Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

COURSE TRANSCRIPT

Guidelines for Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome

Overview

Anna Nowak-Węgrzyn, MD, PhD, examines the clinical presentation of Food Protein-Induced Enterocolitis Syndrome (FPIES); summarizes common food triggers of FPIES; distinguishes FPIES from other major non-IgE-mediated food allergies; discusses oral food challenges for patients with suspected FPIES; and identifies medical and nutritional strategies using current FPIES guidelines.

Content Areas

- Examine clinical presentation of FPIES
- Summarize common food triggers
- Distinguish FPIES
- Discuss oral food challenges for patients
- Identify medical and nutritional strategies using current guidelines

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:

- Describe the clinical presentation of FPIES
- Identify strategies to avoid FPIES reactions

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The estimated time to complete the activity is 1.0 hour.

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This activity was released on November 9, 2020 and is eligible for credit through November 9, 2022.

Contact Information

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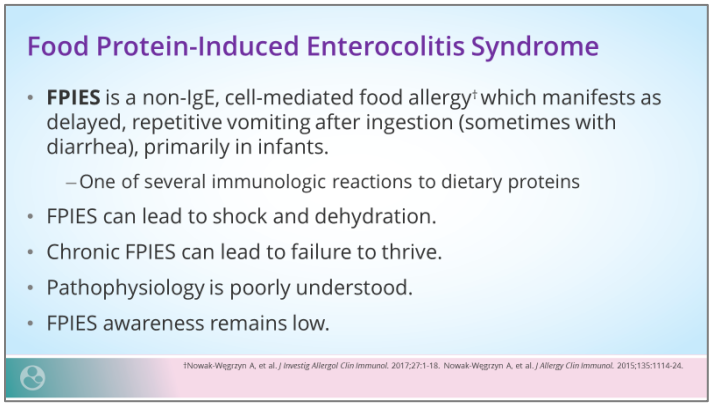
Module 1: Introduction

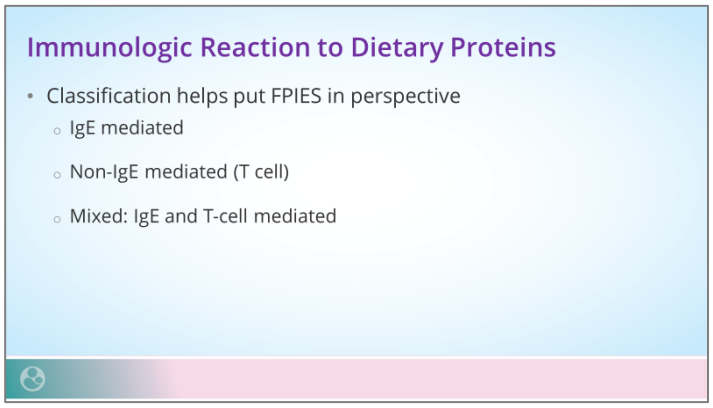
Dr. Anna Nowak-Węgrzyn: Welcome and thank you for joining the FPIES webcast. During the first module, I'll discuss what defines food protein-induced enterocolitis syndrome, or FPIES for short. I will review common symptoms and food triggers for this disorder, and I will differentiate FPIES from other major non-IgE-mediated food allergies.

Food protein-induced enterocolitis syndrome is a non-IgE, presumably, 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. This is one of several immunologic reactions to dietary food proteins.



FPIES is probably 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. At this time, we don't have a good understanding of the pathophysiology of FPIES. We find no evidence of systematic IgE, but we suspect there is a cell-mediated disorder [for which] we have no clear understanding of the mechanism. At this time, the FPIES awareness remains low, and patients are frequently misdiagnosed, and the diagnosis is significantly delayed.

The classification of food allergy is based on IgE antibody involvement in pathophysiology. You are probably familiar with the IgE-mediated food allergies, which manifest in the most severe form as anaphylaxis that can be potentially life threatening. There is a category of non-IgE mediated, presumably T-cell mediated disorders, which include FPIES, and there is also a group of mixed pathophysiology disorders, which are represented by eosinophilic gastroenteropathies, as well as atopic dermatitis.



FPIES's prevalence is not well described; there's very little data known. Until recently, it was presumed or

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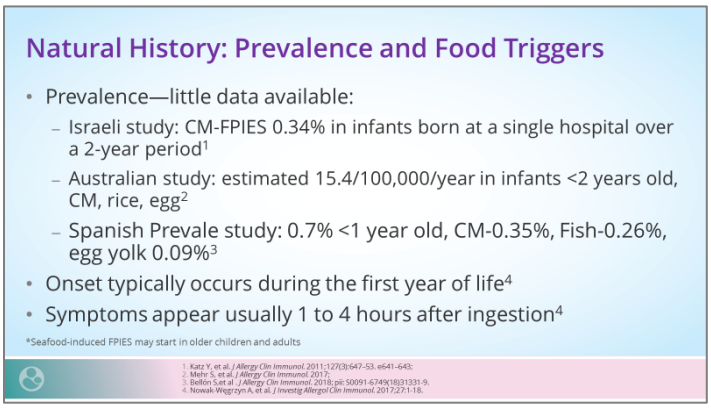
believed that FPIES is a very, very rare food allergy; however, recent studies indicate that it may be more common than previously appreciated.

The first study that really puts some numbers on FPIES's prevalence was a study from Israel, which established prevalence of cow's milk-induced FPIES in a single center birth cohort at 0.34%, and this was over a 2-year period.[1] For comparison, the prevalence of IgE-mediated cow's milk allergy at the same center was, at that time, about 0.5%. An Australian study, which was a national study, estimated there are about 15.4 cases of FPIES, acute FPIES, over 100,000 per year in infants younger than 2 years old.[2] The major triggers are cow's milk, rice, and egg. For comparison, the prevalence of—or the estimated prevalence of—infantile inflammatory disease in the same population in Australia was about 2 cases per 100,000 patients per year.

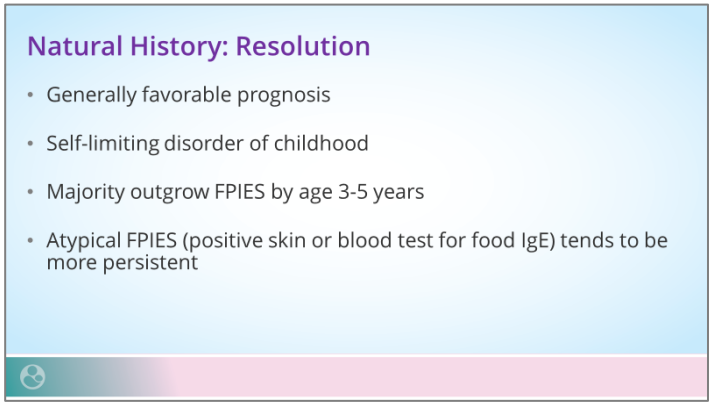
The most recent study from Spain from a single center estimated or found prevalence of FPIES at 0.7% in infants younger than 1 year old,[3] with the most common triggers being cow's milk, fish, and egg yolk.



You can learn from here, from this slide, that the onset of FPIES typically occurs during the first year of life, and that the symptoms do appear usually 1 to 4 hours after ingestion, in acute form.

Parents who present with infants who went through FPIES reaction, especially if they had several accidental exposures, can be very distressed, and are very worried because the diagnosis has been delayed. However, it is very important to understand that FPIES is a self-limiting food allergy of childhood, with a generally very favorable prognosis. This is a self-limiting disorder. The majority of infants outgrow FPIES by age 3- 5 years. Of course, there is a spectrum, and those with the more persistent form or phenotype can have symptoms until later years, but the majority—the vast majority—from the general population will be FPIES-free by age 5 years.

There is also a phenotype of FPIES called atypical FPIES, where there is some positivity, usually quite weak, skin testing or blood testing for the food that is triggering FPIES. It is recognized that patients who develop specific IgE to the FPIES trigger tend to have a more persistent disease.



I'm really pleased to base this presentation on the discussion of the *First International Consensus Guidelines for the Diagnosis and Management of FPIES*, which was published in 2017. It was driven by the parents of infants, of children who had very difficult experiences, and felt there was a big need to provide guidance to physicians and other practitioners taking care of children with FPIES. It was an initiative within the American Academy of

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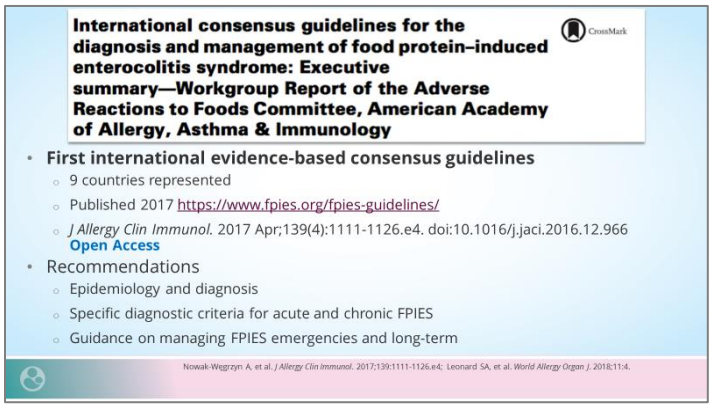
Allergy, Asthma & Immunology, with combined expertise from all over the world. The complete guidelines have been published in the *Journal of Allergy and Clinical Immunology* in April of 2017. They are available and open access, as well as available through the website of the International FPIES Association on fpies.org.

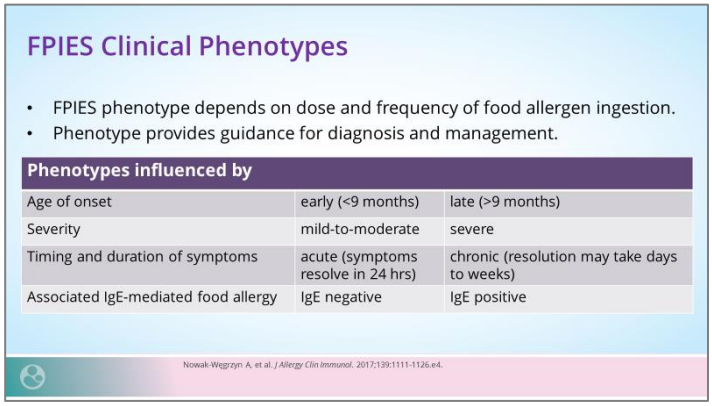
The guidelines provide very specific, very practical recommendations regarding epidemiology and diagnosis. They spell out specific diagnostic criteria for acute and chronic FPIES, and they provide very practical guidance on managing FPIES for acute emergencies, as well as long-term.



FPIES is a unique condition in many aspects, but the most important message I want to give you is that the clinical phenotype of FPIES is dependent on the amount, the dose, and frequency of food allergen ingestion. Phenotyping patients provides some guidance for diagnosis and management. What I mean by that is some patients will have acute symptoms, some patients will have chronic symptoms.

> *"The clinical phenotype of FPIES is dependent on the amount, dose, and frequency of food allergen ingestion."*

Let's talk about other factors that define the phenotype. There is an early FPIES phenotype with onset by age 9 months, and also, but rarely, it is possible to have FPIES starting at an older age. For severity, obviously, there is a spectrum. Most infants will have mild-to-moderate symptoms, but there is a subset of those with very severe, potentially life-threatening reactions. The timing and duration of symptoms in acute FPIES is onset within 1 to 4 hours, and the resolution of symptoms within 24 hours. In contrast, chronic FPIES is when symptoms develop over a period of days to weeks, and also resolution of symptoms may take days to weeks. The majority of patients with FPIES have no evidence of IgE, so they're IgE negative, by skin testing, by serologic testing, but in the atypical FPIES, there is positivity to the FPIES trigger, and as mentioned before, this can be associated with a more protracted phenotype.



I want to describe a case of acute FPIES caused by soy. This is a 14-month-old girl who was breastfed, and she is avoiding, at this point, soy, as well as all legumes. She's avoiding milk, as well as most dietary food proteins. Her diet includes fruits, vegetables, grains, and hypoallergenic amino acid-based solid food. Her history is that she was born at term via spontaneous vaginal delivery. Her mother was a group B strep positive. [The infant] was breastfed without any symptoms, on a regular, unrestricted maternal diet. However, at 3 months, on her second

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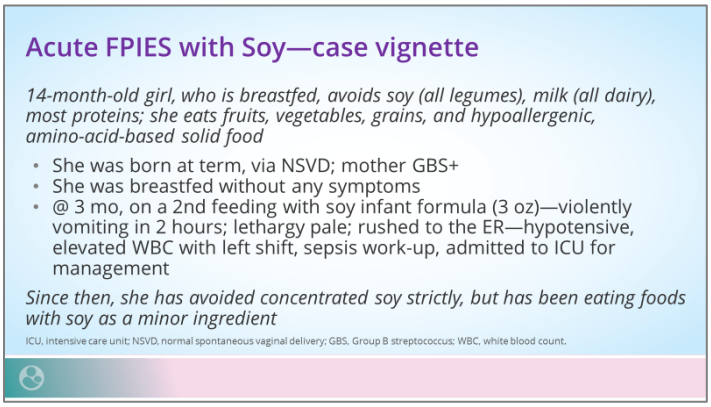
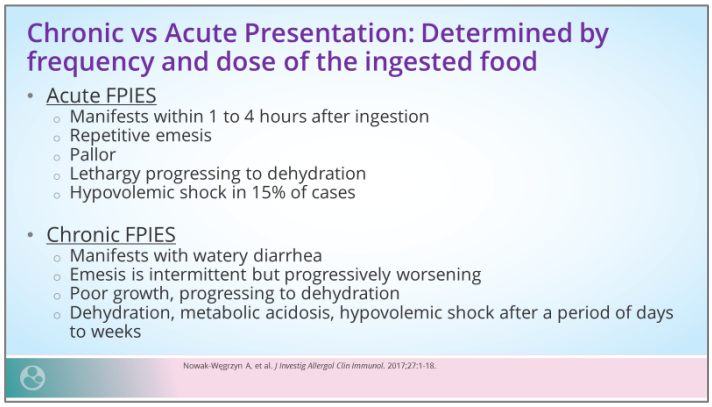
feeding with soy infant formula (about 3 oz), she developed violent vomiting in 2 hours, and vomiting was usually very forceful through projectile. She became lethargic and pale, and she looked very unwell. So, she was taken to the emergency room, where she was found to be hypotensive. Because she looked so septic, she underwent a full sepsis workup, which showed elevated white-blood count with left shift, and infection was suspected.

She was admitted to the ICU for management, and for rehydration. The infectious workup was negative, and the child was discharged from the hospital with a presumptive diagnosis of viral gastroenteritis. A physician and the mother suspected that this was a reaction to soy. Considering the timing of the symptoms, as well as elevated white blood count—which is typically seen in acute FPIES reactions—she was diagnosed with soy FPIES. She avoided soy strictly, and she was able to tolerate food that has soy as a minor ingredient. This is a very classic example of an acute FPIES, which results in dehydration.



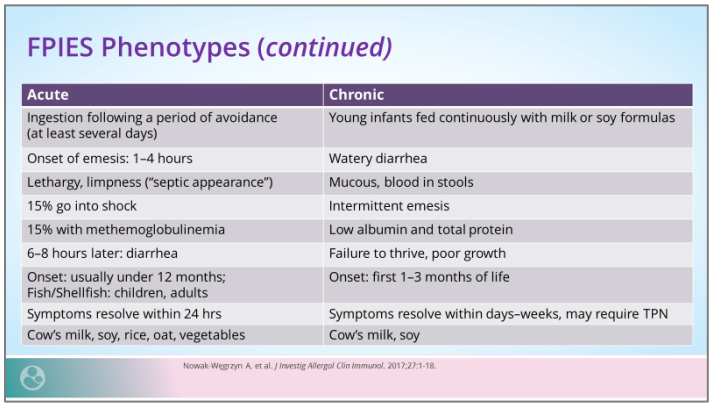
As I mentioned before, acute and chronic FPIES have different presentations. Acute FPIES manifests usually within 1-4 hours after ingestion, typically at 2 hours, which is substantially delayed compared to the immediate food-allergic reactions. It manifests as projectile, repetitive emesis. In severe cases, this is 20, 30 times. Children are pale; they are lethargic; they may develop dehydration; and in 15% of the cases, they actually become hypovolemic (like in the case I just described).



This is a different presentation from chronic FPIES. The most prominent symptom [in chronic FPIES] is watery diarrhea, very thin, watery, rarely containing mucous or blood. [This] is accompanied by emesis, which is initially intermittent, but is progressively worsening over the course of days to weeks, and kids are not growing. It usually starts in young infants, so they have poor growth, and they ultimately become dehydrated. When they are admitted to the hospital, they are dehydrated, [with] metabolic acidosis. They frequently have hypovolemic shock. And among my patients—those who have presented with chronic FPIES in the first few weeks of life—actually, had the most severe presentation. Those are the children that end up admitted to the Intensive Care Unit for management.

The FPIES guidelines do spell out the features of those phenotypes. In acute form, the ingestion of the food is intermittent, following a period of avoidance of at least several days, or frequently—when the child has a reaction as a young infant—then the subsequent testing during the food challenge several years later. Emesis starts within 1 to 4 hours, typically at 2 hours after ingestion of the food. Kids are dusky, lethargic; they're very limp;

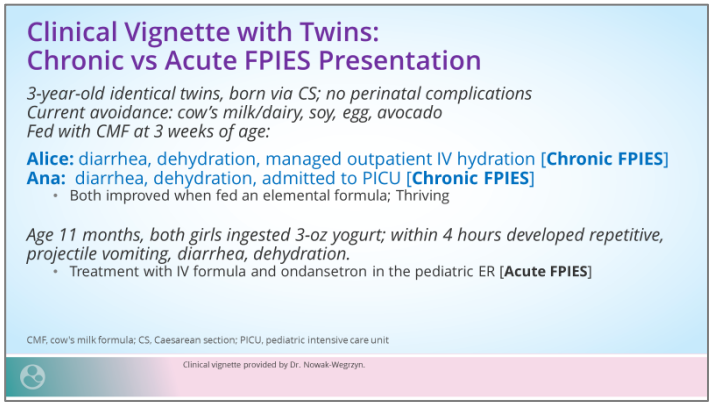
they have this so-called septic appearance, and, indeed, 15% go into shock. There could be also methemoglobinemia observed in some of those cases. In younger infants, and with a more severe reaction, there is diarrhea that usually starts later—about 6 to 8 hours later.



The onset of acute FPIES is usually under 12 months, although fish and shellfish FPIES may be observed in children and adults, with a new onset in children and adults. The good thing about acute FPIES is that the symptoms resolve within 24 hours, and in between the episode, infants are well and thriving. 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** has only been described in young infants who are fed continuously with milk, cow's milk, or soy-based formulas, and it starts within the first weeks of life. The most common manifestation is watery diarrhea, with infrequent mucous or blood in stools, with intermittent emesis, but this emesis is getting progressively worse. This is a chronic condition, but it's escalating quickly. They develop low albumen and total protein. They are failing to thrive. The onset is within 1-3 months of life; these are young infants. The symptoms may take days or weeks to resolve. Some of those children require TPN [total parenteral nutrition]. So, this is a serious condition, and the triggers are cow's milk and soy-based formulas.

I want to show you the concept of the phenotype depending on frequency of the food ingestion. There are patients I've seen in my clinic, 3-year old identical twins, who are born via C-section without perinatal complications, who are currently avoiding a number of foods, including all dairy, cow's milk products, as well as soy, egg, and avocado. But the pertinent history for FPIES is that both girls were fed with a cow's milk formula for the first 3 weeks of age, and by 3 weeks, both of them developed symptoms. They had diarrhea—chronic diarrhea—which resulted in dehydration. Alice was managed as an outpatient with intravenous fluids, whereas her sister, Anna, was more ill. She was admitted to the Pediatric Intensive Care Unit. Both girls presented with a picture consistent with chronic FPIES to early life, continuous feeding with cow's milk formula.



They were empirically placed on an elemental formula while in the Pediatric Intensive Care Unit, and all of their symptoms resolved. The girls were thriving and doing very well until 11 months, when both girls were fed 3 oz of yogurt. Within 4 hours, [they] developed repetitive projectile vomiting, with diarrhea and dehydration, which was treated in the Pediatric Emergency Room with an intravenous fluid, as well as ondansetron.

The second reaction is an example of an **acute FPIES**. Those 2 phenotypes do occur in the same

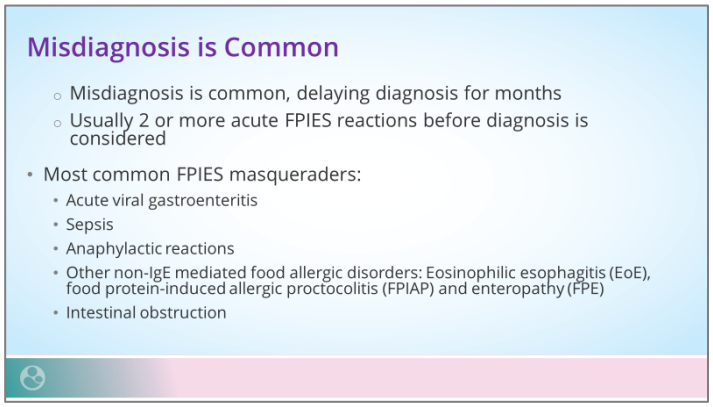
patient, it really depends on the age, and on the frequency of the ingestion. Also, it's a lesson that if there is a suspected FPIES—chronic FPIES—the reintroduction of the trigger food should be performed under physician supervision, not at home, because the reactions can be quite severe.

Module 2: Diagnosis and Management

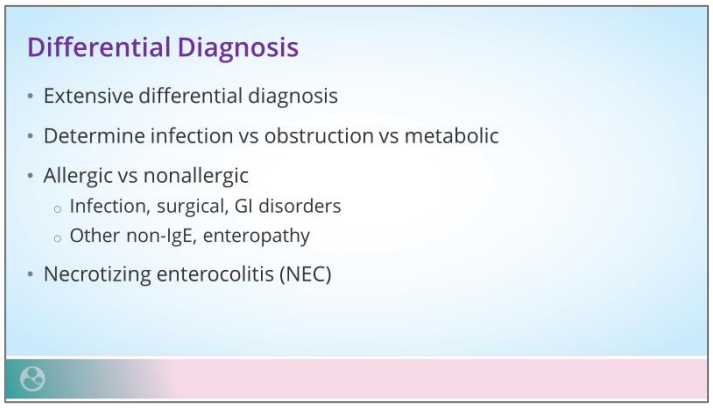
We're moving on to Module 2 in which we will discuss the most prominent clinical feature of FPIES. We'll distinguish it from other major non-IgE-mediated food allergies. We'll incorporate the latest FPIES guidelines on how to improve the diagnosis, and how to proceed with an oral food challenge. Unfortunately, in FPIES, misdiagnosis is common, and this can delay diagnosis for months. Many studies have reported that usually 2 or more acute FPIES reactions have been experienced by infants before diagnosis is considered. Frequently the diagnosis is made by the parent who finally says, "Well, this cannot be another stomach virus. This is happening every time I feed my child oat."

The most common FPIES masqueraders include acute viral gastroenteritis, sepsis—so, infectious diseases. Also, anaphylactic reactions should be included in differential [diagnosis], especially with the reactions that occur within an hour to 2 hours, which are also within the timeframe for the classic IgE-mediated food allergies.

Chronic non-IgE-mediated food allergic disorders, like eosinophilic esophagitis, food protein-induced allergic proctocolitis, and enteropathy are also in differential, however, the patients usually present with more chronic symptoms that are waxing and waning, and not progressively getting worse. In severe cases, infants with FPIES present with distended abdomen, and frequently they're suspected of having intestinal obstruction. [There are] several case reports in the literature reporting on laparotomy performed in infants with cow's milk FPIES in the first few weeks of life.



It is not easy to diagnose FPIES upon the first reaction because there is this extensive differential diagnosis. When the baby presents ashen and pale, and lethargic, obviously, every physician in the emergency department will consider a sepsis infection, and will also think about serious problems, such as obstructive GI problems or metabolic diseases. Allergic vs non-allergic conditions have to be included in the differential. We mentioned infections, surgical, emergencies, as well as gastrointestinal disorders, as well as other non-IgE-mediated food allergies.

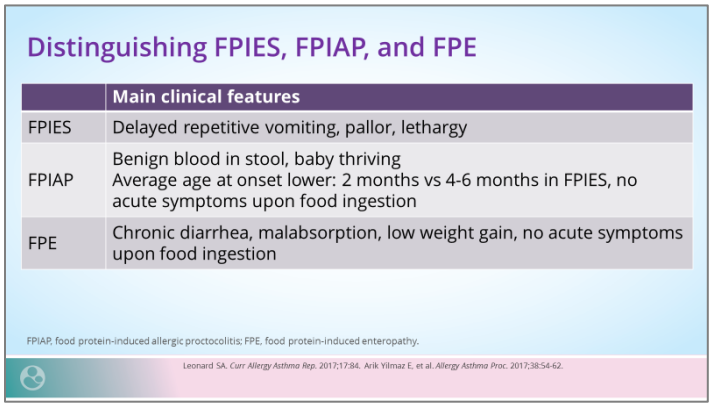


One of the conditions that is also in the differential is necrotizing enterocolitis (NEC). It can be seen in full-term infants and can have a very dramatic course. I think [it is] important to recognize that once feeding with the offending food is

discontinued, the infants with FPIES do recover. The most common form or phenotype of FPIES currently being seen is acute FPIES, so then by 24 hours the child is back to normal health.

"Once feeding with the offending food is discontinued, the infants with FPIES recover."

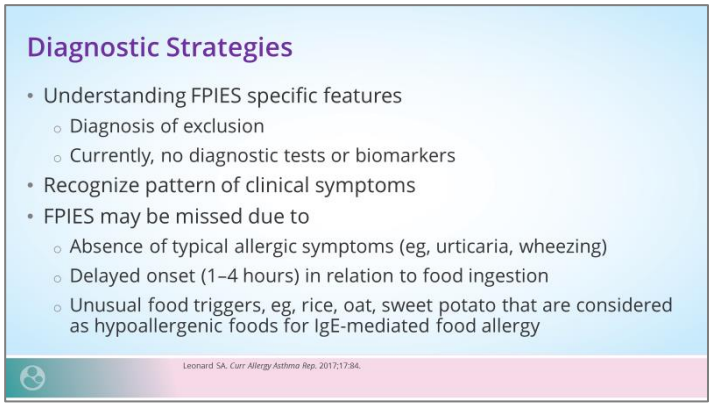
I would like to spend some time on comparing FPIES to other non-IgE-mediated food allergies. Food protein-induced allergic enterocolitis and enteropathy, FPIES, could be a serious reaction, and it's dramatic, and a patient can become dehydrated. In contrast, proctocolitis is a benign condition, baby is thriving and appearing well. Average age of onset is around 2 months vs older age for FPIES, about 4-6 months, and more importantly, 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 quite common, it's equally common in formula-fed as breastfed babies. FPIES is very uncommonly seen in exclusively breastfed infants.



Enteropathy manifests with chronic diarrhea, malabsorption, low weight gain, but there's no acute symptoms upon food ingestion. If a proctocolitis or enteropathy is suspected, food can be reintroduced at home. The food that usually is implicated in those conditions is cow's milk, and the reintroduction of cow's milk occurs at home. In case of FPIES to cow's milk, or FPIES to any other food, reintroduction to test for development of tolerance has to be done under physician supervision in the office or in the hospital.

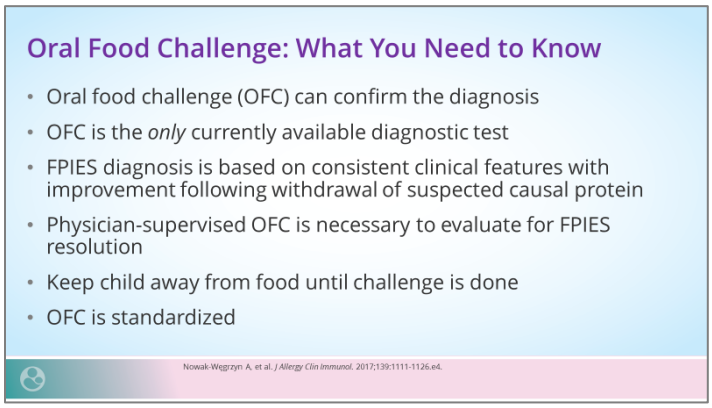
It is important to understand that **FPIES is a diagnosis of exclusions**. Similar to anaphylaxis, there are no diagnostic test or biomarkers, and **the clinician needs to recognize a pattern of symptoms**. As I mentioned before, it's not difficult to misdiagnose, because there are no typical allergic symptoms, which we associate with food allergy, so those infants have no urticaria, no itching, no coughing, wheezing. The onset is delayed. I told you it's between 1-4 hours, typically 2 hours after food ingestion. This is substantially later than IgE-mediated food allergies, which usually start within minutes, up to an hour.

Another thing that throws physicians off is that those food triggers, for instance cow's milk and soy, are common food allergens in classic food allergy, but rice, oats, sweet potato, or other vegetables are considered hypoallergenic for IgE-mediated food allergy; they show up as the most common solid food triggers for infants with FPIES.



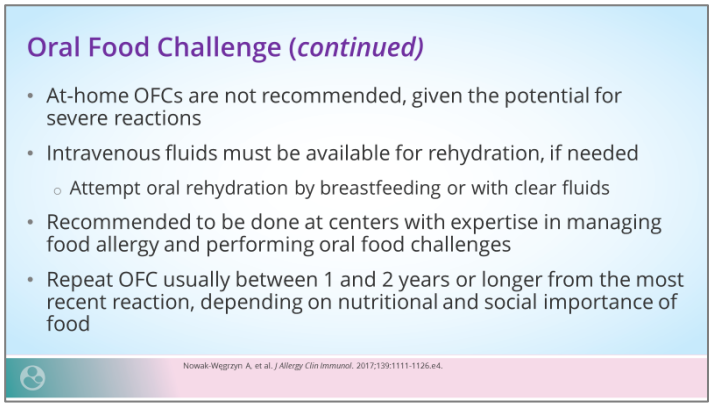
If there is uncertainty, an **oral food challenge can**

be conducted to confirm the diagnosis. It is the only currently available diagnostic test. Because, as I mentioned before, we have no biomarkers, and clinicians needs to be familiar with the features—typical features—timing and onset of symptoms, with improvement, which follows withdrawal of suspected causal protein. However, physician-supervised oral food challenge is necessary to evaluate for FPIES resolution.



In my practice we make the diagnosis of FPIES based on the review of the history. But, let's say a year or 2 years later, we are discussing evaluating the child for outgrowing FPIES, then we are discussing a supervised food challenge. In the meantime, we continue to maintain food avoidance. The food challenges that are being done by the physicians (who are familiar with food allergy) differ from the typical, classic food challenge for the IgE-mediated food allergy; the protocols are available for those specific procedures for the physicians.

We do not recommend introduction of foods at home nor to perform so-called home food challenges because of this potential for severe reactions. Because of dehydration, because of this inability to predict if the child is already outgrowing this condition, we do recommend that intravenous fluid should be available for rehydration, if needed. Obviously, in milder reactions, it's reasonable to attempt oral rehydration (breastfeeding or with clear fluids), but for that there should be at least a reasonable period between—the time period between—the episodes of vomiting and [when] the child cannot be lethargic, unresponsive. If those features are present or the child keeps vomiting, then it's recommended to take those children to the emergency room.



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 even longer from the most recent reaction; it really depends on how important the food is, nutritionally and socially. To give you an example, usually cow's milk or soy—to a lesser extent—are considered as very desirable food for the diet, because they're ubiquitous. On the other hand, some parents would delay challenges for sweet potato, corn, rice, or oat. However, if the child is attending a daycare, they might be motivated to perform the food challenge for oat at a younger age. To tell you that this is a very individualized decision: when to perform a food challenge for evaluation for resolution.

Module 3: Management Strategies

We are moving on to Module 3, in which we'll discuss treatment and strategies for FPIES. We'll talk about management of acute reactions, and we'll examine management, nutritional management,

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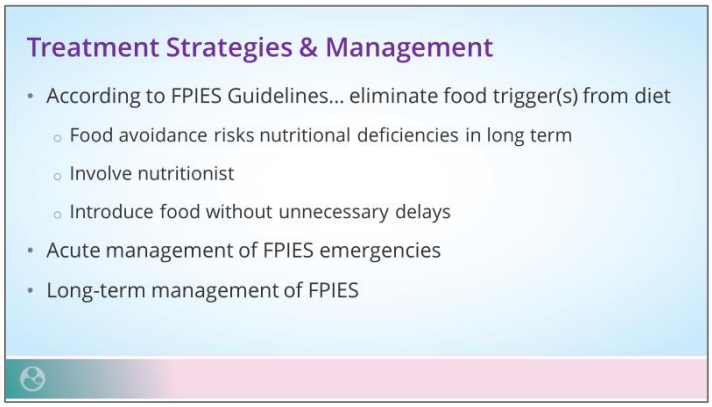
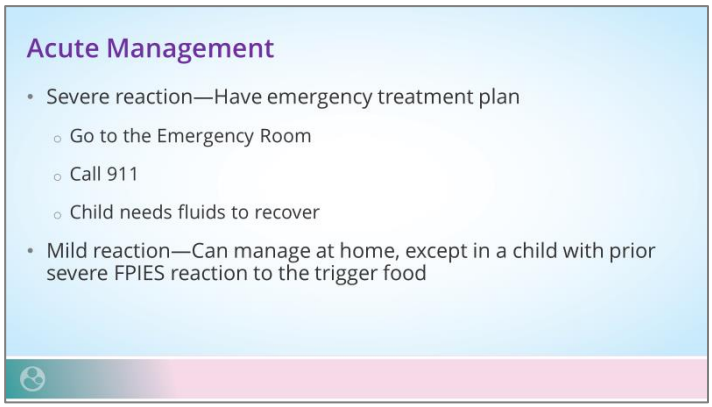
which is very important in FPIES during breastfeeding, and when breastfeeding is no longer possible.

The current standard of care of food allergies is elimination of the offending food from the diet, which obviously eliminates or reduces the risks of symptoms. However, it carries or is associated with a nutritional deficiency in [the] long term. Even avoidance of a single nutrient, like cow's milk, is associated with impaired weight gain and growth parameters in infants. Therefore, if possible, the guidelines endorse and recommend involving a nutritionist in the management process, to utilize all possible resources to introduce food without unnecessary delays, and to avoid unnecessary restrictions of the diet.



It is not uncommon to see infants with FPIES, who are 1 year old or 1 ½ years old, who are on incredibly restrictive diets, or still breastfed in addition to the mother avoiding major allergens from the diet. Definitely, we don't want to see a child like that...with only a couple of foods in the diet.

We discussed acute management of FPIES emergencies, as well as strategies for long-term management. Reactions—accidental reactions—may happen; they do happen. Patients have to be prepared, and because the recognition of FPIES is still not great, **we recommend a patient have a written emergency treatment plan**. They are told to go to the emergency room, to call 911, and in a more 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 is a child who has a very severe reaction, previously, to the same food. In that case, we do recommend going to the emergency room; call 911, because we are worried that those reactions are going to be very difficult to manage.



Every patient should have an individualized allergy action plan for FPIES. This is the letter that can be provided to the emergency room staff, basically explaining what FPIES is, how it differs from classic food allergy, and suggesting the treatments that should be provided to the child.

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

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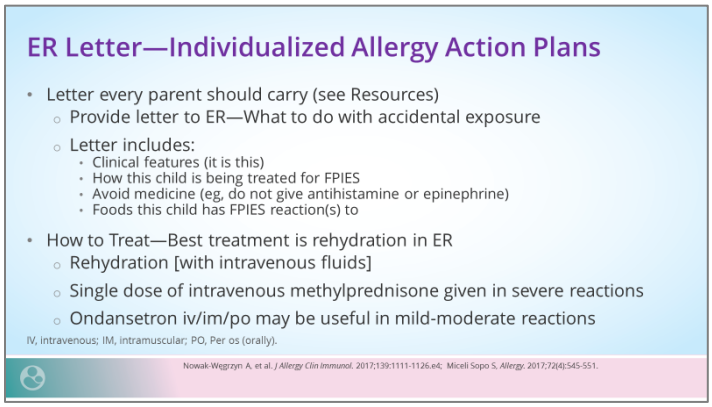

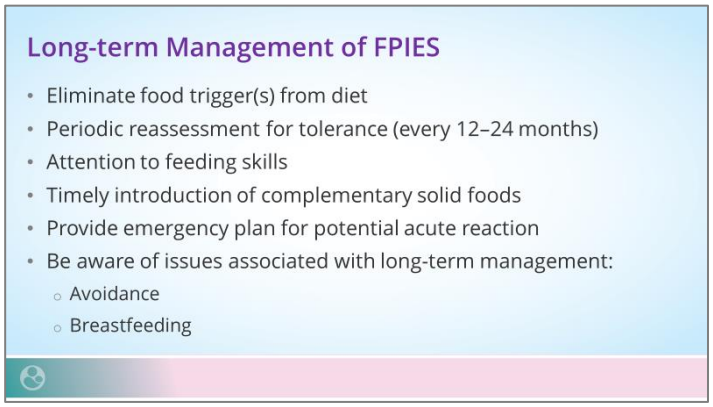

In severe reactions, a single dose of methylprednisolone is given. There is no clinical trials evidenced; it's an empirical, experienced-based decision. Ondansetron, which is antiemetic, can be used in mild-to-moderate reactions. Obviously, it also can be used given IV in severe reactions, but its efficacy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

Long-term management of FPIES is a work in progress. If you evaluate a 6-month-old infant, we have had at least 2 or 3 years of food avoidance. We do teach the patients how to eliminate food triggers from the diet. It's usually less strict than a classic IgE-mediated food allergy. In a sense, children or infants with FPIES do not react to trace amounts of food, such as from potential cross-contamination. They avoid large concentrated amounts of the food, unless they reacted before to a minuscule amount. We direct a periodic reassessment for tolerance every 12- 24 months. I want to emphasize again that this is a very individual decision; this could be a decision to attempt a food challenge within 6 months, if the food is extremely important or the child had accidental exposure to a large amount of food without any symptoms in the interim.

It is very important to pay attention to feeding skills and timely introduction of complementary solid foods. This is something we see very frequently, those children having been—or infants having been—through a couple of the reactions, they lose interest, and the parents are totally traumatized by those reactions. You should see a reaction because it's very stressful if the child looks unwell. Even though nobody has ever died from FPIES, they look like they're about to die. It's incredibly difficult for the parents to then compel themselves to feed this child another food, and this will require active involvement of the physician's allergist who can offer to introduce those complementary solid foods in the office under supervision, to encourage the parents, caregivers, to build their confidence. Obviously, you want to maintain and update emergency plans for a potential acute reaction, and then monitor for the issues that can be associated with long-term management, such as nutritional deficiencies.

In the long-term management of FPIES, nutritional management is most critical. If you have access to a nutritionist, you should utilize it. It's important for the parents, and for the children, as well as for the physician, to emphasize that we want to avoid any nutritional deficiencies, because restricted diets are restrictive for many nutrients, such as fiber, micro and macro elements, and vitamins, which may not be so obvious if the child is not being fed with

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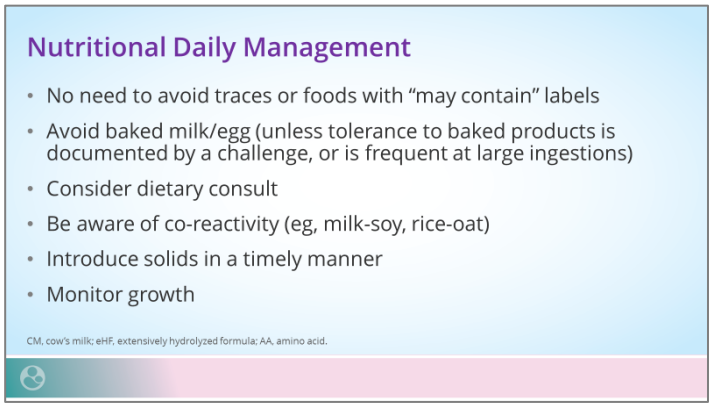
appropriate formula. Then, obviously, nutritional support [is essential]: how to identify the foods for introduction and to avoid the unnecessary delays.

[In] daily management, as I mentioned before, there is no need to avoid traces or food with precautionary labeling, such as, "they may contain trace amounts."

In general, we do recommend avoidance of baked milk and egg. You may know the majority of children with IgE-mediated classic food allergy can tolerate milk and egg in the baked products, such as muffins or cakes. In FPIES, unless the child has had a challenge to the baked milk or egg, or has had documented frequent ingestion—at large—without any symptoms, they should avoid baked milk and egg. As I mentioned before, dietary consultation/ guidance 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 younger infants under 6 months of age. Frequently, those who react to milk will also react to soy. Those who react to solid foods, for instance grains, such as rice, will also have a high risk of reacting to oat—about 40% to 50%. This has to be kept in mind when choosing foods—new foods—additional foods for introduction, because we want to minimize the risk of potential reaction.

We do 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 actually counter-productive. It can be detrimental and can promote [the] development of new allergies. This is an area that should be actively explored, and of course monitoring growth, and that things are on top of their nutritional intake.

I mentioned before that FPIES, in contrast to allergic proctocolitis, is uncommon in exclusively breastfed infants. It may occur; those infants may have acute or chronic symptoms, and those symptoms are attributed to the foods that are ingested in maternal diet. There are a couple messages here: If a child reacts to milk upon direct feeding, but it's thriving and growing when the mother is ingesting dairy in her diet, there is really no recommendation to eliminate dairy products from maternal diet.

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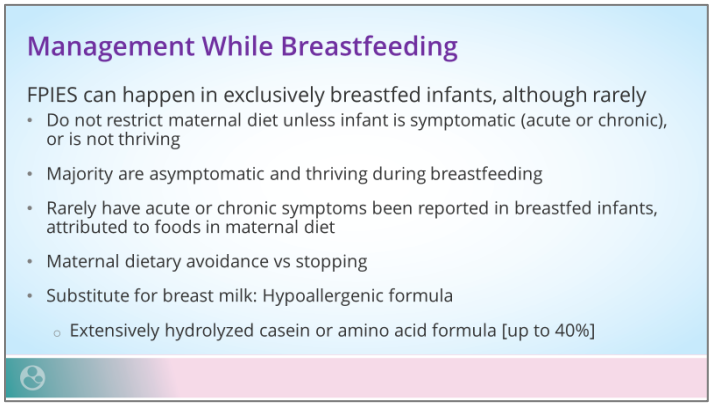
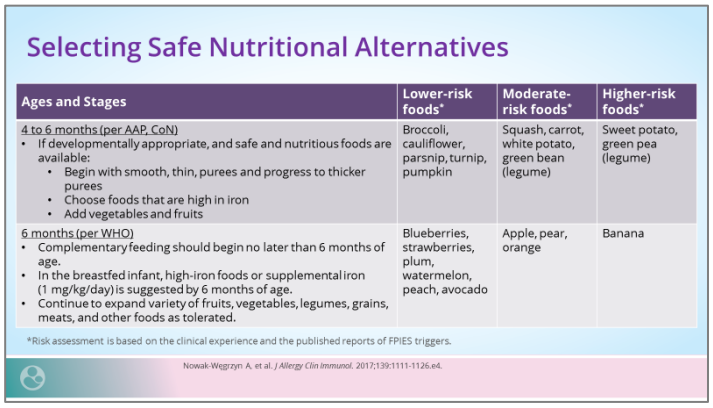
At some point, if the child reacts to multiple foods or is having problems with growth or chronic symptoms, and the offending food cannot be clearly diagnosed, or maternal dietary modifications are too expensive, and we would consider stopping breastfeeding, [then] it is important to provide a nutritionally complete substitute for breast milk. In case of infants with FPIES, we have to 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.



This is a table from the guidelines we published. This is a table that was based on the collective experience of all of the physicians [and] nutritionist who were writing the guidelines. We basically put our heads together to come up with a list of so-called lower-risk foods that could be used for introduction. For instance, in the youngest infants, between 4-6 months of age, we would recommend starting with vegetables, such as broccoli, cauliflower, parsnip, turnip, and pumpkin. Then we have also a category of moderate-risk and higher-risk foods that has been compiled based on the published reports and our experience.



For 6 months of age, we have guidance to introduce some other foods, in addition to the ones that have been introduced at younger ages, as well as at 8 months, we do move into lamb and quinoa, as well as millet, as lower-risk foods. Then we also have other choices for moderate-risk foods and higher-risk foods. Then at 12 months of age we start talking about introducing tree nuts and seed butters, as well as peanut as a moderate-risk food. Because there have been cases or reports of peanut FPIES in [the] literature, it's considered as a food with a potential, but in reality, any food can cause FPIES, like for IgE-mediated food allergy.

This is just a general guide, and obviously, you are going to manage a child who reacted to a single food, and has been tolerating every solid that has been introduced into the diet differently, more liberally with a faster progression compared to a child who has already reacted to 7 different solids, as well as cow's milk and soy formula, because in this child you will be particularly careful, and you'll be introducing foods that are the lowest risks to minimize the future reactions.

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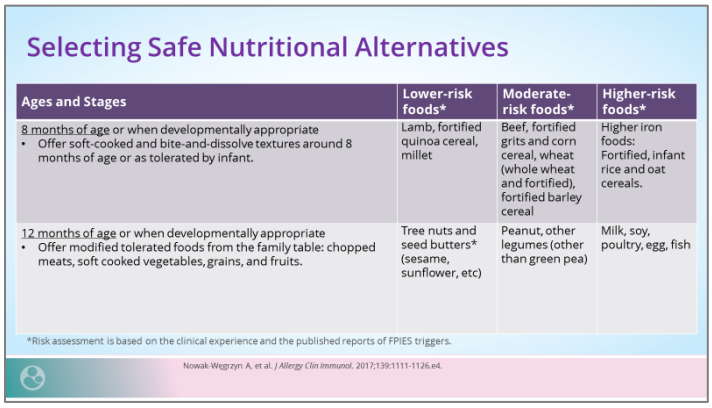
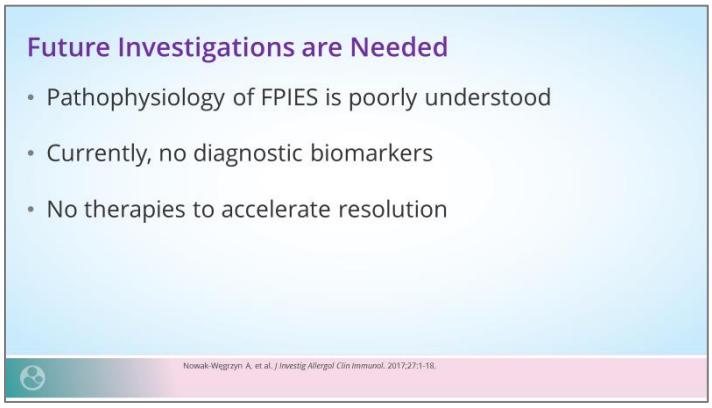


I want to point out that these tables are practical, and also point out that with certain foods, you can become very creative. You can provide different textures and different amounts of the food, finger food as well as spoon-fed food. This is a very important part of the management. It's very appreciated by the parents.

Clearly, there are many unmet needs in FPIES. We have to understand the pathophysiology. We are trying, but it's very challenging because of the age of the patient it is difficult to access their blood. Usually we do not perform endoscopies and biopsies in infants who recover within 24 hours and are growing and thriving in between episodes. But because we don't know pathophysiology, we are lacking diagnostic biomarkers, and because we don't understand pathophysiology, we don't have therapies to accelerate resolution.



You might ask, "Why do we worry about that if everybody outgrows or the majority outgrow FPIES by age 3-5 years?" FPIES has a significant impact on quality of life to caregivers. This is associated with significant financial costs to the parents who have to make special arrangements for a child's care. It's not an unimportant condition to consider for potential treatment.

The takeaways from today's presentation are, remember that FPIES is a delayed food allergic reaction that can be very serious. To date there are no fatalities from FPIES, but some of the reactions I have witnessed during the supervised food challenges are among the worst allergic reactions I've ever seen. Those are the patients who end up in the Intensive Care Unit, on life support, because of the dehydration, hypertension, acidosis.

Still, FPIES misdiagnosis is common, and a diagnosis is delayed. We are trying to raise awareness. Have these symptom patterns in mind when you're seeing young infants.

Obviously, we want to study pathophysiology as we are. At this point, we think this is not humoral. This is not antibody-mediated reaction, so it must be cell-mediated, but we don't exactly know which cell subset is causing it.

But with all of that, it is a very important message to give to the parents that this is a self-limiting disorder of infancy with a favorable prognosis. It resolves within 1-5 years in the vast majority of infants. And at this point, based on the experience with the patients we have seen, there are no long-term consequences. There is no association with inflammatory bowel disease or eosinophilic esophagitis. The management of FPIES relies on avoidance of the food trigger and periodic re-evaluation for resolution, during a supervised oral food challenge.

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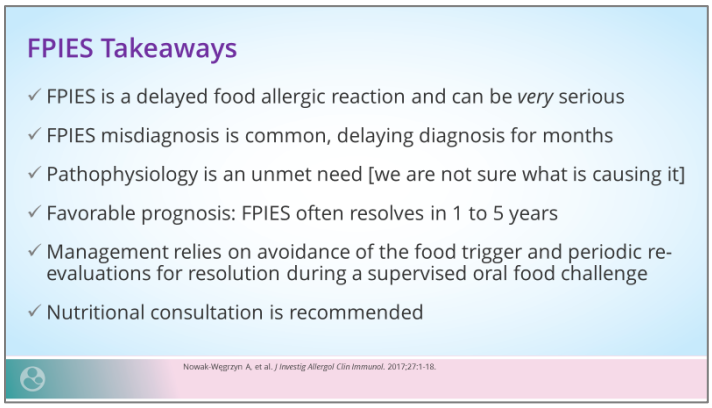
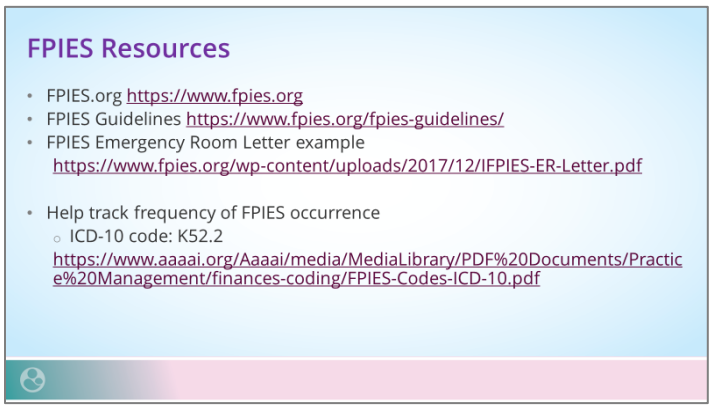
I keep emphasizing that this is the only known IgE-mediated food allergy that has the potential to cause serious reactions. If you are considering a diagnosis of chronic FPIES in an infant, then it means you should be referring this patient for a food challenge when it's time to try this food again.

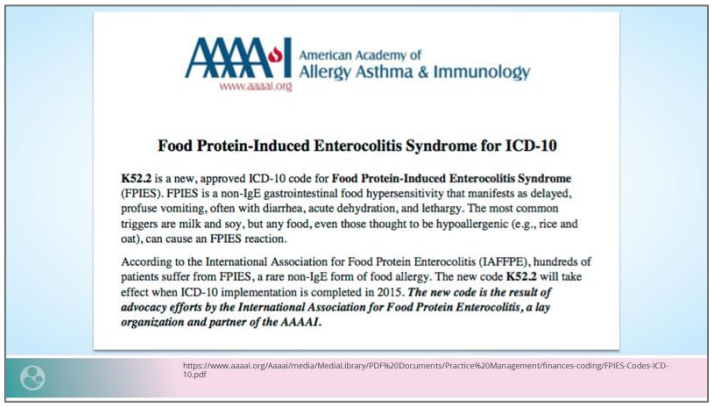
I hope that it was clear from the presentation that nutritional consultation is very helpful, and is recommended, especially in breastfed infants, as well as in infants who have multiple food triggers.



Here are some very helpful resources that are available to you online: fpies.org, which is [the] International FPIES Association. You can access FPIES guidelines through that website, as well as a template for the emergency room letter.



Also, I want to share with you that we have an FPIES ICD 10 code, which is K52.2. We do encourage you to use that code when you're seeing patients, because it will be helpful tracking the frequency of this diagnosis, giving us a better idea about the impact or the importance of this condition.



Question & Answer

Editor's Note: This is a transcript of audience questions together with Dr. Nowak-Węgrzyn's responses from the November 6 and 8, 2018, audio webcasts.

Once diagnosed with FPIES, what potential nutritional deficiency should you be aware of?

Dr. Nowak-Węgrzyn: It really depends on the current feeding mode. Usually this diagnosis is made under 1 year of age. A lot of the time we're dealing with babies who are exclusively breastfed. Obviously, we want to make sure there is enough iron, there is enough vitamins, as well as, [and in] particular, vitamin D. The most common food trigger is cow's milk. Elimination of dairy from the diet of an infant would require a substitute formula. Hopefully, the formula that is chosen—a hypoallergenic formula—will provide appropriate nutrition as well as vitamins. The bigger problem is in infants who are on extremely restricted diets, and they have only formula; they are not being exposed to any solid foods.

It's not strictly a nutritional deficiency, but those kids are not being exposed to vegetables and fruits, and they don't have enough fiber in their diet to

modulate the immune system development in the gut. And the lack of diversity in the diet is an important risk factor for prolonged food allergies or multiple food allergies. Clearly, if there is no substitute formula, then we are worried about major issues. We are worried about calories, protein, calcium, vitamin D. Also, iron is a very big concern of ours in those developing infants, especially if there's a concern for cereal reactions, such as rice and oat, then frequently there is no good sources of iron in the diet.

What is the difference between extensively hydrolyzed and amino acid-based formulas?

Dr. Nowak-Węgrzyn: Basically, both types of formulas are considered as hypoallergenic formulas, but extensively hydrolyzed formula is obtained from cow's milk, and can be based on casein fraction or whey fraction. Essentially, the proteins in milk are subjected to hydrolysis, [which is an] enzymatic process that chops off, breaks down the protein into small peptides. But those small peptides are still immunologically active, and while they're being tolerated by the vast majority of the infants with cow's milk protein allergy, about 10% may still react to peptides.

In contrast, amino acid-based formula is a gold standard of hypoallergenicity. The protein is broken down into single amino acid. Single amino acids are not recognized by the immune system, so there is no possibility that a child, an infant, might react to them with an allergic a reaction. One hundred percent of infants will tolerate amino acid-based formulas. Those who report symptoms or problems with amino acid-based formulas, those are not allergic-type symptoms caused by amino acids. It's potentially problems of molality with some other minor ingredients, or just taste incompatibility, but it's basically nonallergenic from the immunologic point of view.

What is the prevalence of IgE-mediated vs non-IgE mediated cow's milk allergy?

Dr. Nowak-Węgrzyn: It's hard to know exactly. I can provide some estimates, but milk allergy, cow's milk protein allergy, is one of the most common food allergies in childhood. It tends to go away with age, so we refer to it as being outgrown. Depending on which population of patient you look at, it ranges between .5% to 2%, depending on the study and the country. It's probably around 1%, 1.5%. And there is no clear evidence that prevalence of cow's milk protein allergy has increased over the past decades, unlike that of peanut allergy, for instance. Among all cow's milk protein allergy, we guesstimate that about 30%, 40% may be caused by non-IgE-mediated reactions, but the majority are IgE-mediated-type reactions.

In the NICU we have had a case of a late pre-term infant who we thought was repeated NEC, but was diagnosed with FPIES. Do you know how to differentiate FPIES from NEC in the NICU?

Dr. Nowak-Węgrzyn: I don't see those patients, and necrotizing enterocolitis (NEC) is a very serious, potentially life-threatening condition. It may be hard to differentiate when it's happening. Usually FPIES is associated with [the] introduction of the feeding, and in such a young infant, it may take several days to a couple of weeks to produce serious symptoms. They may present with abdominal distention. They usually do not have pneumatosis intestinalis on the x-ray, and I think, when it's happening, it's very difficult to say a 100% that this is not NEC. In FPIES, typically you see elevated white blood count with left shift, this may also be a confusing factor.

To be honest with you, I cannot say 100% that I am able to give you advice how to differentiate it. I mean, certainly recurrent NEC is unheard of. In a situation that you repeat, that you reintroduced the feedings, and you have similar reaction, then I

would strongly suspect that this is a reaction to the feeding. But this came up several times, and indeed, we worry that it may be a presentation.

Is it possible to have a chronic reaction to one trigger and an acute reaction to another?

Dr. Nowak-Węgrzyn: Right, it is possible. But keep in mind that chronic FPIES is—I mean, in my experience, and obviously my experience is not everybody's experience—but chronic FPIES has been described in little infants, like really young infants, a couple of weeks, a couple of months of life, and shortly within days or weeks after introducing the feeding with cow's milk or soy formula. Yes, absolutely, an infant like that. Remember, 30% of infants do have reactions to more than 1 food: you have probably 1 in 3 chances that it could be something more than milk or soy. Yes, usually the acute symptoms occur when they are older, when you introduce solid foods. Or you could also introduce milk or soy in an older infant, and they can have acute reactions.

Remember that the infant who presents with chronic symptoms when they were very little, when you reintroduce cow's milk or soy when they're older, but they still have active FPIES, they will manifest acute symptoms. It's a bit of a mystery at this point. We think that this has to do with the immaturity of the gut. Instead of mounting acute reactions, you have this more protracted, more chronic course; but [with] chronic FPIES, if it's undiagnosed, they get very, very sick.

When starting complementary feeding at 6 months, what is a simple, practical approach to recommend?

Dr. Nowak-Węgrzyn: Keep it simple. I showed you the table from the guidelines... I would advertise it. It's not a 100% guarantee, foolproof, but it's as good as it gets, based on a collective experience from all the experts who put their brains together to write this. Basically, start simple and be smart about it. This is the situation: it's like chasing a moving target. It depends how things progress, because if you have an infant who has reacted to several different foods, obviously your plans or expectations will be lower compared to a kid who has tolerated every single food solid that has been introduced recently. Basically, choose 1 food that will provide a variety of textures and presentations.

Also, choose the food that the child is ready for. You are not going to start with meat, which requires some sophisticated chewing behaviors in a younger infant. Usually, choose 1 vegetable or choose a grain, like quinoa, or maybe choose a vegetable, like corn. This one food will give you a lot of options how to present this food to the child. Follow, and take a look at the table, because it really tells you what the least risk-associated foods are. Usually, green vegetables are our [go-to] foods when introducing it to a high-risk patient as a first food.

Then I do recommend—just to follow-up on that, which may be relevant—I do emphasize that the feeding should be started from a small amount, and then increased, double amount every feeding, and then continue this for at least several days consistently; continue when new foods are being added. Basically, we want to encourage regular intake of the food. We don't want to work on this food for a week, and then once you start introducing another food you stop for a couple of weeks, and then restart. We think that—even though this is not really backed up by any evidence—from all we know about the immune system and how it works in IgE-mediated food allergy, that continuous exposure is really important for tolerance development.

If we don't have the resources and staff to complete an oral food challenge for FPIES in our

hospital, how would you recommend to best introduce new foods?

Dr. Nowak-Węgrzyn: The answer is it depends. If you're talking about the infant who ended up in the emergency room and had to be rehydrated with intravenous fluids, and you were talking about giving them the same food—retain the same food—then you have to refer them to a center that is able to provide a supervised oral food challenge. If you are talking about introducing a solid food—so, a different food—there is a hypothetical concern. I would say you can do it in the clinic, and watch them, especially with those low-risk foods. With every new food that the child can tolerate, you gain confidence, and then the parents gain confidence, and then you will not have to do those challenges in the office; you'll encourage them to do it.

That's the best I can say. I mean it's really the risks. The older they are, the lower the risks they would react with a new food. It's sometimes just introducing a couple of the foods under supervision if parents are worried, which is often the case, so empower them.

For a child who has reacted to multiple foods, and the parent is avoiding new foods, what do you suggest they do to expand their diet? For instance, should they test new foods in a doctor's office or at home?

Dr. Nowak-Węgrzyn: That's a very practical question, and I would say it requires a conversation with the parents because a lot of them almost behave like they have a post-traumatic stress disorder caused by those reactions. They are really traumatized by that, so I have to admit that this is hard for them. I think it depends [on] how much concern, how much anxiety they have. If they are willing to try, after discussion, that those are the low risks, their low-risk foods, and they still are apprehensive, I basically give them an option, "Would you like to come to my office and eat the food?" It's usually once or twice that you need to do it, because then they become more confident, and they are much more comfortable.

I think it's just this fear that they have. Certainly, they do require some hand-holding and talking to them; try to understand what their experience was, and if they are too afraid to introduce the food at home. Then, the only thing we can do to support them is to offer a safe environment to do this.

Is a partially hydrolyzed formula considered hypoallergenic?

Dr. Nowak-Węgrzyn: No, this is not a hypoallergenic formula. Remember, we talked about extensively hydrolyzed and amino acid-based formulas that are considered hypoallergenic formulas because they meet specific criteria developed by the Committee on Nutrition of American Academy of Pediatrics.[4] Partially hydrolyzed formulas are also derived from the cow's milk proteins, it could be whey or potentially casein, but the peptides that are produced as a result of this partial hydrolysis are much larger. The larger the protein, the larger the peptide, the higher allergenic potential. A lot of children with cow's milk protein allergy will react to partially hydrolyzed formulas on the food challenge, they just don't meet the official criteria. They wouldn't be an appropriate formula in an infant who has a history of severe reaction to cow's milk-based formula or soy-based formula.

What is the difference between extensively hydrolyzed and amino acid-based formulas?

Dr. Nowak-Węgrzyn: Well, those are both types of hypoallergenic formulas as defined by criteria by the American Academy of Pediatrics commenting on nutrition. The difference is that extensively hydrolyzed formulas are based on proteins from

cow's milk that are broken down, or hydrolyzed, into small peptides. They can be based either on caseins or whey proteins, and they are tolerated by about 90% of the cow's milk protein allergic infants, either with IgE- or non-IgE-mediated food allergy disorders, but they have a residual allergenicity. Up to or about 10% of infants might react to those formulas.

In contrast, amino acid-based formulas are the gold standard for hypoallergenicity. Protein is broken down into single amino acids, and single amino acids are invisible to the immune system. They're incapable of producing allergic reactions. If you have an extremely allergic infant, either with immediate IgE-mediated milk allergy or severe manifestations of the non-IgE-mediated food allergy, then amino acid-based formulas are the best option.

Following up with that, what are the appropriate circumstances to use amino acid-based formula vs EHF [extensively hydrolyzed formulas]?

Dr. Nowak-Węgrzyn: In an infant who has had severe reactions, let's say, to proteins in maternal breast milk, because then we are suspecting they will react to the hydrolyzed protein, or in infants who had a history of very serious life-threatening reaction to the cow's milk or soy protein. There's no absolute indication for using amino-acid formula as a first-choice treatment in FPIES. It depends on the severity, on the vulnerability of the infant, [on their] nutritional status.

In long-term management, it may be beneficial to use the least hydrolyzed protein for managing cow's milk protein allergy or cow's milk FPIES. But, take into consideration the risk for potential immediate reactions in those who have life-threatening reactions. This is the safest choice. Obviously, in those infants, if a decision was made for whatever consideration (eg, cost, insurance coverage, etc), the introduction of extensively hydrolyzed formulas would be done best under physician supervision. But this is a very small percentage of infants with FPIES or other non-IgE- and IgE-mediated cow's milk protein allergies.

There's a very, very, very special subset that this would be an automatic choice to start with amino acid-based formula.

What is the incident rate in premature infants? Are the symptoms similar?

Dr. Nowak-Węgrzyn: This is a great question, but we have absolutely no data. To be absolutely honest, we don't even have a good idea how common or prevalent FPIES is in the US in healthy babies. And, certainly, I am not aware of any studies that have looked specifically into premature babies with those symptoms.

Yet another unmet need in FPIES.

Can you explain why 15% of patients with acute FPIES develop methemoglobinemia?

Dr. Nowak-Węgrzyn: Well, this has been observed in the studies that looked at very severe cases. This is attributed to the intense intestinal inflammation, essentially, causing this reaction to produce methemoglobin. But this is restricted to very severe reactions, with severe dehydration, and very severe symptoms.

How can we differentiate between a feeding intolerance vs chronic FPIES, especially in premature infants?

Dr. Nowak-Węgrzyn: Well, let's start with chronic FPIES. Chronic FPIES is a very specific diagnosis. In a young infant, whether premature or full-term, continuous feeding with a formula—either milk or

soy formula—will ultimately lead to very severe symptoms. You will not have symptoms that are just getting better, a little worse, a little better, a little worse, sort of relapsing, recurring.

In chronic FPIES, there's a progression of symptoms, which involves watery diarrhea with multiple stools per day, with intermittent vomiting that is becoming more and more severe. Kids are not growing. They're losing weight; they're really becoming very sick over the course of days or weeks. A lot of the kids with chronic FPIES end up in the hospital or in the emergency room needing IV hydration.

With a feeding intolerance, you don't get those very dramatic symptoms. It'll be the first differentiating factor: the children are not gaining weight, and they have progressive escalating symptoms over time.

Can a newborn who presents with a bloody stool and is breastfeeding exclusively be diagnosed with FPIES?

Dr. Nowak-Węgrzyn: It could be allergic proctocolitis. If the baby is happy, if the baby is growing, if it doesn't seem to be in discomfort, then a diagnosis of FPIES is unlikely. This would be more consistent with allergic proctocolitis, which is a mild condition that is also a self-limiting disease or disorder of infancy.

The major differentiating factor is that in allergic proctocolitis, bloody stools or blood-streaked stools are present in an infant who is either breastfed or formula fed but is otherwise looking well. This is a baby who is not getting sicker and sicker. Obviously, sometimes it's difficult to make this diagnosis, or our patients are not classically presented by every potential possible symptom. The message I want to give you is that **to suspect chronic FPIES or FPIES in an infant, the symptoms are getting severe over time.**

Initially, it may be truly impossible to figure out what's going on, but most of the time, this would be allergic proctocolitis, if it's isolated blood in the stool. Because in FPIES, diarrhea is watery. I mean, blood in the stool is not the most prominent symptom from the lower GI tract.

When starting complementary feeding at 6 months, what is a simple and practical approach to recommend?

Dr. Nowak-Węgrzyn: I would refer you to guidelines, which are open access and can be freely downloaded, either from *Journal of Allergy and Clinical Immunology* or from International FPIES Association,[5] fpies.org.

A table gives examples of foods that we consider—that the experts consider—low risk, moderate, and high risk for each age group. You want to start slowly.[6] You want to start with 1 or 2 foods and see, to build up the confidence of the parents and the baby [and their] feeding skills. Then the more foods they can tolerate, the more rapidly you can introduce additional foods.

The majority of the infants do react to 1 single food, so the odds are in favor of tolerating solid foods. But, if the baby presents with already having reactions to a couple of those solids, then a more cautious approach is warranted. But we don't want to keep the baby exclusively bottle or breastfed for months on end, as I emphasized. We want to limit those dietary restrictions to the minimum. We want to provide as regular, as full nutrition as possible within the ramification of the disease.

Go slowly. Build up confidence and use the table from the guidelines. Remember, the goal is not to have this baby on full regular table foods within a couple of months. This is going to be a slower process, but you want to choose foods that provide

a variety of textures and presentation so the infant can practice feeding skills.

How common is FPIES in siblings, especially newborns of patients already diagnosed?

Dr. Nowak-Węgrzyn: You know, that's another great question I don't have a straight answer for. There's no data, absolutely no published evidence. We have had cases of FPIES in twins over the years at our hospital, at our practice. I think that this is something we should be looking into. I've heard some anecdotes, yes, that siblings may exhibit similar symptoms or exhibit a certain degree of other forms of non-IgE-mediated gastrointestinal food allergy that doesn't necessarily fit all of the criteria, or meet all of the criteria, for an FPIES diagnosis.

I think, intuitively, we know allergic diseases run in the family. So, a sibling will be at an increased risk, but I couldn't give you a percent or a number. Is it twice as common as the general population? I couldn't say that. It will be more common, but I cannot say how much more common.

Does a mother need to restrict her diet when breastfeeding an infant with an IgE-mediated food allergy?

Dr. Nowak-Węgrzyn: Not unless the baby is symptomatic. If you are thinking that the child is getting hives after every time the mother eats the food, or has horrible eczema that cannot be controlled with good medical regimen and skin care, then you need to make a decision: Is this really caused by this food? And then, should we restrict it from the maternal diet?

Usually the approach, as allergists, we would deal with just testing, and if it supports diagnosis of IgE-mediated food allergy, we could consider a trial of dietary restriction in the maternal diet. Limit it. You want to make sure that there is an improvement in the symptoms. Then we'll do a re-challenge for the breast milk, to reproduce the symptoms to make sure this is the right recommendation for the mother.

Obviously, restricting dairy in a maternal diet has risks, as I mentioned before, so calcium, vitamin D..., the mother would need to be supplemented for those potential deficiencies.

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6. 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