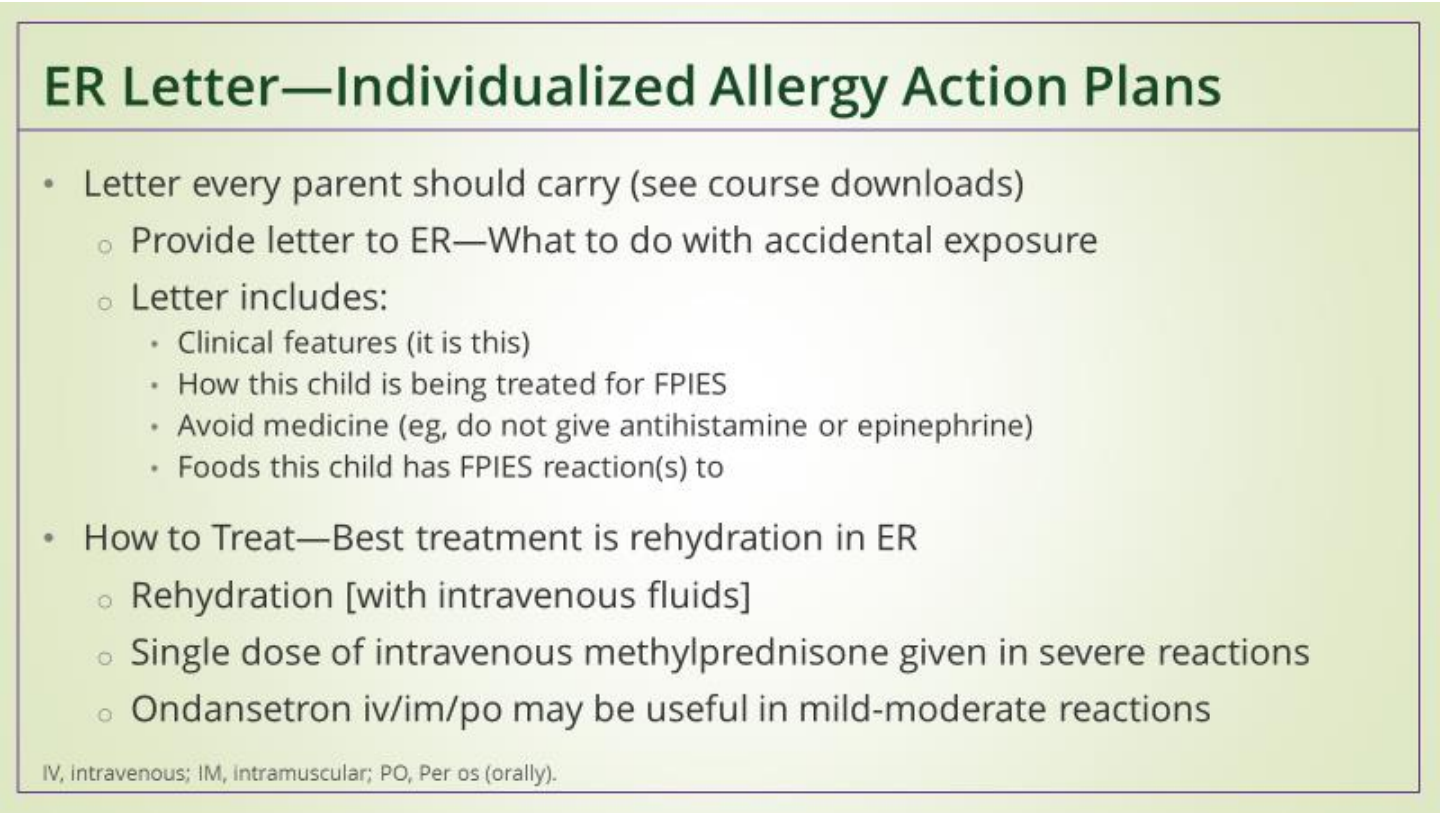


Figure 9–ER Letter—Individualized Allergy Action Plans

In severe reactions, a single dose of methylprednisolone is given. There are no clinical trials evidenced; it's an empirical, experienced-based decision. Ondansetron, which is antiemetic, can be used in mild-to-moderate reactions.[29] It also can be used given IV in severe reactions, but its efficacy is better in mild and moderate reactions.

Children or infants with FPIES do not usually react to trace amounts of food, such as from potential cross-contamination. They should avoid large concentrated amounts of the food, unless they reacted before to a minuscule amount. A periodic reassessment for tolerance should be done every 12 to 24 months. You could attempt a food challenge within 6 months, if the food is extremely important or the child had accidental exposure to a large amount without any symptoms in the interim.

It is important to pay attention to feeding skills and timely introduction of complementary solid foods. This will require active involvement of an allergist, who can offer to introduce complementary solid foods in the office under supervision, to encourage the parents, caregivers, to build their confidence.

In the long-term management of FPIES, nutritional management is critical. We want to avoid any nutritional deficiencies from restricted diets, which may restrict many nutrients, such as fiber, micro and macro elements, and vitamins. Nutritional support is essential. The assistance of a dietician is recommended to help identify foods for introduction and to avoid unnecessary nutritional delays.

In daily management, there is no need to avoid traces or food with precautionary labeling, such as, "they may contain trace amounts." In FPIES, unless the child has had a challenge to baked milk or egg, or has had documented frequent ingestion without symptoms, they should avoid baked milk and egg. Dietary consultation is always welcome and should be considered in those with multiple reactions, as well as in breastfed infants.

There is a concern for co-reactivity, especially in infants less than 6 months of age. Frequently, those who react to milk will also react to soy. Those who react to solid foods, such as rice, will also have a high risk of reacting to oat—about 40% to 50%. Keep this in mind when choosing new or additional foods for introduction, to minimize the risk of reaction.

Introduce solids in a timely manner. From IgE-mediated food allergy we have learned that unnecessary restriction and delay of introduction of potential food allergens is counter-productive. It can be detrimental and promote the development of new allergies.

FPIES, in contrast to allergic proctocolitis, is uncommon in exclusively breastfed infants. It may occur; those infants may have acute or chronic symptoms attributed to the foods ingested in a maternal diet. If a child reacts to milk upon direct feeding but is thriving and growing when the mother is ingesting dairy, there is no recommendation to eliminate dairy from maternal diet (see **Figure 10**).

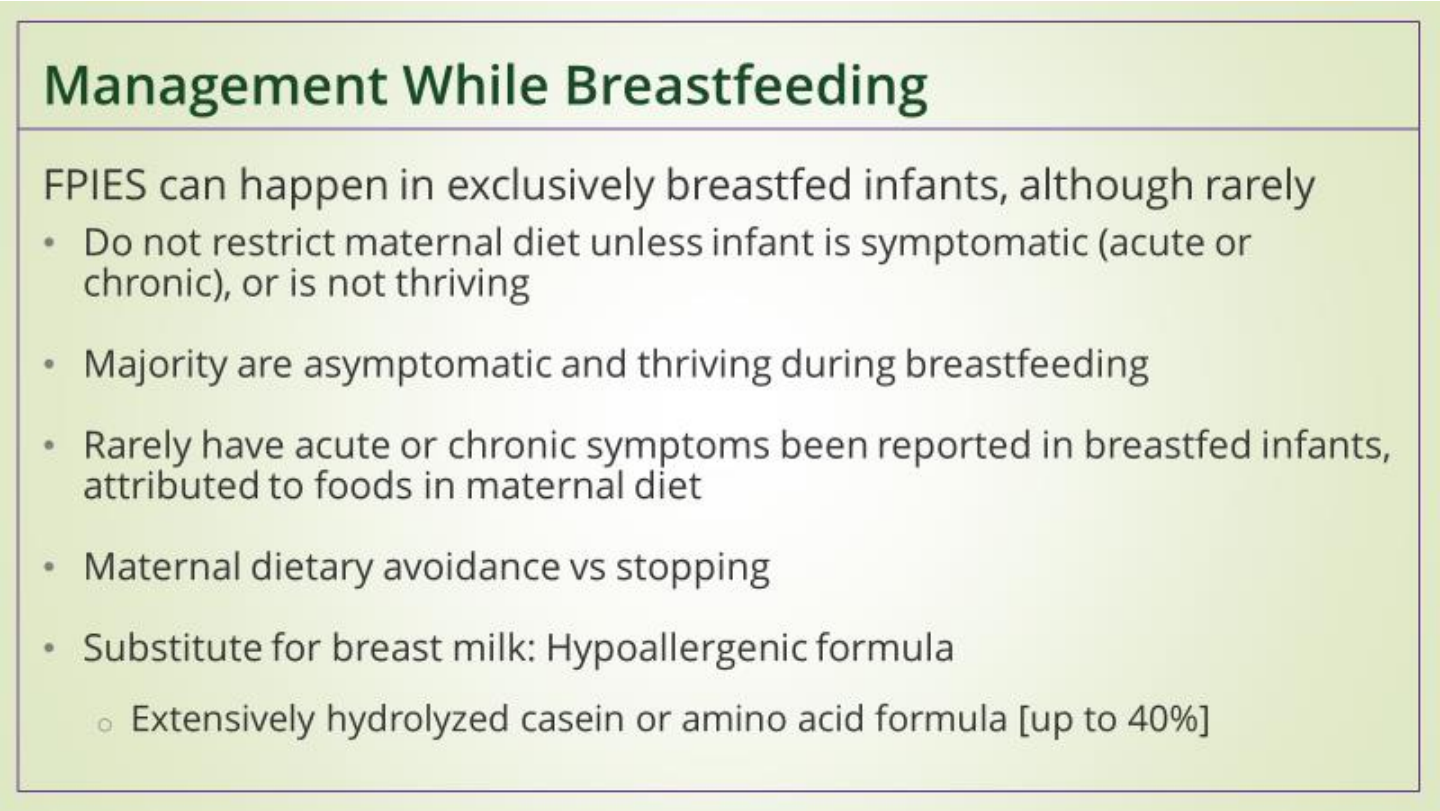


Figure 10–Management While Breastfeeding

If the child reacts to multiple foods or is having problems with growth or chronic symptoms, and the offending food cannot be clearly diagnosed, we would consider stopping breastfeeding. Then, it is important to provide a nutritionally complete substitute for breast milk. In case of infants with FPIES, we use a hypoallergenic formula. A majority do tolerate extensively hydrolyzed casein-based formulas, however, up to 40%—it's probably a higher percentage among those with very severe reactions—may require an amino-acid formula for long-term management.

Table 5 is based on the collective clinical experience of the physicians and nutritionists writing the guidelines.[25] The list of lower-risk foods can be used for introduction. In the youngest infants, we recommend starting with vegetables, such as broccoli, cauliflower, parsnip, and pumpkin. The moderate- and higher-risk foods are based on published reports and experience.

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Table 5– Selecting Safe Nutritional Alternatives

Ages and Stages	Lower-risk foods	Moderate-risk foods	Higher-risk foods

4 to 6 months (per AAP, CoN)
• If developmentally appropriate, and safe and nutritious foods are available:
  • Begin with smooth, thin, purees and progress to thicker purees
  • Choose foods that are high in iron
  • Add vegetables and fruits
	Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)

6 months (per WHO) • Complementary feeding should begin no later than 6 months of age. • In the breastfed infant, high-iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age. • Continue to expand variety of fruits, vegetables, legumes, grains, meats, and other foods as tolerated.	Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
8 months of age or when developmentally appropriate • Offer soft-cooked and bite-and-dissolve textures around 8 months of age or as tolerated by infant.	Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Higher iron foods: Fortified, infant rice and oat cereals.
12 months of age or when developmentally appropriate • Offer modified tolerated foods from the family table: chopped meats, soft cooked vegetables, grains, and fruits.	Tree nuts and seed butters* (sesame, sunflower, etc)	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

For 6 months of age, other foods are listed, in addition to those introduced at younger ages, as well as at 8 months. At 12 months, introduce tree nuts and seed butters, as well as peanut as a moderate-risk food. Any food can cause FPIES. This is a general guide.

Note that you can provide different textures and different amounts of the food, such as finger food, as well as spoon-fed food.

FPIES has a significant impact on quality of life to caregivers. It is associated with financial costs to parents who make special arrangements for a child's care.

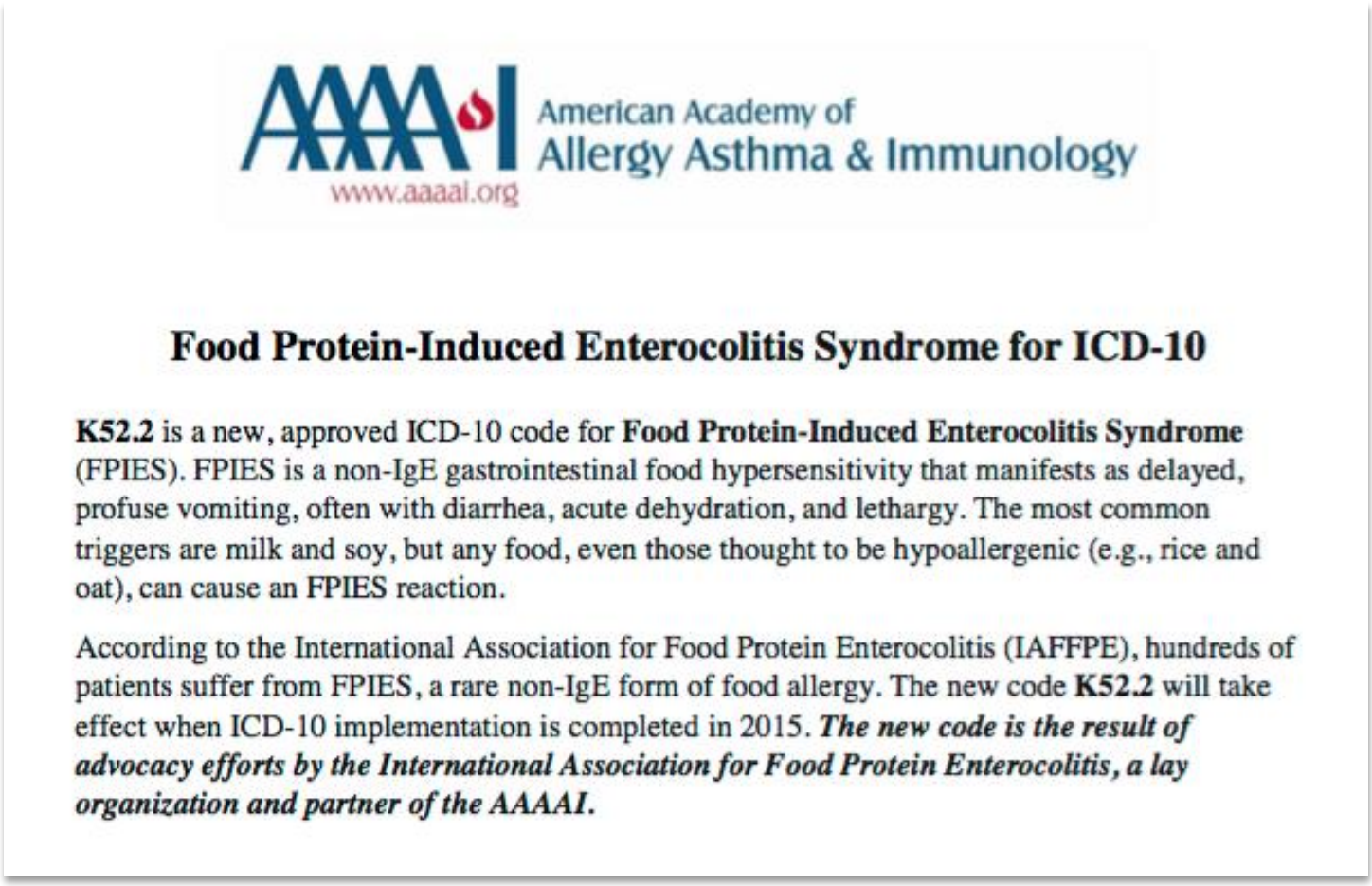
Remember **FPIES is a delayed food allergic reaction that can be very serious.** To date there are no fatalities from FPIES, but some reactions during supervised food challenges are among the worst I've seen. Those patients end up in the ICU and on life support because of dehydration, hypertension, acidosis.

This is not antibody-mediated reaction, so it must be cell-mediated, but we don't exactly know which cell subset is causing it. The management of FPIES relies on avoidance of the food trigger and periodic re-evaluation for resolution, during a supervised oral food challenge.

Clearly, there are many unmet needs in FPIES. Because we don't know the pathophysiology, we are lacking diagnostic biomarkers, and because we don't understand pathophysiology, we don't have therapies to accelerate resolution.

This is the only known IgE-mediated food allergy that has the potential to cause serious reactions. If you are considering a diagnosis of chronic FPIES in an infant, it means you should be referring this patient for a food challenge when it's time to try this food again. Nutritional consultation is recommended, especially in breastfed infants, as well as in infants who have multiple food triggers.

The FPIES ICD-10 code is K52.2 (see **Figure 11**) and we encourage you to use this code when seeing patients, because it will help track the frequency of this diagnosis, giving us a better idea about the impact of this condition.


American Academy of Allergy Asthma & Immunology
www.aaaai.org

Food Protein-Induced Enterocolitis Syndrome for ICD-10

K52.2 is a new, approved ICD-10 code for **Food Protein-Induced Enterocolitis Syndrome** (FPIES). FPIES is a non-IgE gastrointestinal food hypersensitivity that manifests as delayed, profuse vomiting, often with diarrhea, acute dehydration, and lethargy. The most common triggers are milk and soy, but any food, even those thought to be hypoallergenic (e.g., rice and oat), can cause an FPIES reaction.

According to the International Association for Food Protein Enterocolitis (IAFFPE), hundreds of patients suffer from FPIES, a rare non-IgE form of food allergy. The new code **K52.2** will take effect when ICD-10 implementation is completed in 2015. ***The new code is the result of advocacy efforts by the International Association for Food Protein Enterocolitis, a lay organization and partner of the AAAAI.***

Figure 11–Food Protein-Induced Enterocolitis Syndrome for ICD-10

With a greater understanding on how to recognize and distinguish FPIES from other major non-IgE-mediated food allergies, how to address acute reactions, and how to proceed with an oral food challenge for patients with suspected FPIES, we continue our discussion with the immunopathogenesis of eosinophilic esophagitis (EoE).

· Return to Index ·

Immunopathogenesis of Eosinophilic Esophagitis (EoE)

Mirna Chehade, MD, MPH, associate professor of pediatrics and medicine and director of Mount Sinai's Center for Eosinophilic Disorders and the Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai in New York, defines eosinophilic esophagitis (EoE) as a chronic immune or antigen-mediated esophageal disease with 2 features.[30] One feature is clinical symptoms related to esophageal dysfunction, and the other is the histological counterpart, which is an eosinophil-predominant inflammation of the esophagus.

There are 2 triggers that cause EoE: one is food allergens, based on multiple patients who went on food elimination trials with a change in their EoE disease activity. The other is environmental but the evidence for environmental allergens is still debatable. This is based on observations of patients with EoE who have a flare-up of their disease during the pollen season.

If we look at the allergic histopathology of EoE, we find eosinophils. **The eosinophils are the hallmark of the disease**, and they infiltrate esophageal mucosa.

The eosinophils are activated. **Figure 12** shows degranulation of the eosinophils by a special stain on the tissue.[31] We also see other inflammatory cells, such as mast cells, different types of lymphocytes, the CD4 lymphocytes, or the T helper lymphocytes. We have CD8 lymphocytes or T suppressor lymphocytes. We see dendritic cells in the esophagus, as well.

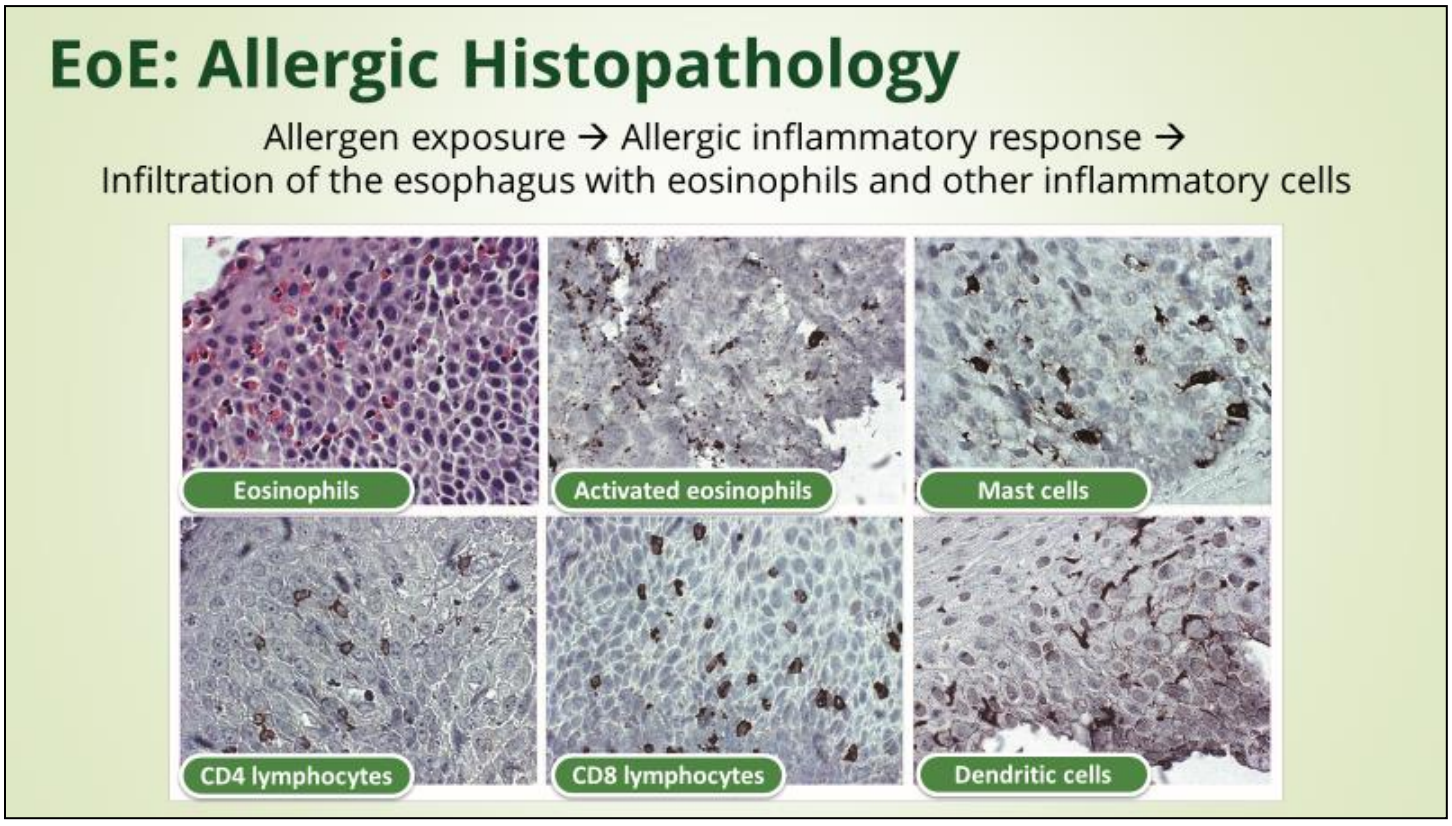


Figure 12–EoE: Allergic Histopathology

If we replace epithelium in this tissue with lung epithelium or skin epithelium, it would look like other atopic diseases, such as asthma or atopic dermatitis. The immune cells point to an allergic etiology.

When we look at the different cytokines in the esophageal tissue of patients with EoE (see **Figure 13**), we see an increase in IL-4, IL-13, and IL-5. All are known to be allergic T helper type 2 type of cytokines.[32]

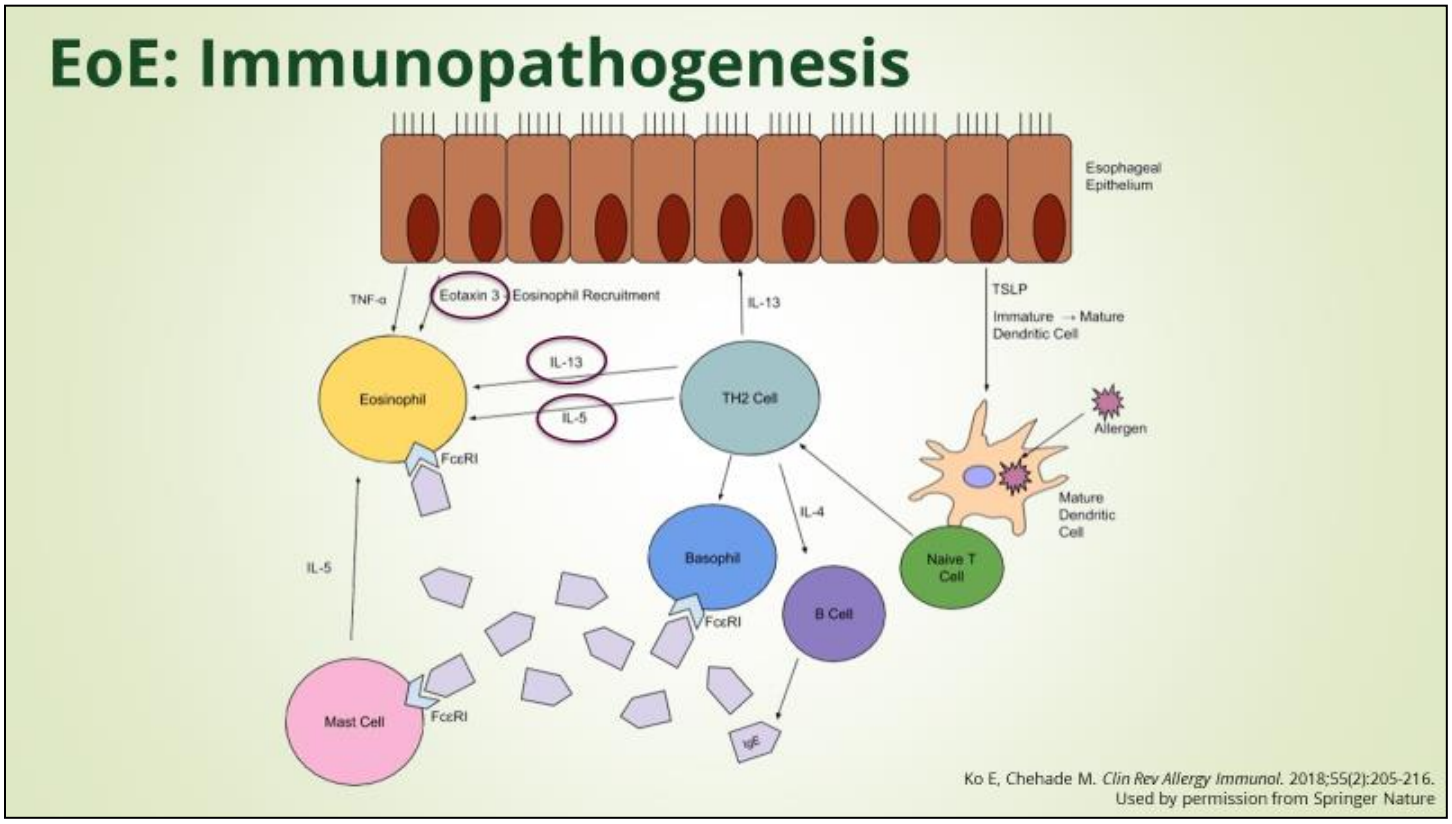


Figure 13–EoE: Immunopathogenesis

Upon exposure to a food trigger, the food goes into the esophageal mucosa, and it is taken up by dendritic cells that will transform the naïve T cells into a Th2 allergic type of lymphocyte. This results in secretion of IL-4, an allergic cytokine, as well as IL-5. IL-5 is responsible for eosinophilic proliferation on migration to the esophagus. The Th2 cell also produces IL-13, which induces the esophageal epithelial cells to secrete eotaxin-3, which in turn results in eosinophilic proliferation and chemotaxis to the esophagus.

With the understanding of the immunopathogenesis of EoE, with established allergic disease caused by food triggers and potentially by environmental triggers, **who are the patients that develop EoE, and how do we diagnose it?**

EoE can occur at all ages—anywhere from infancy to adulthood.[33] In terms of race, EoE has been more frequently reported in whites, but racial minorities are likely underdiagnosed.[34] EoE seems to be more common in males than females, with a male-to-female ratio of 3:1. EoE also tends to be more common in

patients with atopy and in patients with food allergy, specifically, IgE-mediated immediate food allergy.[35] It's also more common in patients with atopic diseases, such as asthma, allergic rhinitis, or atopic dermatitis.

There is also familial history in some patients with EoE. There may also be a genetic component to familial history, as well as potentially shared environmental effects.

· Return to Index ·

Diagnosing EoE in Children

Diagnosing EoE in children is challenging because symptoms vary with age. The younger the patient, the more nonspecific the GI symptoms, which can pose challenges in clinical practice. To differentiate EoE, look for the following signs: early satiety, failure to thrive, personal or family history of food allergy, personal or family history of atopy, and history of allergic gastrointestinal symptoms in infancy.

If the child has a history of blood in the stool in infancy and responds to a hypoallergenic formula instead of a cow's milk-based formula, that patient could have had an allergic GI manifestation in infancy, and has a red flag to suspect EoE.[36, 37]

The other challenge identifying children with EoE is the potential for subtle symptoms due to feeding behaviors. EoE is a chronic disease, and it smolders slowly where you have progression over time.

If you ask the patient or the parent, "Is there trouble swallowing?" They may say no. You need to ask additional questions: Does the child take too long to finish a meal? Does the child have prolonged chewing? Does the child pocket food in the mouth? Is there a need to drink with every bite of food? Does the child cut foods into very small pieces? Do they need to lubricate tough or lumpy foods with condiments or dunk them in liquids? Or do they avoid tough or lumpy foods, or refuse certain foods?

Adults may tell you they avoid meat or dense breads due to EoE; however, a child may not be able to differentiate which foods are the problem. They may generalize and start avoiding foods.

It is important to ask, “What do you like to eat?” I always ask, "Can you handle a bagel?" If they say yes, then do not stop there. Ask, "How do you eat it? Do you always add cream cheese?" This is just one example of how you can adapt questions according to what your patient eats.

Now that we know what to ask in terms of symptoms, how do we diagnose it? The diagnosis still rests on an endoscopy with esophageal biopsies.

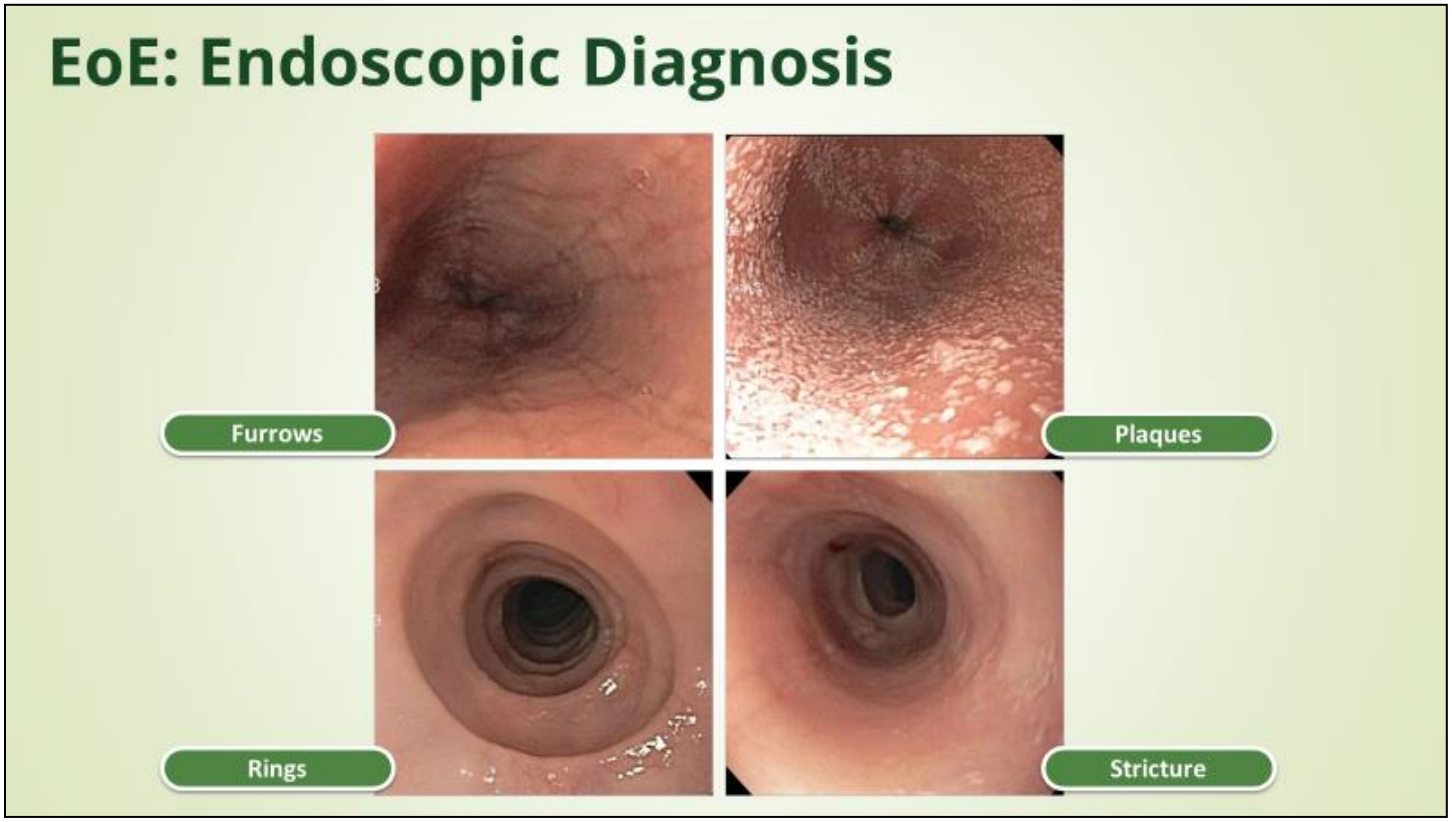


Figure 14–EoE: Endoscopic Diagnosis

See the examples from an endoscopy (see **Figure 14**). On the top left, furrows go down the links of the esophagus. Or plaques can appear, seen here as white dots on the right top panel. These are not due to a candida infection of the esophagus but are a collection of eosinophils up the surface lining. Sometimes you have rings, as seen in the lower left. That is also referred to as trachealization of the esophagus. Patients with severe disease may have a stricture, as seen in the lower right panel, which is rare in the pediatric population.

Note that an endoscopy can be completely normal in 20% of patients. **This emphasizes the importance of taking biopsies regardless of the endoscopic findings.** If we see a normal mucosa, but you suspect EoE, a biopsy is important. Multiple biopsies are important so as not to miss the diagnosis of this patchy disease.

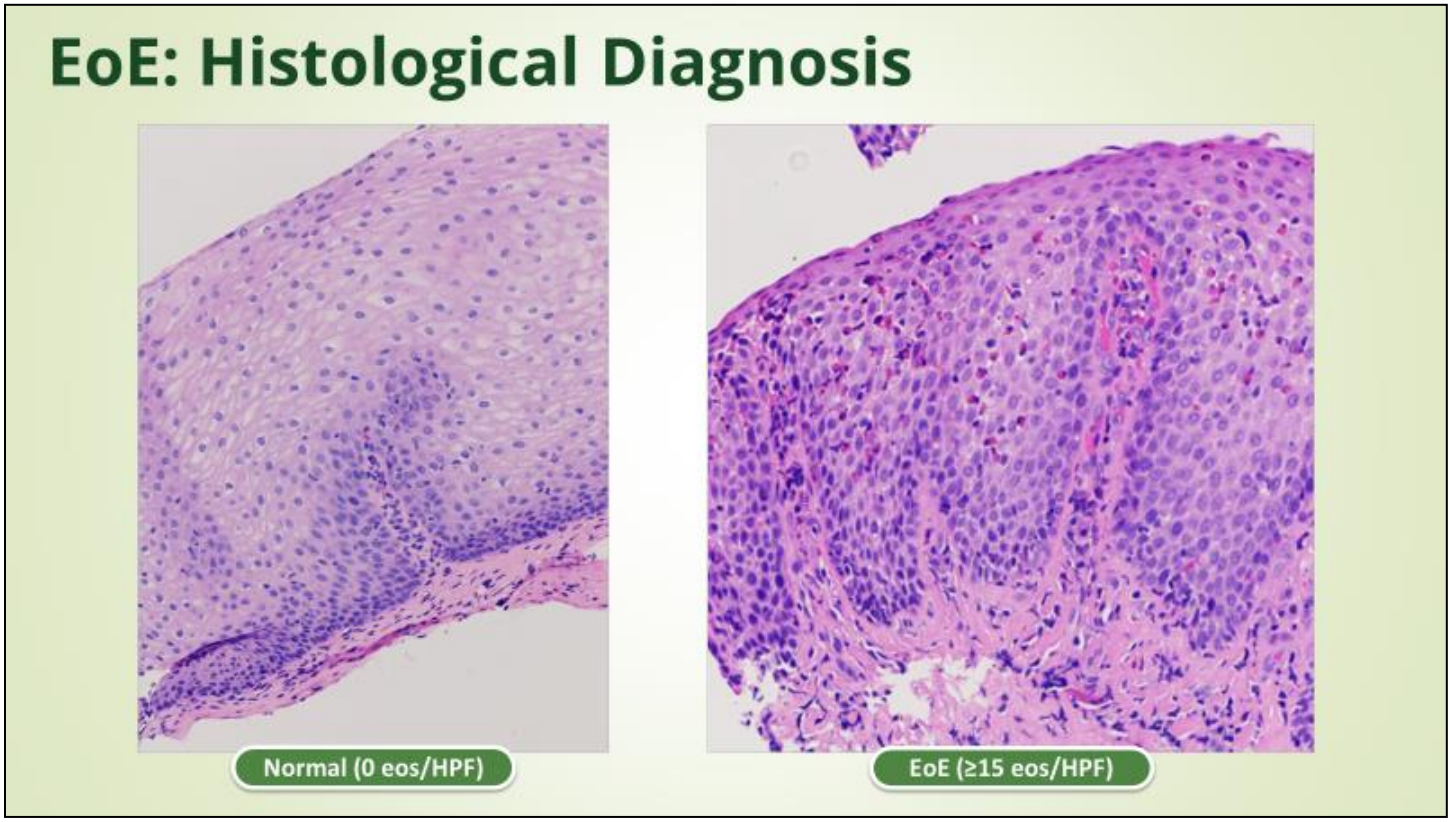


Figure 15–EoE: Histological Diagnosis

The left panel (see **Figure 15**) is what a section or a hematoxylin, eosin stain section from a biopsy of a healthy individual would look like. You can see the stratified squamous epithelium. The top part is the luminal. The lower end is the deep end of the biopsy. You can see it is staining blue, without eosinophils. We should have zero eosinophils in the esophagus of a healthy individual without any esophageal disease.

On the right, in contrast, you see a hematoxylin and eosin stain section from a biopsy of a patient with EoE. Notice the pink-stained cells infiltrating the esophageal mucosa. If we have 15 or more eosinophils per high-power field (HPF), this establishes the histological diagnosis of EoE.

Sometimes eosinophils go all the way to the surface layer. The top is the luminal, where the esophagus is exposed to food. The lower section is the deep end of the biopsy.

In **Figure 16**, notice the eosinophils accumulating and layering, causing a micro abscess, resulting in the white plaque appearances, seen in the endoscopy earlier. If you look at the right panel, you see degranulation of these eosinophils. With these little dots outside the cells, you can demarcate by the eosin stain, which is another feature present in EoE.

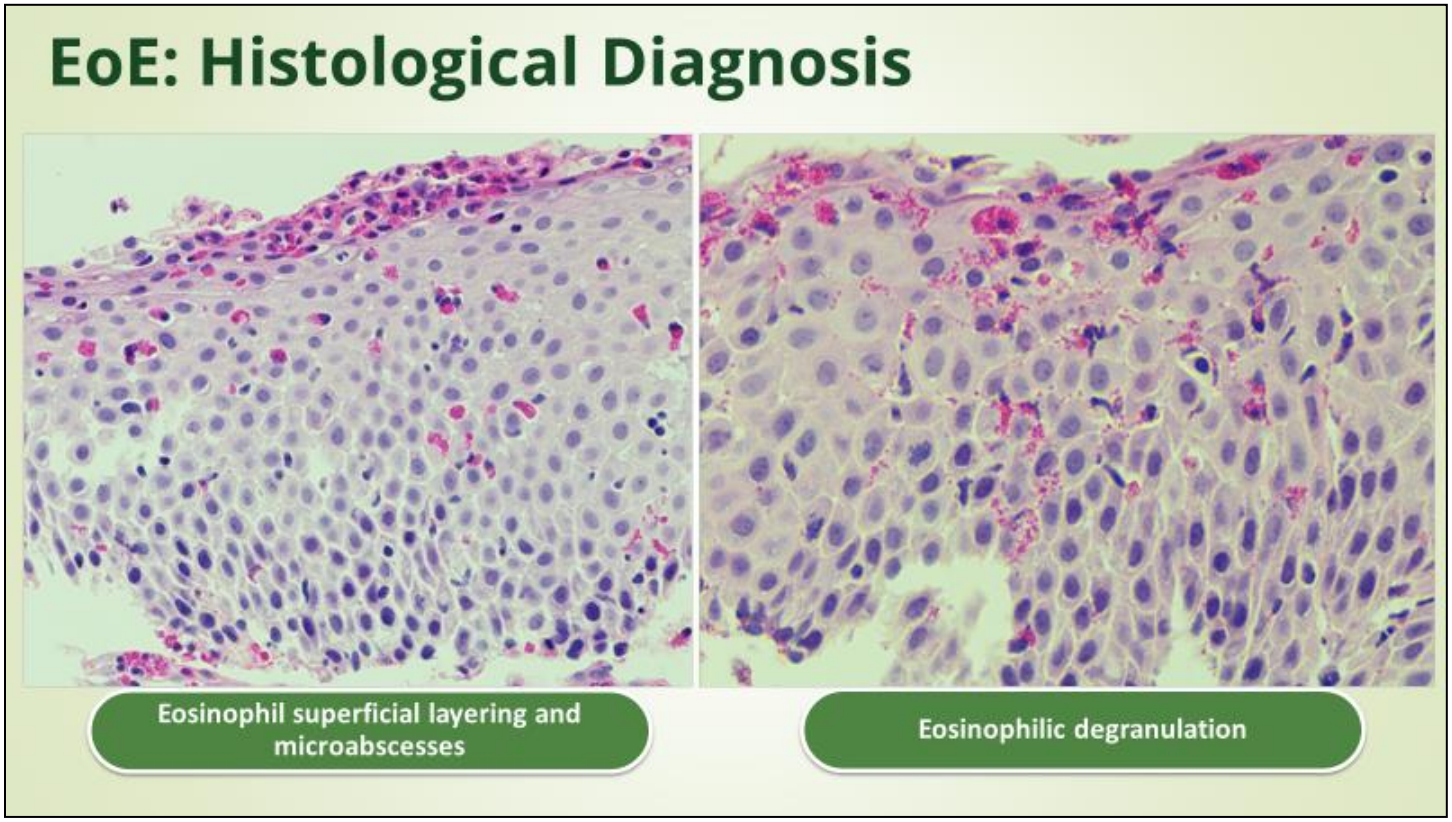


Figure 16–EoE: Histological Diagnosis

Symptoms along with an endoscopy, and a biopsy showing eosinophils, provides the diagnosis. According to the 2011 guidelines,[38] however, we needed to diagnose EoE symptoms with a trial of proton pump inhibitor (PPI) therapy—PPIs being antacids—to rule out PPI-responsive esophageal eosinophilia or PPI-REE. This is because many patients who had symptoms of EoE and the histological features of EoE, responded to PPIs at a high dose. These patients need to be ruled out to confirm the diagnosis of EoE.

Research since 2011 has shown similarities between PPI-REE and EoE, almost indistinguishable clinically, endoscopically, and histologically.[39, 40, 41, 42, 43] These reports show adults with PPI-REE respond to an elimination diet therapy targeted for EoE instead of a PPI.

With evidence indicating EoE and reflux can concurrently exist, a recent update has been made to the EoE diagnostic criteria stating if you have a clinical presentation suggestive of EoE, and you do an upper endoscopy with biopsies demonstrating esophageal eosinophilia (ie, ≥15 eosinophils per HPF in the esophagus), all you need is to evaluate for non-EoE disorders that can cause or potentially contribute to esophageal eosinophilia.[44]

If these are ruled out, you have the diagnosis of EoE. You do not need to use a PPI therapy as an empiric trial to confirm the diagnosis of EoE. PPI is offered to the patient as a treatment option as opposed to a diagnostic test.

We know EoE is a chronic disease. It can progress if left untreated from an inflammation-predominant to a fibrosis-predominant disease.

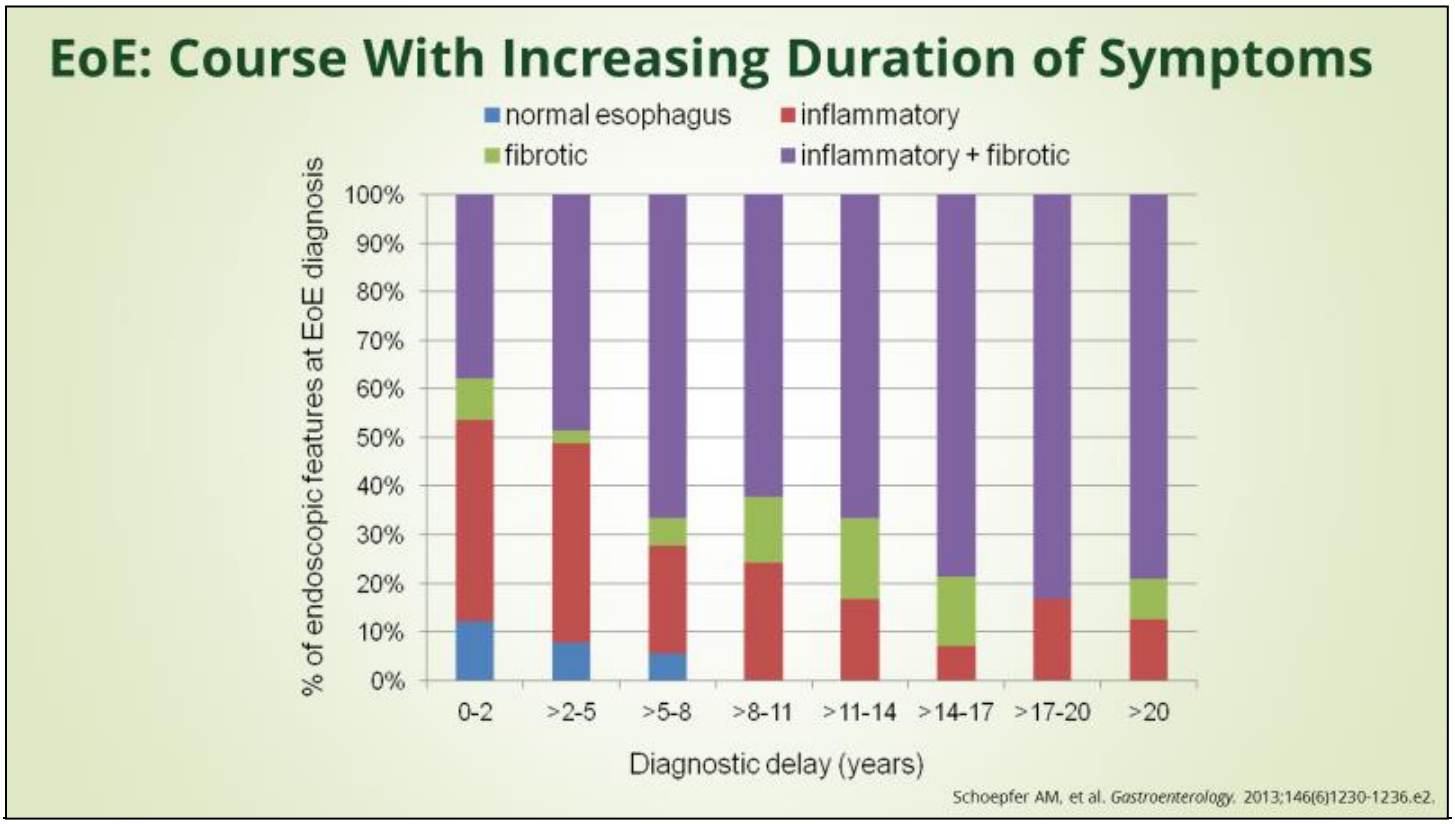


Figure 17–EoE: Course With Increasing Duration of Symptoms

In this chart (see **Figure 17**), the red bars represent inflammatory disease and the purple bars represent inflammatory *plus* fibrostenotic disease.[45] The longer the patients had symptoms before they got treated, the higher chance they had of both inflammatory and fibrostenotic features.

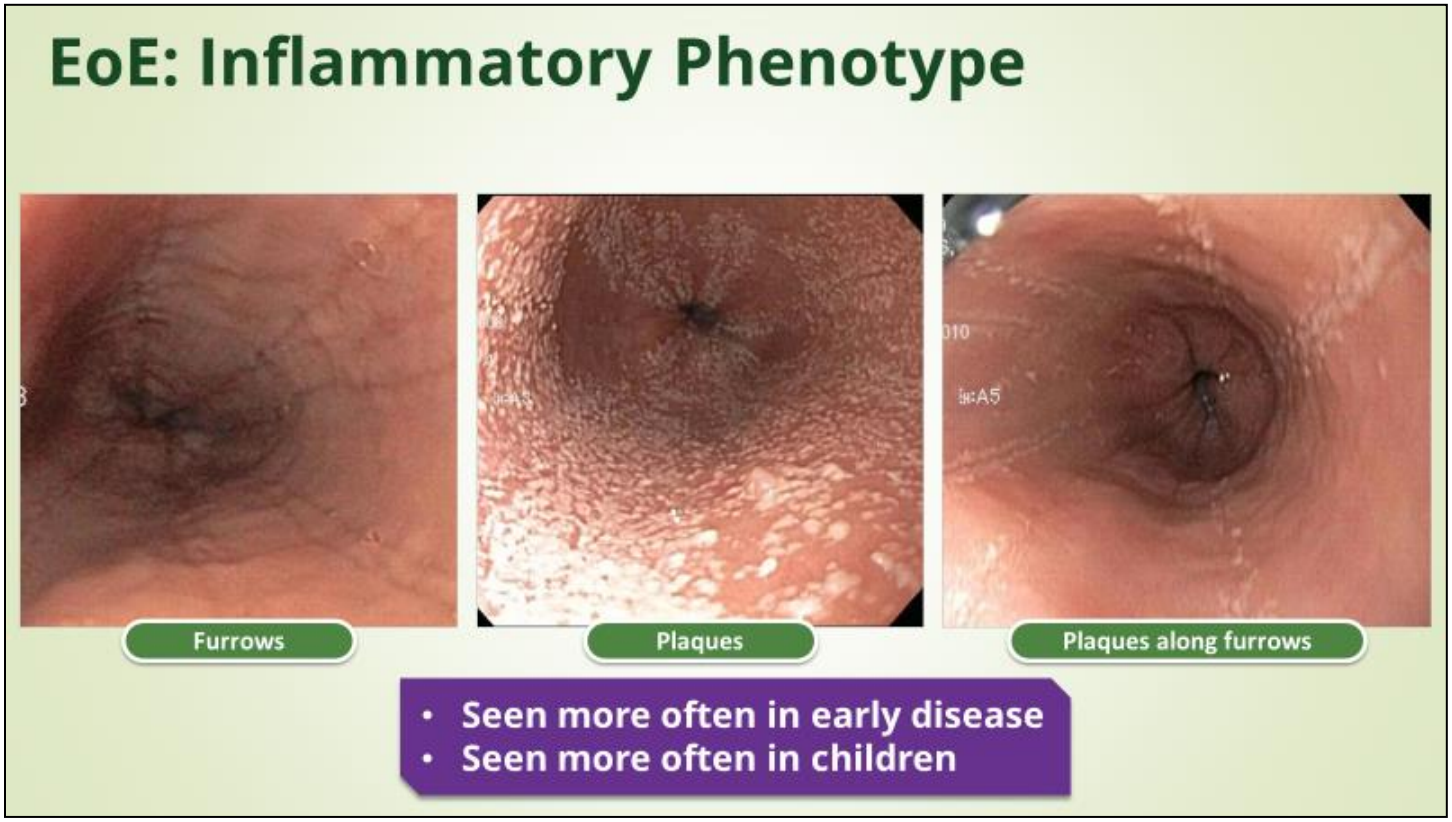


Figure 18–EoE: Inflammatory Phenotypc

What do inflammatory and fibrostenotic phenotypes look like? If we look at the esophagus with the endoscope in **Figure 18**, we can see the furrows, white plaques, as seen earlier. Sometimes you see the plaques lining up along the furrows. These represent the inflammatory phenotype, which is seen more often in early disease and in children.

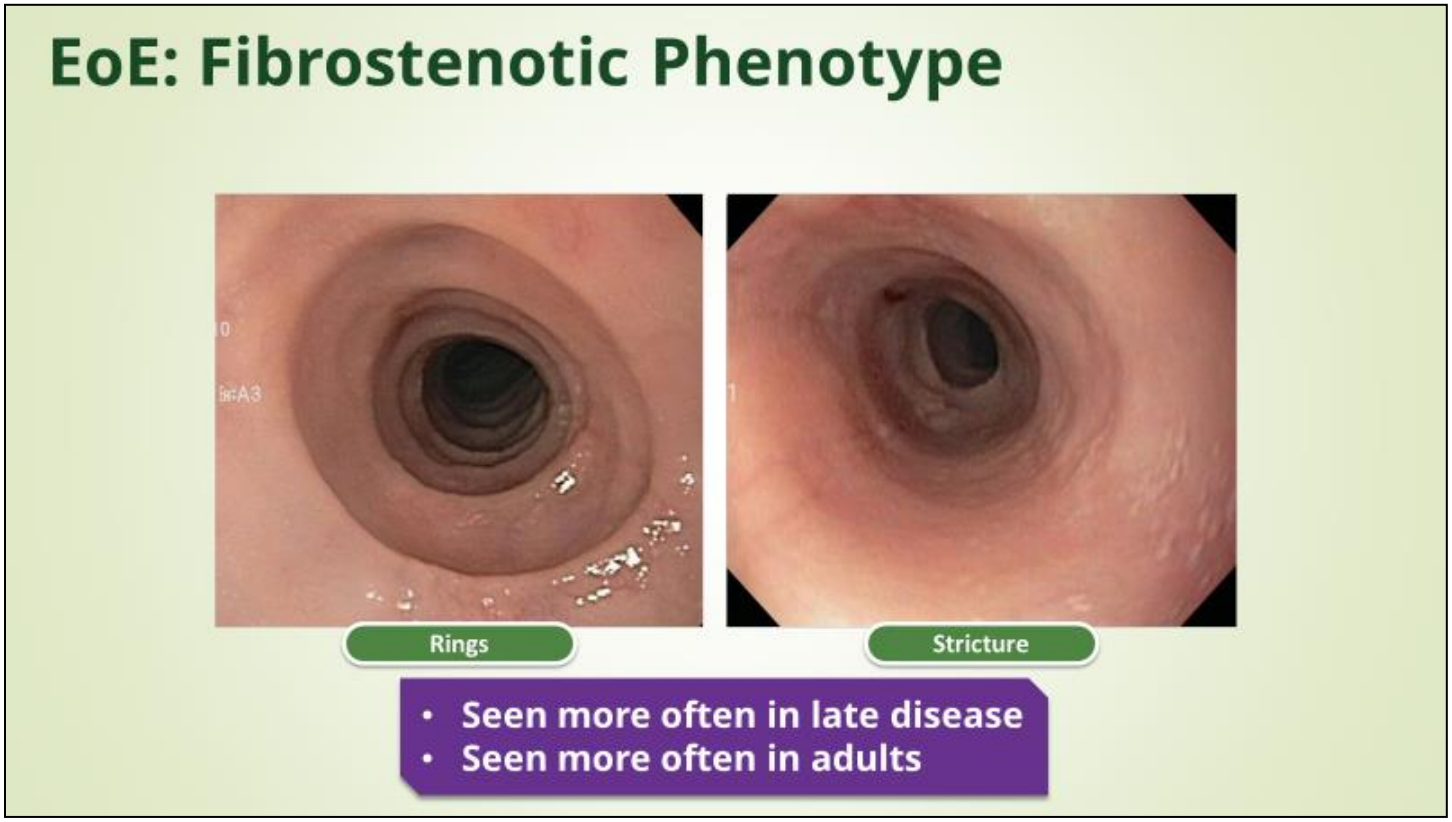


Figure 19–EoE: Fibrostenotic Phenotype

In the fibrostenotic phenotype, we see features of remodeling. Rings, as described earlier, are an example of fibrostenotic phenotype, and a stricture (as seen in **Figure 19**) is due to esophageal remodeling and fibrosis formation. These features are seen more often in late disease and, therefore, seen more in adults whose diagnoses have been missed.

Luckily in children, fibrosis can be reversed with diet or with topical corticosteroids. This was the result from a study, published in 2012.[46] With only 3 months of therapy, we saw a reversal of the fibrosis.

This (see **Figure 20**) shows a trichrome stain of a biopsy section from a patient with EoE.[46] The top is the epithelium—the stratified squamous epithelium in red. The bottom is the collagen, which sits under the epithelium.

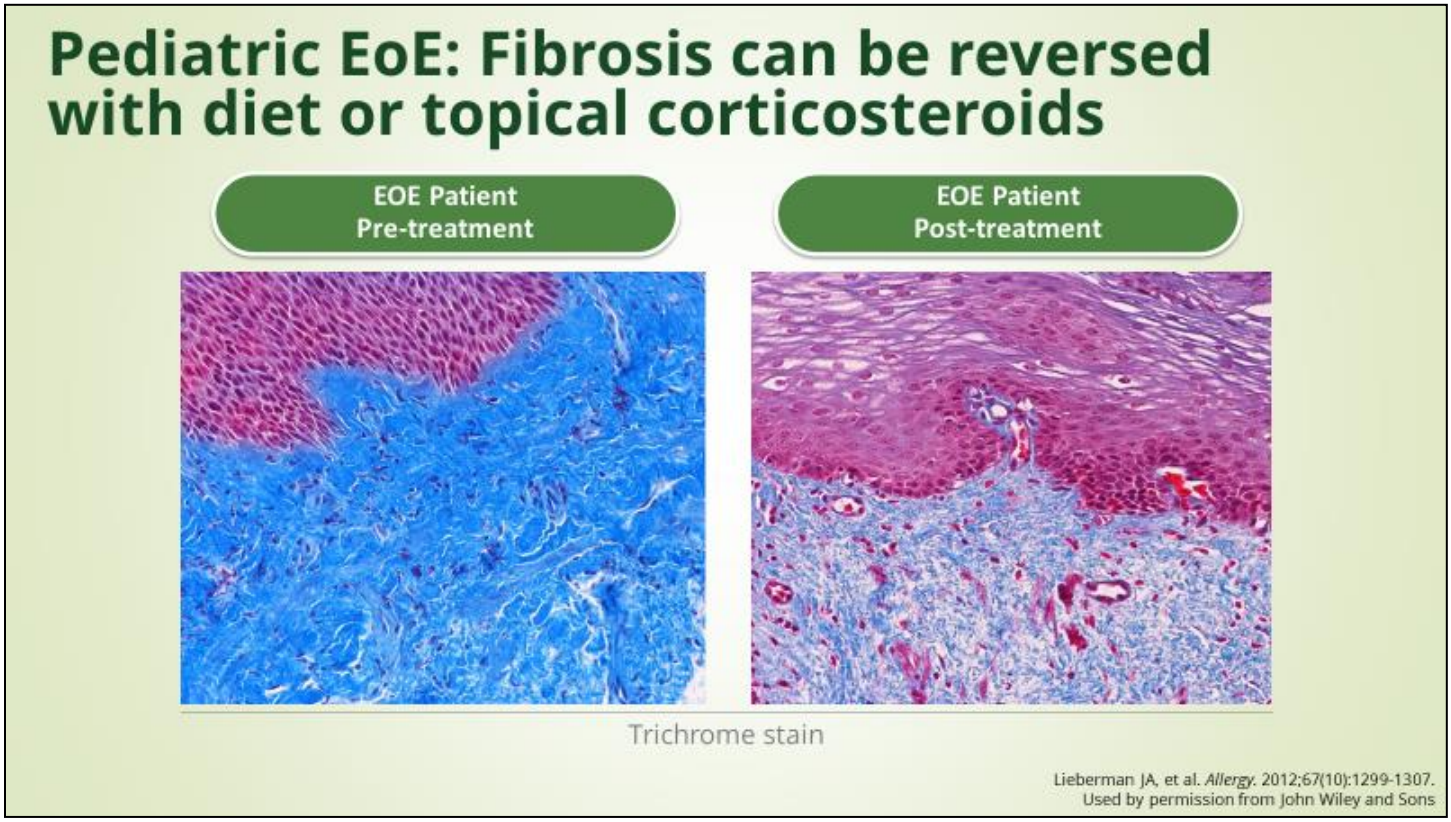


Figure 20–Pediatric EoE: Fibrosis can be reversed with diet or topical corticosteroids

On the left panel, dense collagen strands form the fibrosis. After 3 months of treatment, notice the blue lacy appearance of the collagens after treatment, which emphasizes the importance of treating children with EoE, not only to reverse their symptoms but also potentially to reverse long-term complications.

An EoE diagnosis is based on clinical, endoscopic, and histological criteria. Symptoms can be nonspecific in children with EoE. It is important to be aware of the red flags, so you don't miss them. If left untreated, EoE can lead to fibrostenotic complications, hence the importance of treatment.

· Return to Index ·

Treatment options for EoE—Focusing on diets and medications

When we treat EoE, we want to reduce symptoms of esophageal inflammation, reverse existing disease complications, and prevent future complications. Commonly used therapies include dietary restrictions and topical corticosteroid therapies. Another commonly used modality is dilation of the esophageal strictures; however, we will not be discussing dilation because strictures are not as common in children as adults. Also, dilation does not help as an anti-inflammatory treatment; it only breaks down fibrotic tissue to relieve symptoms.

Three different diets have been accepted as "standard of care." One is the **elemental diet**, consisting exclusively of feeding a child with an amino acid-based formula. Also, there is a modified elemental diet, which is exclusive feeding with an amino acid-based formula, but adds 1 to 2 foods to the child's diet. The second is the **test-directed elimination diet**, where you remove foods based on the results of skin tests, including both prick skin and patch tests. The third diet is the **empiric elimination diet**, which removes foods known to be common food allergens, without any testing.

The histological remission with the elemental diet means feeding the patient with an amino acid-based formula. Studies show a 91% efficacy,[47] without much difference between children and adults. Children had a 90% chance of histological remission with the elemental diet. This diet is effective; however, it can be hard to achieve, even in motivated patients. It can be hard to push the large volume of amino acid-based formula to meet the caloric requirements and may result in the use of tube feeding. As a result, other less restrictive diets have evolved, such as the test-directed elimination diet and the empiric diet.

Data from a meta-analysis shows histological remission to a 6-food elimination diet, which means avoiding milk, wheat, egg, soy, nuts (ie, peanuts and all tree nuts), and seafood (ie, fish and shellfish). We have a combined histological remission rate of 72%, so it performed slightly better than a test-directed elimination diet. Again, we have comparable results in children at 73% and adults, at a 71% remission rate.[47]

Again, these diets are not easy, even when removing 6 foods. An attempt was made to reduce the extent of this dietary restriction further, which resulted in the 4-food elimination diet. This evolved by having patients who responded clinically and histologically to a 6-food elimination diet. Then we re-challenged with one food at a time to establish the most common foods among those removed.

A multicenter study by Kagalwalla and colleagues was conducted,[48] where 78 children underwent a 4-food elimination diet for 8 weeks. Foods removed included milk, wheat, egg, and soy, and resulted in a 64% remission rate. Then sequential reintroduction of foods was followed by biopsies. Triggers were identified and rated according to which was more to least common. The study showed milk was the most common food trigger, in 85% of patients, followed by wheat, egg, and then soy.

The empiric elimination diets are based on these results in children, including the 6-food elimination diet, with a remission rate in children of 73%. Four-food elimination diet has a 64% remission rate. The 2-food elimination diet, includes the removal of milk and wheat, resulted in 43% remission rate.[47, 49, 50]

If we restrict this to just 1 food—milk elimination only—the remission rate is not yet established. However, this is now a trial,[51] and results are to be determined for the 1-food vs 4-food elimination diet: milk vs elimination of milk, wheat, egg, and soy.

Looking at the pros and cons of dietary restrictions, some diets are highly effective and allow identification of food triggers in a patient.[52] They also prevent the need for chronic medications with their potential side effects, and may reduce systemic inflammation vs local effect of medication.

Cons are the large effort diets require by the patient and family. Most of these diets require a specialized dietitian. Also, multiple endoscopies are needed to identify the food triggers. These diets are not effective when suspecting environmental allergens to trigger EoE in addition to the food elimination.

The best way to determine which children should get dietary therapy is to have a discussion with the family and to choose the patients who are right for this therapy. Factors to consider before choosing which type of dietary therapy include age and nutritional status of the child, feeding difficulties (if present), and self-restrictive behaviors towards foods. If a child has feeding difficulties and does not accept new foods when you remove foods, the diets become difficult.

The motivation of the patient, as well as the family, is important. The support system is also important—social support or the financial support system. Some specialized diets become expensive. The acceptance for multiple endoscopies and determining the minimum number of foods to be removed, is also to be taken into consideration.

A useful report, supported by the American Academy of Allergy Asthma & Immunology, published in 2017 in the *Journal of Allergy and Clinical Immunology in Practice,* outlines 5 steps implementing the diets.[53] First, assist the nutritional status, then eliminate dietary antigens. The third step is to individualize to meet nutritional needs. The fourth is to give practical tips on substitutions, and the fifth step is to provide monitoring.

Dietary therapy can also be used as a maintenance therapy. Diets can be gradually liberalized, reintroducing foods that do not trigger EoE, so the fewest number of foods are removed over time.

The challenge with food introductions is the difficulty identifying safe foods to add through trial and error. It is also important to watch for the rare chance of *de novo* acute allergic reactivity to a food that has been removed over a long time for EoE.[54] The role of the allergist becomes very important to clear that food

medically for food reintroduction. After long-term avoidance, the allergist will conduct a skin prick test, check serum food-specific IgE levels, or other criteria.

What's commonly used in a food challenge algorithm? When a food is challenged for 6 to 8 weeks, the patient is eating that food at home after clearance from the allergist is obtained, and no acute reaction will occur while eating it at home. The family is watching for any symptoms with that food. Then at least 8 weeks later, an endoscopy with biopsy is done.

If the biopsy shows eosinophilic esophagitis relapse, that food is a trigger, and the food is eliminated from the diet. If on the other hand, after adding that food, the biopsy shows the EoE is in continued remission—which means that food was never a trigger—that food can be kept in the diet. Then we move on to the next food, and the next. Each added, individually, until the minimum number of foods is avoided over the long run.

Dietary therapy can be effective in children with EoE. It is an optimal choice for eligible patients and motivated families, but ongoing support is needed for its success.

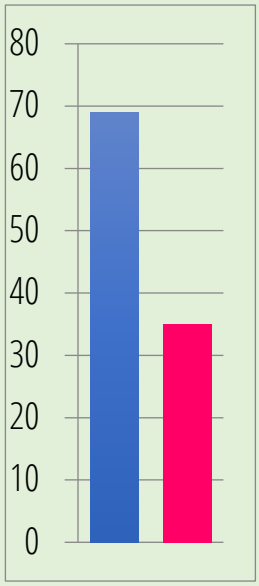
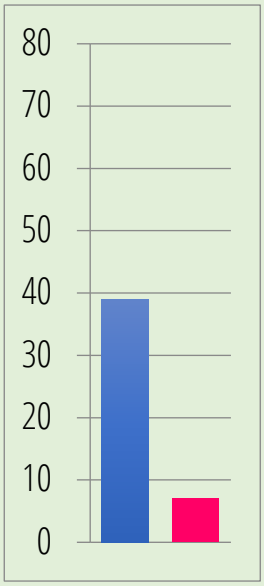
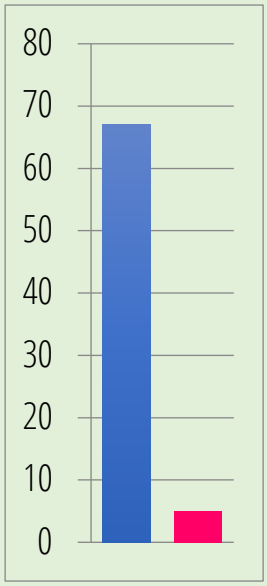
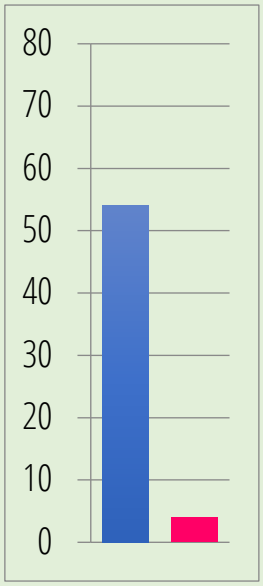
Let's discuss the role of proton pump inhibitors (PPIs) as a treatment, while referencing the changes in the guidelines noted earlier. The rate of histological remission using PPI is a combined remission rate of 50%. Children and adults are not much different: 54% remission rate in children and 50% in adults.[55] The dose of PPI used is 1–2 mg per kg per day in children, up to a maximum dose equivalent to an adult dose.

What about other medications? Topical corticosteroids are commonly used in children with EoE. The 2 commonly used formulations are fluticasone to swallow and oral, viscous budesonide to swallow. Note that none of the corticosteroids or other medications for EoE are approved for EoE by the FDA, yet.

How effective are topical corticosteroids? Table 6 shows the first randomized controlled trials, where topical corticosteroids were used in children.[56, 57, 58, 59] In this chart, see the agent in purple, which show budesonide and fluticasone were used in different studies. The treatment duration (in pink) was anywhere between 4 and 12 weeks. If you look at the corresponding graphs at the bottom, the blue bars represent pre-treatment with steroids, topical steroids, and the pink bars are post-therapy. The *y* axis is eosinophils per HPF in the esophagus. Some of the formulations, depending on the dose used and the drug used, were very effective.

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Table 6– EoE: Histological response to topical corticosteroids in children

RCT	Konikoff Gastro 2006	Schaefer CGH 2008	Dohil Gastro 2010	Butz Gastro 2014
No. subjects	36	80	24	42
Drug	**fluticasone**	**fluticasone**	**budesonide**	**fluticasone**
µg/day	880	880/1760	1000/2000	1760
Control group	placebo	prednisone	placebo	placebo
Blinding	DB	open	DB	DB
Rx duration	**12 weeks**	**4 weeks**	**12 weeks**	**12 weeks**
Eos/HPF 				

The 2011 guidelines state the recommended dose for fluticasone for children is 88–440 mcg, 2 to 4 times daily.[60] For budesonide, for children less than 10 years, the dose is 1 mg daily. For older children, it is 2 mg daily. The reason for the wide dose ranges is because effective doses have not yet been established.[60]

Currently ongoing studies include an oral budesonide suspension in phase 3, multicenter trial with an extension in teenagers and adults. (See ClinicalTrials.gov NCT02605837 and NCT02736409, if you would like to look it up further.)[61, 62]

The pros and cons of topical corticosteroids therapy: Some formulations are highly effective. Also, you don't have to remove foods when using steroids. These treatments will allow ingestion of the EoE food triggers and, therefore, improve the quality of life for patients with EoE. The cons include needing daily medication, and in most occasions, twice a day. There is also the concern for side effects, which can be topical, such as local candidal infection or oropharyngeal and/or esophageal. That may require treatment if it causes symptoms.[63] There is also a potential for systemic side effects, such as adrenal suppression. Some patients are more sensitive, or if we're using higher doses, we need to watch for potential adrenal suppression.

Which children should get topical steroids as opposed to a diet? Patients are selected based on a discussion with the family. Factors to consider before opting for medications are similar to diet and include the following: age, social settings, motivation of the patient and family, social, and financial support system, and when dietary therapy proves to be unsuccessful or too difficult to implement or continue in a child with EoE.

We can use topical steroids as maintenance therapy.[64] What often occurs is EoE relapses once topical corticosteroids are discontinued. Remember, EoE is a chronic disease. If topical steroids are controlling the disease and you stop them, without a plan, EoE will relapse. Hence, the need for long-term use of topical steroids. The effectiveness of long-term use, however, has not been well studied.

What about other medications? No talk can be complete without mentioning biologics to manage chronic diseases. **Figure 21** shows there are multiple ways cytokines could be targeted.

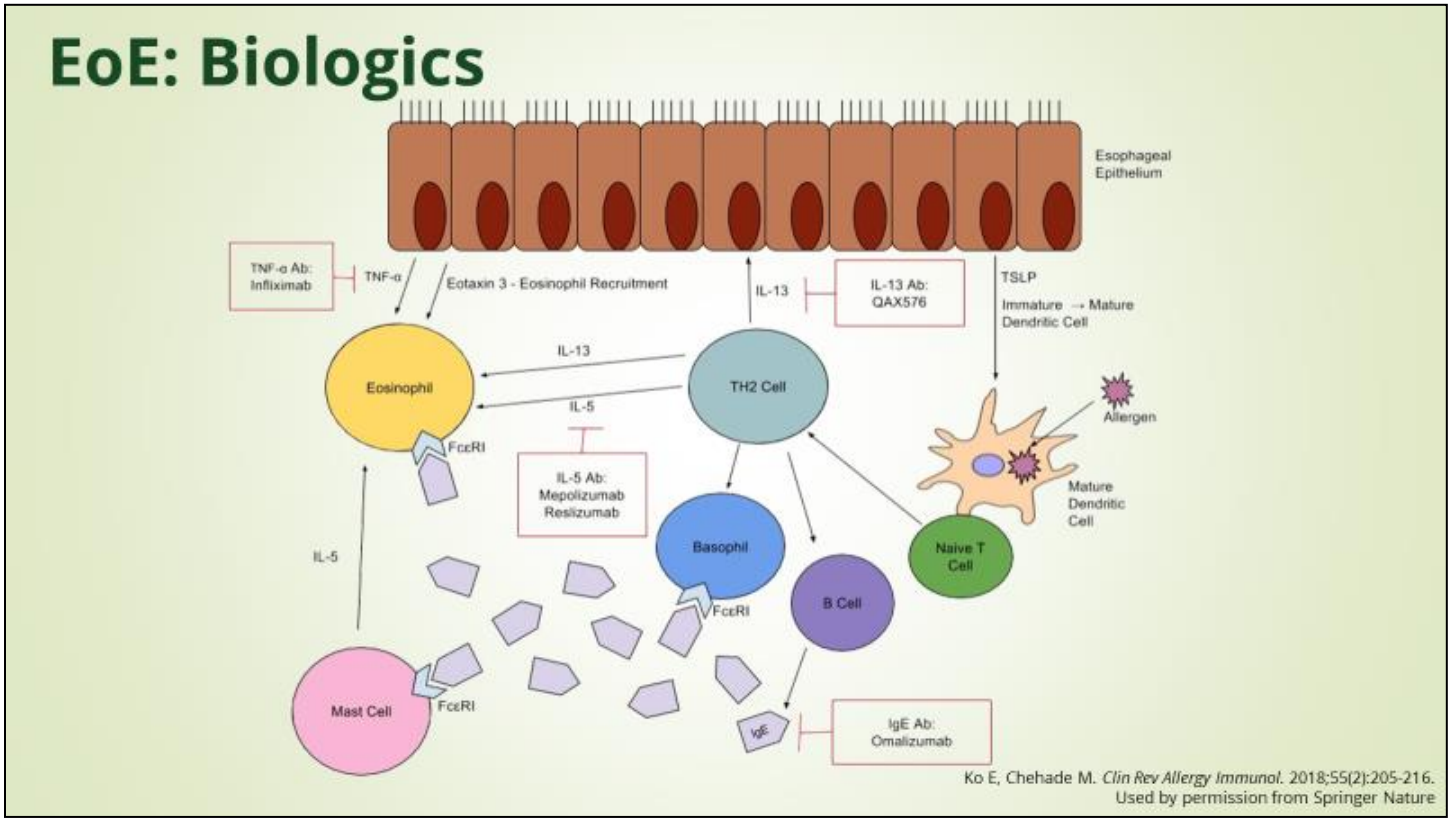


Figure 21–EoE: Biologics

An antibody to interleukin-5 (IL-5) has been used in 2 different trials. One using mepolizumab and the other using reslizumab.[65] Both resulted in histological improvement, but not much clinical improvement to warrant FDA approval.

The antibody to TNF-alpha (infliximab), as well as the antibody to IgE (omalizumab) were tried in a single-center, investigator-initiated study, but did not result in improvement. Anti-IL-13 was used (antibody QAX576) in a multicenter study in adults, and it showed histological improvement and a trend towards clinical improvement.[66]

Unfortunately, none of the biologics for EoE are currently under study for children, but 2 potential antibodies are being studied in adults. One is an IL-13 inhibitor (RPC4046), showing possible histological and clinical improvement in steroid refractory patients.[67, 68] Another targeting the IL-4 receptor to decrease IL-4 and IL-13 secretion, is dupilumab, also showing possible histological and clinical improvement in adult atopic patients.[69]

Note, none of the medications for EoE are FDA approved. Chronic therapy is needed. But the future does look promising, given the multiple studies being conducted in adults, and hopefully, if they show positive results, then potentially they will be studied in children.

Remember that EoE is a chronic disease. Left untreated, EoE can lead to fibrostenotic complications; hence, the need for early recognition and referral. Diagnosis is based on clinical, endoscopic, and histological criteria. Long-term treatment for EoE, whether by diets or medications, is essential to prevent complications. Ongoing involvement of pediatrician, pediatric gastroenterologist, allergist, and a dietitian provide the best outcomes for these children.

· Return to Index ·

Conclusion

Severe cow's milk allergy, Food Protein-Induced Enterocolitis Syndrome, and EoE, are unique IgE-mediated and non-IgE-mediated food allergies distinguished through the patient's clinical history, medical symptoms, as well as age and trigger of onset.

Cow's milk allergy is the most common allergen in infants, with milk accounting for approximately 95% of IgE-mediated food allergy in children. FPIES is a delayed allergic food reaction, which can be serious and is often misdiagnosed or delayed. It is a self-limiting food allergy of childhood, with a favorable prognosis, often resolving by age 3 or 5. Eosinophilic esophagitis is a chronic esophageal disease. Left untreated, EoE can lead to fibrostenotic complications. Diagnosis is based on clinical, endoscopic, and histological criteria. Biopsies are important when suspecting EoE so as not to miss the diagnosis.

The current standard of care treating an IgE-mediated allergy or a non-IgE, such as FPIES, EoE, and CMA, relies on identifying and then avoiding that food trigger. Management includes periodic re-evaluations with resolution recommended through a supervised oral food challenge elimination diet, which confirms the diagnosis of the specific food trigger. A nutritional consultation is recommended for all severe food allergies. It is important not to reduce nutritional consumption when removing specific food from the diet. It is also important to have an individualized allergy action plan ready, distinguishing the condition from related severe food allergies. Ongoing involvement of a pediatrician and specialists, such as pediatric gastroenterologist, allergist, as well as a dietitian, provides the best outcomes for children suffering from severe food allergy.

· Return to Index ·

Nutritional Strategies for Severe Food Allergy: CMA, FPIES, and EoE

Abbreviations

AAF	amino-acid formula	**HPF**	high-power field
AAP	American Academy of Pediatrics	**IgE**	immunoglobulin E
EHF	extensively hydrolyzed formula	**IL-5**	interleukin-5
ESPGHAN	European Society for Gastroenterology Hepatology and Nutrition	**kDa**	kilodalton
EoE	eosinophilic esophagitis	**MCTs**	medium chain triglycerides
FPE	food protein-induced allergic enterocolitis and enteropathy	**NEC**	necrotizing enterocolitis
FPIAP	food protein-induced allergic proctocolitis	**PPI**	proton pump inhibitor
FPIES	food protein-induced enterocolitis syndrome	**TPN**	total parenteral nutrition
GI	gastrointestinal		

Table of Figures

1. Boyce JA, Assa'ad A, Burks AW, NIAID-Sponsored Expert Panel, et al. 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):S1-58. doi:10.1016/j.jaci.2010.10.007
2. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, Holl JL. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics*. 2011;128(1):e9-17. doi:10.1542/peds.2011-0204
3. 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
4. Lifschitz C, Szajewska H. Cow's milk allergy: evidence-based diagnosis and management for the practitioner. *Eur J Pediatr*. 2015;174(2):141-50. doi:10.1007/s00431-014-2422-3
5. Venter C, Brown T, Meyer R, Walsh J, Shah N, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP-an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. *Clin Transl Allergy*. 2018;8:4. doi:10.1186/s13601-017-0189-0
6. 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
7. 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
8. Meyer R, Wright K, Vieira MC, et al. International survey on growth indices and impacting factors in children with food allergies. *J Hum Nutr Diet*. 2018. doi:10.1111/jhn.12610
9. Lifschitz C, Szajewska H. Cow's milk allergy: evidence-based diagnosis and management for the practitioner. *Eur J Pediatr*. 2015;174(2):141-50. doi:10.1007/s00431-014-2422-3
10. Katz Y, Gutierrez-Castrellon P, González MG, Rivas R, Lee BW, Alarcon P. A comprehensive review of sensitization and allergy to soy-based products. *Clin Rev Allergy Immunol*. 2014;46(3):272-81. doi:10.1007/s12016-013-8404-9
11. Klemola T, Vanto T, Juntunen-Backman K, Kalimo K, Korpela R, Varjonen E. Allergy to soy formula and to extensively hydrolyzed whey formula in infants with cow's milk allergy: a prospective, randomized study with a follow-up to the age of 2 years. *J Pediatr*. 2002;140(2):219-24.
12. McCarver G, Bhatia J, Chambers C, et al. NTP-CERHR expert panel report on the developmental toxicity of soy infant formula. *Birth Defects Res B Dev Reprod Toxicol*. 2011;92(5):421-68. doi:10.1002/bdrb.20314
13. Zeiger RS, Sampson HA, Bock SA, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr*. 1999;134(5):614-22.
14. Venter C, Meyer R. Session 1: Allergic disease: The challenges of managing food hypersensitivity. *Proc Nutr Soc*. 2010;69(1):11-24. doi:10.1017/S0029665109991832
15. 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
16. Gernez Y, Nowak-Węgrzyn A. Immunotherapy for food allergy: Are we there yet? *J Allergy Clin Immunol Pract*. 2017;5(2):250-272. doi:10.1016/j.jaip.2016.12.004
17. Burbank AJ, Sood P, Vickery BP, Wood RA. Oral Immunotherapy for food allergy. *Immunol Allergy Clin North Am*. 2016;36(1):55-69. doi:10.1016/j.iac.2015.08.007

18. Freeland DMH, Manohar M, Andorf S, Hobson BD, Zhang W, Nadeau KC. Oral immunotherapy for food allergy. *Semin Immunol*. 2017; 30:36-44. doi:10.1016/j.smim.2017.08.008

19. 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.

20. Nowak-Węgrzyn A, Jarocka-Cyrta E, Moschione Castro A. Food protein-induced enterocolitis syndrome. *J Investig Allergol Clin Immunol*. 2017;27(1):1-18. doi:10.18176/jiaci.0135

21. Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol*. 2015;135(5):1114-24. doi:10.1016/j.jaci.2015.03.025.

22. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol*. 2011;127(3):647–53. e641–643.

23. Mehr S, Frith K, Barnes EH, Campbell DE, Group FS. Food protein-induced enterocolitis syndrome in Australia: A population-based study, 2012-2014. *J Allergy Clin Immunol*. 2017. doi:10.1016/j.jaci.2017.03.027

24. Bellón S, García J, Torija P, et al. FPIES: increased prevalence of this great unknown. Results of PREVALE study. *J Allergy Clin Immunol*. 2018 Sep 20. pii: S0091-6749(18)31331-9.

25. Nowak-Węgrzyn A, Chehade M, Groetch ME, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2017;139(4):1111-1126.e4. doi:10.1016/j.jaci.2016.12.966

26. FPIES Guidelines https://www.fpies.org/fpies-guidelines

27. Leonard SA. Non-IgE-mediated adverse food reactions. *Curr Allergy Asthma Rep*. 2017 Nov 14;17(12):84. doi:10.1007/s11882-017-0744-8

28. Arik Yilmaz E, Soyer O, Cavkaytar O, et al. Characteristics of children with food protein-induced enterocolitis and allergic proctocolitis. *Allergy Asthma Proc*. 2017;38(1):54-62. doi:10.2500/aap.2017.38.4023

29. Miceli Sopo S, Bersani G, Monaco S, et al. Ondansetron in acute food protein-induced enterocolitis syndrome, a retrospective case-control study. *Allergy*. 2017;72(4):545-551. doi:10.1111/all.13033

30. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6; quiz 21-2. doi:10.1016/j.jaci.2011.02.040

31. Chehade M. Translational research on the pathogenesis of eosinophilic esophagitis. *Gastrointest Endosc Clin N Am*. 2008;18(1):145-56; x.

32. Ko E, Chehade M. Biological therapies for eosinophilic esophagitis: Where do we stand? *Clin Rev Allergy Immunol*. 2018;55(2):205-216. doi:10.1007/s12016-018-8674-3

33. Jensen ET, Kappelman MD, Kim HP, Ringel-Kulka T, Dellon ES. Early life exposures as risk factors for pediatric eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2013;57(1):67-71.

34. Moawad FJ, Dellon ES, Achem SR, et al. Effects of race and sex on features of eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2016;14(1):23-30. doi:10.1016/j.cgh.2015.08.034

35. Chehade M, Jones SM, Pesek RD, et al. Phenotypic characterization of eosinophilic esophagitis in a large multicenter patient population from the Consortium for Food Allergy Research. *J Allergy Clin Immunol Pract*. 2018;6(5):1534-1544.e5. doi:10.1016/j.jaip.2018.05.038

36. Chehade M, Sampson HA, Morotti RA, Magid MS. Esophageal subepithelial fibrosis in children with eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr*. 2007;45(3):319-28.

37. Gonsalves N, Policarpio-Nicolas M, Zhang Q, Rao MS, Hirano I. Histopathologic variability and endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc*. 2006;64(3):313-9.

38. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6; quiz 21-2. doi:10.1016/j.jaci.2011.02.040

39. Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy: a prospective cohort study. *Am J Gastroenterol*. 2013;108(12):1854-60. doi:10.1038/ajg.2013.363

40. Moawad FJ, Schoepfer AM, Safroneeva E, et al. Eosinophilic oesophagitis and proton pump inhibitor-responsive oesophageal eosinophilia have similar clinical, endoscopic and histological findings. *Aliment Pharmacol Ther*. 2014;39(6):603-8. doi:10.1111/apt.12636

41. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. *Gut*. 2013;62(6):824-32. doi:10.1136/gutjnl-2012-302250

42. Sodikoff J, Hirano I. Proton pump inhibitor-responsive esophageal eosinophilia does not preclude food-responsive eosinophilic esophagitis. *J Allergy Clin Immunol*. 2016;137(2):631-3. doi:10.1016/j.jaci.2015.07.008

43. Lucendo AJ, Arias Á, González-Cervera J, Olalla JM, Molina-Infante J. Dual response to dietary/topical steroid and proton pump inhibitor therapy in adult patients with eosinophilic esophagitis. *J Allergy Clin Immunol*. 2016;137(3):931-4.e2. doi:10.1016/j.jaci.2015.07.033

44. Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology*. 2018;155(4):1022-1033.e10. doi:10.1053/j.gastro.2018.07.009

45. Schoepfer AM, Safroneeva E, Bussmann C, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology*. 2013;145(6):1230-6.e1-2. doi:10.1053/j.gastro.2013.08.015

46. Lieberman JA, Morotti RA, Konstantinou GN, Yershov O, Chehade M. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy*. 2012;67(10):1299-307. doi:10.1111/j.1398-9995.2012.02881.x

47. Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology*. 2014;146(7):1639-48. doi:10.1053/j.gastro.2014.02.006

48. Kagalwalla AF, Shah A, Li BU, Sentongo TA, et al. Identification of specific foods responsible for inflammation in children with eosinophilic esophagitis successfully treated with empiric elimination diet. *J Pediatr Gastroenterol Nutr*. 2011;53(2):145-9. doi:10.1097/MPG.0b013e31821cf503

49. Kagalwalla AF, Wechsler JB, Amsden K, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2017;15(11):1698-1707.e7. doi:10.1016/j.cgh.2017.05.048

50. Molina-Infante J, Arias Á, Alcedo J, et al. Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: The 2-4-6 study. *J Allergy Clin Immunol*. 2018;141(4):1365-1372. doi:10.1016/j.jaci.2017.08.038

51. NIH ClinicalTrials.gov. Eosinophilic Esophagitis Intervention Trial-1 Food vs. 4 Food Elimination Diet Followed by Swallowed Glucocorticoids. Posted: November 20, 2015. Last Update Posted: August 27, 2018. Available at https://clinicaltrials.gov/ct2/show/NCT02610816

52. Chehade M, Sher E. Medical therapy versus dietary avoidance in eosinophilic esophagitis: Which approach is better? *Allergy Asthma Proc*. 2017;38(3):170-176. doi:10.2500/aap.2017.38.4036.

53. Groetch M, Venter C, Skypala I, et al. Dietary therapy and nutrition management of eosinophilic esophagitis: A work group report of the American Academy of Allergy, Asthma, and Immunology. *J Allergy Clin Immunol Pract*. 2017;5(2):312-324.e29. doi:10.1016/j.jaip.2016.12.026

54. Ho HE, Chehade M. Development of IgE-mediated immediate hypersensitivity to a previously tolerated food following its avoidance for eosinophilic gastrointestinal diseases. *J Allergy Clin Immunol Pract*. 2018;6(2):649-650. doi:10.1016/j.jaip.2017.08.014

55. Lucendo AJ, Arias Á, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: A systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(1):13-22.e1. doi:10.1016/j.cgh.2015.07.041

56. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis. *Gastroenterology*. 2006;131(5):1381-91

57. Schaefer ET, Fitzgerald JF, Molleston JP, et al. Comparison of oral prednisone and topical fluticasone in the treatment of eosinophilic esophagitis: a randomized trial in children. *Clin Gastroenterol Hepatol*. 2008;6(2):165-73. doi:10.1016/j.cgh.2007.11.008

58. Dohil R, Newbury R, Fox L, Bastian J, Aceves S. Oral viscous budesonide is effective in children with eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology*. 2010;139(2):418-29. doi:10.1053/j.gastro.2010.05.001

59. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose fluticasone in patients with eosinophilic esophagitis. *Gastroenterology*. 2014 Aug;147(2):324-33.e5. doi:10.1053/j.gastro.2014.04.019

60. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol*. 2011;128(1):3-20.e6; quiz 21-2. doi:10.1016/j.jaci.2011.02.040

61. NIH ClinicalTrials.gov. A Study in Adolescents and Adults With Eosinophilic Esophagitis (EoE) Measuring Histologic Response and Determine if Reduction in Dysphagia is Achieved. First Posted: November 16, 2015. Last Update Posted: September 20, 2018. Available at https://clinicaltrials.gov/ct2/show/NCT02605837

62. NIH ClinicalTrials.gov. An Extension Study to Evaluate Maintenance of Efficacy and Long-term Treatment Effect of Oral Budesonide Suspension (OBS) in Adults and Adolescents With Eosinophilic Esophagitis (EoE) (ORBIT2). Posted: April 13, 2016. Last Update Posted: June 18, 2018. Avalable at https://clinicaltrials.gov/ct2/show/NCT02736409

63. Chehade M, Sher E. Medical therapy versus dietary avoidance in eosinophilic esophagitis: Which approach is better? *Allergy Asthma Proc*. 2017;38(3):170-176. doi:10.2500/aap.2017.38.4036

64. Andreae DA, Hanna MG, Magid MS, et al. Swallowed fluticasone propionate is an effective long-term maintenance therapy for children with eosinophilic esophagitis. *Am J Gastroenterol*. 2016;111(8):1187-97. doi:10.1038/ajg.2016.238

65. Ko E, Chehade M. Biological therapies for eosinophilic esophagitis: Where do we stand? *Clin Rev Allergy Immunol*. 2018;55(2):205-216. doi:10.1007/s12016-018-8674-3

66. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2015;135(2):500-7. doi:10.1016/j.jaci.2014.07.049

67. Tripp CS, Cuff C, Campbell AL, et al. RPC4046, A novel anti-interleukin-13 antibody, blocks IL-13 binding to IL-13 α1 and α2 receptors: A randomized, double-blind, placebo-controlled, dose-escalation first-in-human study. *Adv Ther*. 2017;34(6):1364-1381. doi:10.1007/s12325-017-0525-8

68. NIH ClinicalTrials.gov. Dose Ranging Study of RPC4046 in Eosinophilic Esophagitis. Posted : March 28, 2014. Last Update Posted : May 9, 2017. Available at https://clinicaltrials.gov/ct2/show/NCT02098473

69. NIH ClinicalTrials.gov. Study of Dupilumab in Adult Patients With Active Eosinophilic Esophagitis (EoE). Posted: March 4, 2015. Last Update February 19, 2018. Available at https://clinicaltrials.gov/ct2/show/NCT02379052