

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

A Case-Based Program

✦ **Course Transcript** ✦

Overview

Anna Nowak-Węgrzyn, MD, PhD, takes a case-based approach to identify and diagnose food protein-induced enterocolitis syndrome (FPIES) in infants and how to manage acute reactions. Dr. Nowak-Węgrzyn reviews common symptoms and food triggers and discusses how to distinguish FPIES from other major non-IgE-mediated food allergies. Owing to the critical importance of avoiding nutritional deficiencies in infants with FPIES, Dr. Nowak-Węgrzyn highlights how to optimize nutritional management while proceeding with an oral food challenge. An overview of new areas of research in FPIES, including the need for better food-challenge procedures, and the burden FPIES places on families, is also presented.

Target Audience

This activity was developed for neonatologists, nurses, advanced practice clinicians, dietitians, and other healthcare providers with an interest in preterm and term infants.

Learning Objectives

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

- Identify an infant with a convincing history of food protein-induced enterocolitis syndrome (FPIES)
- Optimize the nutritional management of an infant with FPIES
- Summarize new areas of research in FPIES

Faculty

Anna H. Nowak-Węgrzyn, MD, PhD

Professor of Pediatrics
NYU Grossman School of Medicine
Director, Division of Allergy and Immunology
Department of Pediatrics
New York University Langone Health
New York, New York

Accreditation and Certification

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

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

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

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

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

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

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Provider number AC857

Activity #171050

Learners may submit additional evaluations of the quality of this program/material at QualityCPE@eatright.org.

Disclosure Statement

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

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

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

Faculty

Anna Nowak-Węgrzyn, MD, PhD

Advisory Board: DBV, Novartis

Clinical Trial: Regeneron

Research Support: Aimmune, Danone

Speakers Bureau: Danone, Nestlé, Thermo Fisher

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

Additional content planners

The following have no significant relationship to disclose:
Erin Allen, MS, RD, LDN (Dietitian Reviewer)
Victoria Anderson (Medical Writer)
Stephanie Leonard, MD (Peer Reviewer)
Heather M. Jimenez, FNP-C (Nurse Planner)

Annenberg Center for Health Sciences

Staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

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

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

This activity is an online enduring material. It has been edited to meet requirements for online learning. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on June 15, 2022 and is eligible for credit through June 15, 2024.

Obtain your CE/CME credit at pnce.org/FPIES-Cases



Contact Information

For help or questions about this activity please contact Continuing Education:
ce@annenberg.net

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Editor's Note: This is a transcript of a live webcast presented online on May 26, 2022. It has been edited and condensed for clarity.

FPIES EPIDEMIOLOGY



Anna Nowak-Węgrzyn, MD, PhD:

Thank you for the opportunity to talk to you about FPIES, which has been my interest for many, many years. I will start with discussing FPIES epidemiology.

To the question, "Have you provided care to a patient with FPIES in your clinical practice?" 38% of the live audience responded yes, and 62%, no.

I think it's interesting that many of you have already had a patient with FPIES, which used to be considered a very rare, unusual food allergy, but it seems this has changed over the course of the past 2 decades.

Let's first define FPIES, food protein-induced enterocolitis syndrome. It is classified as a non-IgE cell-mediated food allergy that manifests with delayed, repetitive vomiting after ingestion of the food. It starts usually in infants. Occasionally, vomiting can be accompanied by diarrhea. You know that food allergies are defined as immune-adverse reaction to food. The majority of the food allergies have IgE-mediated pathophysiology and manifest with more immediate symptoms, and with typical classic allergic symptoms like hives, itching and wheezing.¹

The fact that this is a non-IgE mediated food allergy, it's also associated with the lack of detectable food-specific IgE. So, the typical allergy testing, such as skin test and blood work, do not detect any food-specific IgE. But despite it being a predominantly gastrointestinal food allergy, FPIES can be quite severe. The extreme cases could lead to shock, hypovolemic shock, and dehydration. When it's chronic and evolves over days to weeks, it may result in failure to thrive.

Despite increasing clinical relevance of FPIES, the pathophysiology remains poorly understood, and FPIES awareness is still quite low.

Natural History of FPIES

What is the natural history of FPIES? We believe that FPIES is a very uncommon food allergy, sort of a zebra in the world of food allergies. However, over the years, studies from all over the world—Australia, Israel, and Spain—have alerted us with the possibility that FPIES is more common than previously appreciated, with incidents in the first year of life^{2,3} of 0.7%.

This was a study from Spain.⁴ Our study in the US estimated prevalence in the first year of life showed 0.5%.² This is significantly lower than the classic food allergy, which is estimated at about 8%, but is not negligible.

Food Protein-Induced Enterocolitis Syndrome

- FPIES is a non-IgE, cell-mediated food allergy that manifests as delayed, repetitive vomiting after ingestion (sometimes with diarrhea), primarily in infants.^{[1]-[3]}
 - One of several immunologic reactions to dietary proteins
- FPIES can lead to shock and dehydration.
- Chronic FPIES can lead to failure to thrive.
- Pathophysiology is poorly understood.
- **FPIES awareness remains low.**

1. Nowak-Węgrzyn A, et al. *J Invest Allerg Clin Immunol*. 2017;27:1-18.
2. Nowak-Węgrzyn A, et al. *Allergy Clin Immunol*. 2015;120:114-24.
3. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol Pract*. 2020;8:24-35.

Natural History: Prevalence and Food Triggers

- FPIES may be more common than once thought^[1]:
 - Cumulative incidence of FPIES in infants est. 0.015%–0.7%
 - **Prevalence in US infants 0.51%**
- Onset typically occurs during the first year of life^{[a][2]}
- Diagnosis may be missed due to^{[1]-[2]}
 - Symptoms appear 1–4 hours after food ingestion
 - Lack of typical allergic skin and respiratory symptoms
 - Food triggers perceived to be hypoallergenic (oat, rice, fruits, vegetables)
 - No biomarkers; clinical diagnosis

a. Seafood-induced FPIES may start in adulthood

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol Pract*. 2020;8:24-35.
2. Nowak-Węgrzyn A, et al. *J Invest Allerg Clin Immunol*. 2017;27:1-18.

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Onset typically occurs during the first year of life. This means soon after the introduction of this food. With infant formula, it usually starts earlier. If it's a solid food, then usually after 4 to 5 months of the first month of life. A diagnosis with FPIES can be tricky because the symptoms are quite delayed. Typically, within 1 to 4 hours, usually 2 hours after food ingestion.¹ This is in contrast to a more immediate classic food allergy where symptoms start within minutes.

FPIES is characterized by the absence of typical allergic skin and respiratory symptoms. FPIES reactions occur without hives, itching, swelling, without cough, wheezing. The foods that are causing the FPIES, the solid foods, such as oats and rice and fruits and vegetables, are usually considered to be hypoallergenic in terms of the classic IgE-mediated food allergy. Those are the first solid food proteins that are being introduced into the infant diet.

Because of the poor understanding of the FPIES pathophysiology, we don't have biomarkers. The diagnosis relies on your recognition of the symptoms and the clinical constellation of those symptoms. In that regard, it's very similar to anaphylaxis, and is that is most severe form of IgE-mediated food allergy that has to be recognized clinically. We don't have a test that could facilitate the diagnosis.

Common Food Triggers

The common food triggers I mentioned before tend to be the first foreign food proteins introduced into the infant diet, with the exception of grains, such as oats and rice, as well as fruit vegetables. It also includes cow's milk and hen's egg.

In countries where fish is being introduced early into the diet, so Mediterranean countries, such as Greece, fish is one of the most common solid-food triggers. But in the rest of the world, grains really dominate.^{3,4,5} Certainly, in the US, oat and rice and then vegetables and fruits, such as avocado and

banana are very common, and of course, cow's milk is also among the top allergens.⁶

We are seeing more of the eggs FPIES, as well as more of the peanut FPIES, which may be related to the earlier introduction of those foods for prevention of IgE-mediated food allergy.

Study (country)	N=	Median Age of First FPIES	Median Age of Diagnosis	Most Common Food Triggers
Lemoine et al. 2022 (France)	179	5.8 months	n/a	Cow's milk (60.3%), hen's egg (16.2%), fish (11.7%)
Lee et al. 2021 (Australia)	168	5 months	9 months	Rice (45%), cow's milk (30%), soy (13%)
Blackmann et al. 2019 (US)	74	5 months	11 months	Grains (88%), rice (53%), cow's milk (49%), vegetables (43%), banana (24%), avocado (16%)
Alonso et al. 2019; PREVALE study (Spain)		0.7% <1-year old	n/a	Cow's milk (50%), fish (37.5%), egg yolk (12.5%)

Table 1 — Common Food Triggers

FPIES Phenotypes

FPIES is also confusing because the phenotype or the type of the symptoms is modified by the dose and frequency of food allergen ingestion. You have to be aware that if the food is ingested intermittently, it will be manifesting as more acute symptoms. If the food is ingested on a chronic basis, the symptoms will be more intermittent and evolve over days to weeks. We can also define FPIES phenotype based on the age of onset.⁴ The majority of cases develop symptoms in the first year of life, but adults also [can be diagnosed] with FPIES, and in older children [FPIES] may also appear, although it is less common, and this is typically caused by fish and/or shellfish.

FPIES Clinical Phenotypes

- FPIES phenotype depends on dose and frequency of food allergen ingestion.
- Phenotype provides guidance for diagnosis and management.

Phenotypes influenced by		
Age of onset	infancy	vs older children, adults
Severity	mild-to-moderate	vs severe
Timing and duration of symptoms	acute (symptoms resolve in 24 hrs)	vs chronic (resolution may take days to weeks)
Detectable s-IgE to food trigger	IgE negative (classic)	vs IgE positive (atypical)

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol Pract.* 2020;8:24-35.
2. Nowak-Węgrzyn A, et al. *J Inheri Allergy Clin Immunol.* 2017;27:1-18.

Slide 3 — FPIES Clinical Phenotypes

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

There's a spectrum of severity. The majority of reactions fall within the mild-to-moderate category, but about 15% to 20% will be more severe where you could observe hypotension or shock.

I mentioned before that the acute symptoms are present when the food is ingested intermittently or at least after several days of not eating with any symptoms, starting within 1 to 4 hours, and being quite self-limiting. Within 24 hours, the child is back to baseline, and is normal and thriving well. This is in contrast to chronic FPIES, where symptoms emerge slowly over days to weeks, where it starts initially quite mild, with intermittent emesis and then watery diarrhea. But if feeding with the food continues, then the symptoms escalate, and the child starts losing weight or even develops failure to thrive, and may ultimately become very ill, dehydrated, lethargic, and admitted to the hospital.

Because FPIES is a non-IgE food allergy, the classic FPIES presents without any evidence of IgE to the food that is causing symptoms. The skin test is negative. The blood work for specific IgE is negative, but there is a subset of patients who have so-called atypical FPIES. Over time, those children, usually infants or children who initially presented with the classic FPIES symptoms and negative tests, as they get older, they may develop some positive IgE by skin-prick test or blood testing. Usually, those are low grade to weekly positive tests. Those patients remain with FPIES phenotype, but some of them may transition to more immediate symptoms. This has to be watched, and we have to be aware that there is a possibility of transitioning from the FPIES to classic food allergy for some of the patients.

Acute vs Chronic FPIES

It's important to elaborate more on the differences between chronic and acute phenotype. Acute FPIES will start within 1 to 4 hours—usually 2 hours after ingestion—but it could be a longer time interval. There's **repetitive emesis. That is the most predominant symptom.**¹ It is frequently

associated with pallor, low muscle tones, lethargy, and may lead to dehydration. In a subset of patients, their symptoms may be severe, associated with hypotension or even hypovolemic shock, which we think is a distributed shock due to third spacing and severe intestinal inflammation.

Acute FPIES	Chronic FPIES
Emesis onset 1–4 hours after ingestion	Emesis intermittent but progressively worsening
Repetitive emesis	Watery diarrhea
Pallor	Poor growth / FTT
Dehydration	Dehydration, metabolic acidosis
Lethargy progressing	Lethargy, pallor, abdominal distension
Hypovolemic shock in 15% of cases	Hypovolemic shock after a period of days to weeks

Table 2 — Chronic vs Acute Presentation: Determined by frequency and dose of the ingested food

In contrast, chronic FPIES develops over days to weeks. It manifests with emesis, which is intermittent. It doesn't have that clear-cut association with feeding, but this emesis is progressively worsening, and it's accompanied by watery diarrhea that is also increasing over time. This leads to poor growth, failure to thrive, and ultimately will lead to dehydration and metabolic acidosis. Then the child will look really unwell, like in acute FPIES. But, as we said, this develops over a period of days to weeks.

It's important to know that symptoms of acute FPIES will resolve within 24 hours vs symptoms related to chronic FPIES, which will take much longer because the inflammation that is responsible for the symptoms has been evolving over a longer period of time.¹ It also takes longer to reverse it. It may require NPO or even total parenteral nutrition, because it may take from days to weeks for the symptoms to start resolving.

Common Acute FPIES Triggers

There are different triggers that are more common for acute FPIES. Those involve ingestion of cow's milk, and can include oat and rice and vegetables, as well as fish and shellfish, which are prevalent in older children and adults. For chronic FPIES, the documented cases in the literature were triggered by cow's milk and soy and is usually in a form of the

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

infant formula. However, there are rare cases of infants who develop FPIES, either chronic or acute, while being exclusively breastfed.

FPIES Phenotypes (continued)

Acute

- Ingestion following a period of avoidance (at least several days)
- Onset of emesis: 1–4 hours
- 6–8 hours later: diarrhea
- Lethargy, limpness, ‘septic’ appearance
- 15% with methemoglobinemia
- Onset: usually <12 months
- Symptoms resolve within 24 hrs
- Cow’s milk, soy, oat, rice, vegetables
 - Fish/Shellfish: more common in children and adults

Chronic

- Onset of symptoms: first 1–3 months of life
- Young infants fed continuously with milk or soy formulas
- Watery diarrhea
- Mucous, blood in stools
- Intermittent emesis
- Low albumin and total protein
- Failure to thrive, poor growth
- Symptoms resolve within days-weeks, may require TPN
- Cow’s milk, soy

TPN, total parenteral nutrition.

Nowak-Węgrzyn A, et al. *J Invest Allerg Clin Immunol*. 2017;27:1-18.

Slide 4 — FPIES Phenotypes (continued)

FPIES can have a very dramatic presentation, and parents frequently admit they have post traumatic syndrome because of how unwell the child looks during those reactions. But it is a childhood food allergy, so it's helpful to remind the parents that FPIES has a good prognosis. The majority of children will outgrow FPIES and will start tolerating ingestion of the food by age 3 to 5 years. Of course, there are always exceptions to that with children, or even young adults, achieving tolerance, but those are quite uncommon.

If we have a patient who manifests FPIES but develops specific IgE positivity, so has atypical FPIES, there is a tendency for older age as a resolution. This is consistent with all non-IgE vs IgE-mediated food allergies, that once you develop IgE, your allergies tend to be more persistent.

Natural History: Resolution

- Generally favorable prognosis
- Self-limiting disorder of childhood
- Majority outgrow FPIES by age 3–5 years
- Atypical FPIES (positive skin or blood test for food IgE) tends to be more persistent

1. Nowak-Węgrzyn A, et al. *J Invest Allerg Clin Immunol*. 2017;27:1-18.

Slide 5 — Natural History: Resolution

DIAGNOSING FPIES

How do we diagnose FPIES? FPIES, as mentioned, is a clinical diagnosis because we do not have biomarkers. In 2017, a group of global experts from different specialties—allergy, gastroenterology, nutrition, emergency medicine, intensive care medicine, also registered dietitians and nurses—came together to develop evidence-based consensus guidelines for management, for diagnosis and management.⁷

The JOURNAL of ALLERGY and CLINICAL IMMUNOLOGY

REVIEWS AND FEATURES ARTICLE | PEDIATRIC | 120 (ISSUE 3) | 1111-1126 | FEBRUARY 2017

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

Anna Nowak-Węgrzyn, MD, PhD, Mirna Chehade, MD, Marion E. Groetch, MS, RDN, et al.
Published: February 03, 2017

- First international evidence-based consensus guidelines
 - 9 countries represented
- Recommendations
 - Epidemiology and diagnosis
 - **Specific diagnostic criteria for acute and chronic FPIES**
 - Guidance on managing FPIES emergencies and long term

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4.
2. Leonard SA, et al. *World Allergy Organ J*. 2016;11:4.

Slide 6 — International consensus guidelines

We have formulated specific diagnostic criteria for both acute and chronic FPIES. The criteria for chronic FPIES are quite clear. There is a major criteria that is absolutely necessary to diagnose FPIES, which is vomiting within 1 to 4 hours in the absence of skin and respiratory symptoms.¹ This major criteria should be accompanied by at least 3

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

minor criteria. Those minor criteria could be more than 1 episode to the same food, repetitive emesis to another food, lethargy, pallor, emergency room visit, need for intravenous fluid, and diarrhea within 24 hours, [but] typically within 5 to 10 hours. Although, diarrhea tends to be more common in younger infants, and also more severe reactions. Typically, acute FPIES, will include just vomiting.⁷

Acute FPIES diagnostic criteria

1 Major criterion **+** **≥3** Minor criteria

Vomiting in 1-4 hrs, and absence of skin and respiratory sx's

- >1 episode to the same food
- Repetitive emesis to another food
- Lethargy
- Pallor
- Emergency room visit
- Need for intravenous fluids
- Diarrhea in 24 hrs (5-10 hours)

Slide 7 — Acute FPIES diagnostic criteria

So, that's pretty clear. There's not a lot of debate over diagnosis of acute FPIES if minor criteria are present. It's a bit more challenging in the case of the chronic FPIES. We've agreed, as experts, that the most important **criteria for chronic FPIES resolution of the symptoms within days, following elimination of the offending food, and acute recurrence of symptoms** when the food is reintroduced, with the onset of vomiting in 1 to 4 hours, with diarrhea in 24 hours, but usually 5 to 10 hours.

Diagnostic criteria for patients with possible chronic FPIES

The most important criterion for chronic FPIES diagnosis is **resolution of the symptoms within days following elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 hours, diarrhea in 24 hours (usually 5-10 hours).**

Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

Slide 8 — Diagnostic criteria for patients with possible chronic FPIES

Without a confirmatory challenge, diagnosis of chronic FPIES remains presumptive. That's what the guidelines say. I will say that diagnosis of chronic FPIES is almost always presumptive because once the infants become really ill, and they're admitted to the hospital with symptoms that were evolving over days to weeks, parents are really, really worried. It's very difficult to convince them to subject the child to a challenge, even if it's done in the hospital in the controlled environment, because once they see the child is improving with the hypoallergenic formula or with the dietary elimination from the maternal breast milk, they are very reluctant to go through that experience again.

Another important point is that because chronic FPIES is so elusive, if you have a sick infant who improves after elimination, especially an infant that has been hospitalized, and they improve after elimination of the food, and you suspect food allergy, think FPIES. When you reintroduce the food, be aware that those symptoms may now become more acute and often more distinct. It's usually recommended that the food range reduction occurs under physician supervision in the medical facility.

Differential Diagnosis

Differential diagnosis of FPIES is quite expansive, and this will include infectious causes of vomiting and lethargy. Acute viral gastroenteritis and sepsis are very high in the differential. One of the

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

observations or findings in acute, as well as chronic FPIES, is elevation of neutrophils.¹ This is very confusing, but that's a part of the very strong inflammatory response. I'll elaborate on it later, but the cultures are always negative. Then acute viral gastroenteritis is given as a diagnosis of exclusion.

Most common differential diagnosis	Other non-IgE mediated food allergic disorders
Acute viral gastroenteritis	Eosinophilic esophagitis (EoE)
Sepsis	Food protein-induced allergic proctocolitis (FPIAP)
Anaphylaxis	Food protein-induced enteropathy (FPE)
Intestinal obstruction	
Necrotizing enterocolitis (NEC) ^[a]	

a. Abdominal distension and pneumatosis intestinalis may be seen in FPIES and in NEC; peripheral blood eosinophilia is more common in FPIES.

Table 3 — FPIES Differential Diagnosis

NEC vs FPIES

Anaphylaxis might also be in the differential [diagnosis]. Of course, intestinal obstruction of various etiologies, as well as necrotizing enterocolitis (NEC).¹ I want to comment a bit more about necrotizing enterocolitis because there are reports in literature that suggest a subset of necrotizing enterocolitis might be attributed to FPIES to cow's milk. NEC happens more commonly in babies who are fed formula rather than breastfed. Obviously, abdominal distension and an unwell appearing infant are very suggestive of NEC. But you should recognize that during FPIES reactions, there could be pneumatosis intestinalis and abdominal distension in those very ill infants. There is some evidence that more pronounced peripheral blood eosinophilia is associated with FPIES and would speak against the NEC diagnosis in that infant.

Another differential diagnosis category involves the other gastrointestinal mix or non-IgE mediated food allergy disorders, such as eosinophilic esophagitis, food protein-induced allergic proctocolitis, and food protein-induced enteropathy.

FPIES vs FPIAP vs FPE

I want to focus a bit more comparing FPIES to proctocolitis and enteropathy. FPIES may have those acute symptoms within a couple of hours. If

symptoms are chronic, they become very, very obvious over time and very dramatic and very severe.

	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

Table 4 — Distinguishing FPIES, FPIAP, and FPE

In contrast, allergic proctocolitis usually starts earlier, within a couple weeks or months of life. And despite an alarming presence of fresh blood in the stool, the baby is thriving and is mostly comfortable. There's no vomiting, although there may be some gas or bloating. Proctocolitis is equally as common among formula-fed as breastfed infants, whereas FPIES is not as common in the breastfed infant. Enteropathy has a more protracted and more chronic phenotype of diarrhea, malabsorption, and very rarely is there any significant emesis, but there is low weight gain or failure to thrive. And there are no acute symptoms upon food ingestion.

Usually, when we are talking about reintroducing food to allergic proctocolitis or enteropathy, we're talking about food introduction at home vs supervised food reintroduction in the case of FPIES. The prognosis is quite favorable for proctocolitis with the majority of infants being able to tolerate food by age 12 months, and enteropathy usually resolves within 2 to 3 years.

Diagnostic Strategies

What is the best diagnostic strategy to diagnose FPIES? Because this is a clinical diagnosis, one has to be aware of the phenotypes and the constellation of symptoms, because you cannot rely on diagnostic tests for biomarkers. Also, be aware that chronic FPIES is a diagnosis of exclusion. When you consider chronic FPIES, then be careful about reintroducing the food at home.⁷

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Diagnostic Strategies

- Understanding FPIES specific features
 - No diagnostic tests or biomarkers, currently
 - Chronic FPIES is usually a diagnosis of exclusion
- Recognize pattern of clinical symptoms
- FPIES may be missed due to
 - Absence of typical allergic symptoms (eg, urticaria, wheezing)
 - Delayed onset (1–4 hours) in relation to food ingestion
 - Unusual food triggers: rice, oat, sweet potato, considered hypoallergenic foods for IgE-mediated food allergy

1. Leonard SA. *Curr Allergy Asthma Rep.* 2017;17:384.
2. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4.

Oral Food Challenge: What Clinicians Need to Know

- OFC is usually not necessary for diagnosis but can be used if history is not clear or doesn't meet diagnostic criteria for acute FPIES
- Acute FPIES can be reliably diagnosed based on diagnostic criteria
- Clinician-supervised OFC is necessary to evaluate for FPIES resolution
- Keep infant/child away from food until challenge is done

OFC, oral food challenge.

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4.
2. Leonard SA, et al. *Ann Allergy Asthma Immunol.* 2011;106:482-488.e1.

Slide 9 — Diagnostic Strategies

As mentioned, there could be the chance for misdiagnosis because of the atypical presentations. So, the absence of allergic symptoms, such as urticaria, itching, wheezing, delayed onset in relation to food ingestion within 1 to 4 hours. The unusual food triggers now common in infants include rice, oats, sweet potato, and avocado, which are typically hypoallergenic in terms of the classic IgE-mediated food allergy.

Oral Food Challenges

You probably know that for the IgE-mediated food allergy, we rely on oral food challenges to confirm diagnosis. But, in terms of the FPIES, we don't frequently utilize food challenges to confirm diagnosis. However, they are helpful if we consider a FPIES diagnosis if the history is not that clear or there's no diagnosis of criteria met for acute FPIES diagnosis. However, we do rely on those clinician-supervised food challenges to evaluate for resolution. Until we can evaluate for resolution, which happens usually between 6 to 24 months after the most recent exposure and reaction, then we rely on avoidance of the food in the diet.⁸

Slide 10 — Oral Food Challenge: What Clinicians Need to Know

We do discourage food challenges at home for patients with FPIES because there is the potential for a severe reaction. Because of the third spacing and vomiting, if we undertake a food challenge, we want to be ready to treat more severe symptoms. We would like to place a peripheral intravenous line to be available for intravenous fluids. If the symptoms are mild, we could address rehydration with oral liquids or breastfeeding.

Oral Food Challenge (continued)

- At-home OFCs are generally not recommended, given the potential for severe reactions
- Intravenous fluids must be available for rehydration, if needed
 - If mild, attempt oral rehydration by breastfeeding or with clear fluids
- Recommended to be done at centers with expertise in managing food allergy and performing oral food challenges
- Consider OFC between 6–24 months or longer from the most recent reaction, depending on nutritional and social importance of food

OFC, oral food challenge.

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol.* 2017;139:1111-1126.e4.

Slide 11 — Oral Food Challenge (continued)

We definitely recommend that those challenges are done at centers with expertise in managing food allergy and performing oral food challenges, which is truly, really a barrier to care because there are not that many centers, other than usually big academic centers in big cities. This brings up the question of the restricted access for the underserved populations, and unnecessarily, food restrictions, or

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

maybe even reintroducing food under suboptimal and potentially unsafe conditions.

Food Reintroduction

We usually consider reintroduction of the food within 6 to 24 months, or even longer, from the most recent reaction. The timing of the introduction will depend on how important the food is nutritionally, as well as socially. What I mean by that, obviously, staple foods, milk, eggs, wheat are important because of their nutritional relevance, but there's social significance. How difficult is it to avoid the food; examples would be peanut or oat or rice. I had patients who chose to undergo a rice food challenge because they had a very severe rice FPIES as an infant, and now they're older, and they wanted to eat French fries from McDonald's. And when you look very carefully on the label, it says that French fries from McDonald's are made also with rice flour. So, that was the motivation. For oats, usually it's Cheerios. Cheerios are such a common baby and younger child snack. If the child is enrolled in daycare, there's always a concern that they may grab that food, and parents are very interested in finding out whether oat FPIES has resolved.

ACUTE AND LONG-TERM MANAGEMENT

Let's now talk about the diagnosis and long-term management. This is our case study that will focus first on the diagnosis. This is a story of Isabella. This all started when she was 5 months old and after the third feeding of oatmeal, along with bananas, she developed symptoms. She presents in the emergency room with repetitive, forceful, projectile vomiting that started 3 hours after her last meal. She is lethargic and pale and looking very unwell. On the vital-signs checkup, she's going to be hypotensive. Her prior history was uneventful. She was breastfed without any symptoms. The mother is not restricting any foods in her diet. She has just recently begun feeding with oatmeal.

Case Study 1—Diagnosing FPIES

Isabella, a 5-month-old girl, has had her third feeding of oats, along with bananas, and is having symptoms. She presents in the emergency room with repetitive, forceful projectile vomiting that started 3 hours after her last meal. She is not itching, coughing, or wheezing; however, she is lethargic and pale, and looking very unwell, and is found to be hypotensive.

She was breastfed without any symptoms, on a regular, unrestricted maternal diet, and has recently begun feeding with oatmeal.

1

Isabella

Slide 12 — Case Study 1—Diagnosing FPIES

The question for you is what are the signs and symptoms upon presentation that will help to diagnose Isabella?

As you are thinking about it, let me pull up the potential answer options. If we are considering FPIES in this patient, would it be helpful that there's no allergic skin symptoms, that she's lethargic or that she's had the onset of projectile repetitive emesis within 1 to 4 hours following feeding? Or would you answer that all of the above features would conclude Isabella's diagnosis might actually be food-protein enterocolitis syndrome?

What are the signs and symptoms upon presentation that will help to diagnose this patient?

- A. Lack of allergic skin symptoms
- B. Lethargy
- C. Onset of projectile, repetitive emesis within 1–4 hours following feeding
- D. All of the above

87.5% answered D, all of the above, and 12.5% answered C, onset of projectile, repetitive emesis.

This is great. I'm happy because it means you're listening, and all of the above actually will be helpful for a diagnosis of FPIES for acute FPIES reaction. The lack of allergic skin symptoms together with the vomiting is the major criterion. Then lethargy is

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

among the minor criteria for acute FPIES diagnosis. The correct answer is answer D.

Acute FPIES, as mentioned before, and just review it very quickly... The typical onset is during the first year of life with symptoms appearing within 1 to 4 hours after ingestion.¹ Although, there could be exceptions with later onset of symptoms. The symptoms may occur on the first feeding but more frequently, they do occur after 2 or more feedings with the same food. Sometimes we get a history that the first couple feedings were fine, well tolerated, but the amount of food ingested was really low. Then symptoms appear when the full serving was fed.

More recently, I'm seeing more patients [where they] were saying, "Oh, the child was eating the full servings for a week or so before FPIES started." If you ask me, why did it happen? I don't know. I really don't know what pushes them, so to speak, over the edge. What brings this phenotype to full presentation? And the breastfeeding, the fact that Isabella didn't have symptoms during breastfeeding is actually very, very common.

Case Study 1—Explanation

Acute FPIES typically starts during the first year of life, with acute symptoms appearing 1–4 hours after food ingestion. Note, a child can experience a reaction after 2 or more feedings from an offending food until the full phenotype is displayed. The *International Consensus Guidelines for the Diagnosis and Management of FPIES*, published in 2017, provides specific recommendations and diagnostic criteria for acute and chronic FPIES.^[1] Because she was breastfed without symptoms, and she did not develop violent vomiting until her third feeding with oatmeal, within 2 hours, a careful history and review of symptom pattern can help guide a diagnosis.

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;138:1111-1126.e4.

2

Isabella

Slide 13 — Case Study 1—Explanation

It is uncommon to develop symptoms of acute or chronic FPIES during breastfeeding; although, it is not impossible. So, keep it in mind, again, if you are faced with an infant who is exclusively breastfed but presents very, very ill, and you've excluded all other

etiologies, and the infant improves on hypoallergenic formula.

Slide 14 — International consensus guidelines (continued)

Acute FPIES Management

Now, let's move on to managing FPIES as an emergency, as well as long-term management. The treatment strategies and management are spelled out in the guidelines.⁷ FPIES can be a medical emergency, so we have to prepare our patients on how to manage those emergencies. Long-term management during nutritional management and then decisions on how to time the reintroduction of the food trigger. Because, unfortunately, a majority of the infants with FPIES in children are reacting to 1 or 2 foods, but there is a subset, maybe 10% of all of the patients, [who] have multiple-food FPIES. The more restricted the diet, the more delayed introduction of additional foods, the higher the risk of nutritional deficiencies in the long term. If possible, we would love to involve registered dietitians, and we pay attention to introducing food without unnecessary delays.

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Treatment Strategies & Management

- Acute management of FPIES emergencies
- Long-term management of FPIES
- According to 2017 FPIES Guidelines... eliminate food trigger(s)
 - Food avoidance risks nutritional deficiencies in long term
 - Involve registered dietitian
 - Introduce food without unnecessary delays

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4.

Slide 15 — Treatment Strategies & Management

So, acute management: obviously the child is lethargic, does not tolerate anything by mouth, and is really looking unwell. We recommend activating emergency services, going to the emergency room.¹ Whatever is faster because this child may need fluids to recover. We do provide something called emergency treatment plan, which guides the emergency room physician, explains what FPIES is and what are the treatments because the treatment for FPIES is different compared to the classic IgE-mediated food allergy. Epinephrine is not helpful. Antihistamines are not helpful. You have to have rehydration, potentially steroids and antiemetics, such as ondansetron.

Acute Management

- **Severe reaction**—Have emergency treatment plan
 - Go to the Emergency Department
 - Call 911
 - Child needs fluids to recover
- **Mild reaction**
 - Can manage at home, except in a child with prior severe FPIES reaction to the trigger food

Leonard SA, et al. *Ann Allergy Asthma Immunol*. 2021;126:482-488.e1.

Slide 16 — Acute Management

For the mild reaction, especially in a child who has not had any very serious reactions in the past, you can attempt management at home.⁹ This would require potentially, antiemetics, such as

ondansetron, and rehydration with oral fluids or breast milk.

Let's focus on the selection of foods for introduction for Isabella. Isabella is now 10 months old, and she's on a very restricted diet. She was switched to a hypoallergenic formula, and she's only eating apples, pears, and avocado. She had an acute reaction while being fed oatmeal and bananas. The mother says that Isabella remembers the taste and is refusing to eat any cereal or bananas. This makes the introduction of new foods more challenging. She's not getting any grains, iron-fortified grains or meat in her diet, as well as vitamin B in her diet. She's a difficult eater. She's picky. She doesn't like to try new food.

Case Study 2—Selecting foods for introduction

2

This same infant, Isabella, now 10-months old, is fed with a hypoallergenic formula along with apples, pears, and avocado. Five months earlier she had an acute reaction while being fed oatmeal and bananas. Her mother says her daughter remembers the taste and is refusing to eat any cereal or bananas, creating nutrition concerns about getting enough iron, specifically vitamin B, without cereal grains in her diet. The baby is generally suspicious of any new foods. The parents were also traumatized by the acute FPIES reaction, so they were apprehensive about trying new foods.

Isabella

Slide 17 — Case Study 2—Selecting foods for introduction

And the parents admit they were so traumatized by that experience when she was 5 months old that they were not very proactive. They felt apprehensive and worried about introducing new food.

What would be the best next step to help Isabella's parents provide the necessary nutritional requirement for this young infant? This is a question for our audience. I'll give you some time to reflect on that.

I will read the answer options. Would you tell the parents not to worry and to keep offering a variety of solid foods to Isabella? Would you offer a food challenge to oats. She reacted when she was 5

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

months; now she's 10 months? Maybe a challenge to oats would be indicated. Would you provide a short list of possible new foods and specific instructions for gradual introduction at home or under supervision in the office? Or finally, would you recommend starting introduction with peanuts to prevent development of a peanut allergy? I'm wondering what your approach would be for this child. This is a very relevant question. It is not an isolated case scenario.

What is the next step to help the parents provide the necessary nutritional requirements for this young infant?

- A. Tell the parents not to worry and to keep offering a variety of solid foods
- B. Offer a food challenge to oats
- C. Provide a short list of possible new foods and specific instructions for gradual introduction at home or under supervision in the office
- D. Recommend starting introduction with peanut to prevent development of peanut allergy

100% chose C.

Wow, that's a wonderful job, really great job guys, because that's what you should do to support that family. Obviously, they're very worried and just telling them not to worry, disregarding, ignoring their concerns was not going to take you far, right? You need to do better than that. We wouldn't normally offer a food challenge to oats within such a short period of time, and only would consider that if she was in daycare, and there was a possibility that she would be eating oats. But this was such a traumatic experience that choosing that food for reintroduction when her diet is so limited would be a poor strategy.

So, C is the most practical, more supportive approach. I've offered supervision in my office just for the first food. Obviously, parents will be worried, but the more foods the child can tolerate, the more their confidence will grow. They will become more comfortable, and they will be more willing to reintroduce food. Remember, a child like Isabella

doesn't have to eat every food under the sun. She's a bit different than a child that doesn't have food allergy. It's okay to be more careful, but she needs a variety of textures. She needs to taste, to train her feeding skills. And obviously, we have to make sure that her nutrition is complete.

I wouldn't start introducing peanuts. She doesn't have eczema, so she's not really at the highest risk for a peanut allergy. We would like to introduce peanuts within the first year of life. But peanuts have such a bad reputation as a high allergenic food that we would rather start with fruits, vegetables, or with some alternative grain, such as quinoa or maybe even corn, which is not a grain, but acts as a grain. So, this was our correct answer: provide a short list of possible new foods and specific instruction.

All right. Let's delve more into that. You want to reassure, acknowledge the concerns, and you want to reassure the parents. The important thing to say is that children outgrow FPIES.^{10,11} The older they get, the lower the risk of developing FPIES to a new food. A risk for Isabella at 10 months is probably 50% lower than when she was a 5-month-old, that she would have FPIES to a new food. Most children react to only 1 new food, so from the get-go, our chances are much better. It also helps when you say, "I know you worry, but it's really important for Isabella to try solids and to try new textures because it helps train her feeding skills, and her speech..." all of those muscles are important for speech development.¹²

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Case Study 2—Explanation

It is common for infants and their caregivers to experience difficulties following an acute FPIES episode, just as described in this case.^{[1],[2]} While the apprehension is justified, it is very important to encourage and support introduction of new solid foods to develop feeding skills and to maintain a nutritionally complete diet.^[3] The effective support entails:

1. Acknowledging the concerns while providing reassurance that most children react to only 1 food and that with every month, the risk of FPIES to a new food decreases gradually;
2. Explaining why timely introduction of solids is important;
3. Providing specific instructions for gradual home introduction, including the selection of the foods generally considered to be a low risk for the initial introduction (eg, cauliflower, broccoli, parsnip, etc);^[4]

1. Maciag MC, et al. *J Allergy Clin Immunol Pract*. 2020;8:1702-1709.

2. Bortolikas LM, et al. *Ann Allergy Asthma Immunol*. 2021;126:488-497.

3. Su KW, et al. *J Allergy Clin Immunol*. 2020;145:1430-1437.e11.

4. Goresch M, et al. *Ann Allergy Asthma Immunol*. 2021;126:124-126.

2

Isabella

You have to keep in mind that food from the same food group will be a higher risk. If she reacted to oats, then I wouldn't start with solids, such as rice, barley, and wheat because there's a good chance of co-reactivity, between 40% to 50%.⁷ If you are dealing with such delicate circumstances, you want to choose something, like a vegetable or a fruit, which would be much more likely to be well tolerated.

Also, if the parents are introducing food at home, you want to discuss what they should do in case of an acute reaction.¹³ Say, when it's okay to try home management with oral fluids, with breast milk, or having a prescription for ondansetron for those infants that are 6 months and older is also helpful.

For long-term follow-up with those patients—and remember, those infants with FPIES are overall at a higher risk to develop allergic comorbidities including IgE-mediated food allergy, atopic dermatitis, and allergic rhinitis, as well as eosinophilic esophagitis—those patients should be followed over time and managed appropriately.¹⁴

You are probably familiar with the recommendations for early introduction of allergenic foods, such as peanuts or eggs or tree nuts, in the first year of life. I mentioned that we definitely want to introduce peanuts in the first year of life, but we wouldn't choose peanuts as the first food for such a child. If you have an infant with FPIES and atopic dermatitis, you wouldn't also delay introduction to peanuts significantly because of the risk of a peanut allergy developing, a classic peanut allergy.

After Isabella tolerated a couple of foods from different food groups at this age, she should already be eating meat. She should already be eating alternative grains. Then we would consider introducing peanuts and eggs into her diet.

Long-Term Management

Slide 18 — Case Study 2—Explanation

It's also very helpful to provide specific instructions for gradual home introduction. It's helpful to say which foods you should try. We usually start with some vegetables like cauliflower, broccoli, spinach, parsnip, and pumpkin. Those are traditionally considered low risk for initial introduction.¹³ And you say, start with a small amount and every day increase it. Double the amount until you reach her certain size. As mentioned before, you would do a challenge in the office first with 1 or 2 foods, until the parents are comfortable.

Case Study 2—Explanation (continued)

4. If needed, offering a supervised food challenge to introduce 1 or 2 new foods in the office;
5. Deferring introduction of potentially cross- and co-reactive foods, such as other cereal grains (eg, rice, barley, wheat in the case of our patient) until several other new foods have been tolerated;^[1]
6. Providing a specific plan for managing acute FPIES reactions.^[2]

Infants with FPIES are at high risk to develop other allergic comorbidities, including IgE-mediated food allergy, atopic dermatitis, allergic rhinitis, asthma, eosinophilic esophagitis.^{[3]-[5]}

While risk for peanut allergy is of concern, especially in an infant with FPIES and atopic dermatitis, peanut is not an optimal food for the initial introduction in this setting due to the challenging texture and the recognition of high allergenicity in terms of IgE-food allergy.

1. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4.

2. Leonard SA, et al. *Ann Allergy Asthma Immunol*. 2021;126(5):482-488.e1.

3. Cianferoni A, et al. *Allergy*. 2020;75(9):1466-1469. doi:10.1111/all.14146.

4. Nowak-Węgrzyn A, et al. *J Allergy Clin Immunol*. 2019;144(4):1128-1130.

5. Ruffner MA, et al. *J Allergy Clin Immunol Pract*. 2020;8(3):1039-1046.

2

Isabella

Slide 19 — Case Study 2—Explanation (continued)

If you're a pediatrician listening to this presentation, it's good to have a relationship with a local allergist, pediatric allergist, or someone who is comfortable with the infants. Then when you're choosing a food for introduction, you want to choose the ones that have the best chance of being tolerated.

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

The long-term dietary management of FPIES relies on eliminating the food trigger. Usually, infants or patients don't need to avoid strictly foods that have precautionary labeling. "It may contain" or be "produced in the same facility." We allow those foods, unless you have a history of somebody who really, really had a horrible reaction from an invisible amount of food. We do offer those periodic reassessments for tolerance between 6 and 24 months, or it could be longer if the food is not so important. I have patients with FPIES to sweet potatoes. They may want to wait until they try sweet potatoes until they are much older.

Long-term Management of FPIES

- Eliminate food trigger(s) from diet
- Periodic reassessment for tolerance (every 6–24 months)
- Attention to feeding skills
- Timely introduction of complementary solid foods
- Provide emergency plan for potential acute reaction (see resources)

Slide 20 — Long-term Management of FPIES

We do pay attention to feeding skills and timely introduction of complimentary solid foods because if you miss this window of opportunity, between 4 to 7 months, then children are much more likely to develop feeding aversions and feeding difficulties. We want to introduce solids, such as peanut and egg and tree nuts, within the first year of life after several other first foods were tolerated, especially if those are infants who have both FPIES and atopic dermatitis.

Emergency Plans

We do provide an emergency plan for acute reactions. This is a plan to present in the emergency department because some of the emergency room

physicians may not be familiar with the management of FPIES.

Long-term Nutritional Management

- Nutritional management is most important (once diagnosed)
- Long-term management of food avoidance
 - Potential for nutritional deficiencies
- Anticipatory guidance of complementary feeding
 - Unnecessary delay of solid food introduction, how to reduce this risk

Slide 21 — Long-term Nutritional Management

It's really lovely to have a registered dietician involved in the management of an infant or a child with FPIES who has multiple food triggers or has very serious reactions to a major nutrient, such as cow's milk. Obviously, the avoidance of the food trigger is necessary to control symptoms, but it may lead to nutritional deficiencies. Then we provide anticipatory guidance for introduction of solid foods.

We don't avoid foods with "may contain" labels. A lot of children with classic milk and egg allergies, the majority, in fact 70%, tolerate those foods in the baked form, like a muffin or a cookie.

Nutritional Daily Management

- No need to avoid traces or foods with "may contain" labels
- Avoid baked milk/egg (unless tolerance to baked products is documented by a challenge, or is frequent at large ingestions)
- Introduce solids in a timely manner
- Be aware of co-reactivity (eg, milk-soy, rice-oat)
- Monitor growth
- Consider dietary consult (RD)

Slide 22 — Nutritional Daily Management

But in the case of FPIES, I'm sure there are some children and infants who can tolerate baked milk

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

and baked egg, but we don't know. It's probably the reverse, maybe 1 in 3 would tolerate baked milk and eggs. Therefore, the introduction should be done as a formal challenge, or unless the child is already tolerating a substantial amount of baked products with milk or eggs, then we certainly would like to continue.

When choosing foods for reintroduction or new introduction, you want to start with the foods that have a lower potential for co-reactivity. If you have a baby with milk FPIES, you wouldn't start by introducing soy formula. Or if you have a baby reacting to rice, you wouldn't start introducing oats or wheat or barley. You want to monitor growth. And, as mentioned, a registered dietician can be a great ally.

Breastfeeding and FPIES

FPIES can happen in exclusively breastfed infants, although this is rare. We don't automatically restrict the maternal diet. Remember, the majority of infants are well and thriving during breastfeeding, but if symptoms are observed, then we definitely want to continue breastfeeding for many obvious reasons, but the mother would need to be supported. If the food trigger is not obvious in the maternal diet, then we would provide a substitute for breast milk, such as a hypoallergenic formula. Usually, it is extensively hydrolyzed casein or whey formula or amino acid formula.

Management While Breastfeeding

FPIES can happen in exclusively breastfed infants, although rare

- Do not restrict maternal diet unless infant is symptomatic (acute or chronic), or is not thriving
- Majority are asymptomatic and thriving during breastfeeding
- Rarely have acute or chronic symptoms been reported in breastfed infants, attributed to foods in maternal diet
- Maternal dietary avoidance vs stopping
- Substitute for breast milk: Hypoallergenic formula is recommended if the trigger is thought to be cow's milk
 - Extensively hydrolyzed casein or amino-acid formula [up to 40%]

And guidelines have some suggestions for solid foods to be introduced to infants with FPIES, starting with lower risk food at the age 4 to 6 months and moving to moderate risk and to higher risk food.⁷ You do it at this age level, and then move on to the lower risk for the older age group. This goes through the first year of life.

Peanut FPIES

I mentioned before that peanut FPIES is something we're seeing more often than 20 years ago. There are a couple smaller studies that have been published over the past 5 years.¹⁵ We noticed a higher incidence of peanut-induced FPIES, 12.5%. This is really high. But overall, FPIES to peanuts, is very uncommon, in less than 2% of all FPIES cases.

Ages and Stages	Lower-risk foods ^[a]	Moderate-risk foods ^[a]	Higher-risk foods ^[a]
4–6 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 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 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	Apple, pear, orange	Banana, avocado
8 months of age or when developmentally appropriate • Offer soft-cooked and bite-and-dissolve textures around 8 months 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 ^[a] (sesame, sunflower, etc)	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

Table 5 — Selecting Safe Nutritional Alternatives

It's important to introduce peanuts early. If you have an infant with a known FPIES, you don't want to introduce peanut as your first food after the reaction. But we will continue introducing peanuts and eggs early because the benefits outweigh those of FPIES. Remember, FPIES is 0.5% overall in children, peanut allergy is about 2.2%, egg allergy about 1%. I'm talking about IgE-mediated food allergy.¹⁶

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Peanut FPIES

- Early peanut introduction may contribute to peanut-induced FPIES
- Small study (n=32) 2017 Wu et al.^[1]
 - Higher incidence of peanut-induced FPIES (12.5%) in atopic infants with early peanut introduction
 - FPIES to peanut is uncommon; only 1.9% of all FPIES cases
- Early introduction of nuts is important; however, it can be a potential risk factor for FPIES <<clinicians need to be aware>>
- Continue to introduce peanut and egg early, as benefits outweigh risk for FPIES
- **Be aware of a potential FPIES diagnosis**

1. Wu V, et al. *J Allergy Clin Immunol*. 2019; Abstract 143C2 suppl AB263.

Slide 24 — Peanut FPIES

Timing Reintroduction of Food

This is a third case study, regarding the timing of reintroduction of the offending food. Our infant is now 1½ years old. Isabella is ready to enter daycare. Her parents are going back to work after the COVID lockdown, and they worry what will happen if she's exposed or ingests oat cereal. When is the optimal time to reintroduce the food that has triggered FPIES? This is the question to our audience.

Case Study 3— Timing of Reintroduction of Offending Food

Our case infant is now a toddler at 1.5 years and ready to enter daycare. Her parents are returning to their offices after working from home during Covid. They worry about what will happen if she grabs oat cereal from another child, picks it up from a table, or is fed oats incidentally.

Isabella

Slide 25 — Case Study 3—Timing of Reintroduction of Offending Food

That's an easy question. Let me go over the options. A, it is recommended to retry food for introduction every 3 to 6 months; B, not sooner than 24 months from the most recent reaction; C, when the child is older than 3 years; and D, it really depends on the nutritional and social importance of the food, as

well as the severity of the past reaction. I'm giving you some time to reflect on that question.

When is the optimal time to reintroduce the food that has triggered FPIES?

- It is recommended to re-try food reintroduction every 3–6 months
- Not sooner than 24 months from the most recent reaction
- When the child is older than 3 years
- Depends on the nutritional and social importance of the food, as well as the severity of the past reaction

60% answered D. 20% answered C, and 20% answered A.

That's interesting. The correct answer is D. We would like time for the reintroduction of the food, and the importance of the food to the diet or socially. We definitely don't need to wait until the child is older than 3 years. We don't have to reintroduce..., we don't have to wait 2 years from the most recent reaction. We could, but usually it's between 6 to 24 months, but this is modified by how important the food is.⁷

Case Study 3—Explanation

The decision to reintroduce the FPIES trigger is made empirically because there are no biomarkers to guide the timing.^[1] It is a shared decision between the caregivers and the physician, taking into consideration the nutritional and social importance of the food. Usually, foods that are dietary staples, such as cow's milk, egg, or wheat, tend to be reintroduced sooner than foods that are not as prevalent in the diet, eg, sweet potato, or fruits.

In one approach, food can be re-tried within 6–24 months following the most recent reaction. Generally, the more severe the most recent reaction was (especially to small amount of the food), the more worried and more apprehensive the caregivers / patients are to re-try the food, which leads to a more deferred reintroduction.

1. Nowak-Wegzyn A, et al. *J Allergy Clin Immunol*. 2017;139:1111-1126.e4.

Isabella

Slide 26 — Case Study 3—Explanation

So, that's the explanation for that slide. It's a shared decision. You have to discuss this with the parents. If they are willing to try the food, especially if this is milk, if this is egg, something that's very important to nutrition, they cannot afford elemental formula or hypoallergenic formula. You definitely have a

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

good reason to try the food, as long as you do it in a supervised environment. Also, in [the] case of Isabella, we're talking about the social importance.

NEW AREAS OF RESEARCH IN FPIES

We are going on to close this presentation highlighting the new areas of research in FPIES. As I mentioned before, we don't really know FPIES type of mechanism, but we know that there's no humoral or antibody responses to the food. With my collaborator, Cecilia Berin, we have provided some important evidence that FPIES is like a bridge between innate immune reaction to food vs the adaptive immune response.² It's unique in the world of food allergy. However, we still haven't uncovered the mechanism of what determines the specificity of the food recognition. There are infants who react only to 1 specific food. We really don't know what the mechanism is for that specificity.

Immune Mechanisms of FPIES

- Limited insights into FPIES pathomechanism
- No detectable antigen-specific antibody response
- Berin et al. (2021): Systemic innate immune activation combined with Th17 and innate lymphocyte activation; unique innate and adaptive immune activation
- Mechanism of specific food recognition (antigen specificity) by the immune system remains unclear

Berin MC, et al. J Allergy Clin Immunol. 2021;148:895-901.e6.

Slide 27 — Immune Mechanisms of FPIES

I want to also highlight that FPIES can start in adults. Seafood is most often the cause. The guidelines that we published in 2017 did not focus on adults. There could be a delay in diagnosis. Most adults have multiple reactions because their symptoms are mistaken for food poisoning. We are definitely seeing an in the increasing number of adults. In the US, we have estimated that FPIES affects 0.2% of adults.¹⁷ It seems like it's becoming more relevant.

FPIES in Adults!

- FPIES can also start in adulthood
- Seafood most often the cause
- Guidelines did not focus on adults, who may (or appear to) have a different clinical presentation than children.
- Delay in diagnosis!
 - Adult FPIES is often mistaken for food poisoning
- Need to advance our understanding of FPIES in adults

Li DH, et al. Allergy Asthma Clin Immunol. 2020;16:99.

Slide 28 — FPIES in Adults!

In adults, in contrast to children, females are more affected than males. The food triggers are typically seafood, fish or crustaceans. The onset may be different; it may be more delayed and the symptoms sometimes involve very severe abdominal pain without vomiting.¹⁷

Characteristics	Children	Adults
Sex	Male > Female	Female > Male
Food trigger	Cow's milk, soy	Seafood, crustaceans
Onset (range)	1-4 h	3 min-6.5 h

Table 6 — Characteristics in Children vs Adults

Ongoing Unmet Needs

There are many unmet needs in terms of FPIES. We need a biomarker. We would like to improve our food challenge procedure because the availability of the food challenge is quite limited. It leads to unnecessary delayed introduction of food. And even though the prognosis is favorable, FPIES is causing a bigger burden to families. We'd like to define it: how does it affect the quality of life for caregivers and the quality of feeding in children; what is the financial burden?

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

Unmet Needs-I

- Laboratory biomarker
- Standardized food challenge procedure
 - Accessibility for oral food challenges primarily at large academic centers
 - IV access
 - Prolonged observation
- Burden of FPIES for families
 - QoL of caregivers and feeding children
 - Impact on families who stop working or move for family support
 - Financial burden—Out-of-pocket costs for FPIES

QoL, quality of life.

Federal-Funded Research Is Lacking

- Lack of federally funded research is an impediment
- First NIH workshop to be held June 2022
 - NIH recognizing FPIES as a public health topic
- In addition to pathophysiology research there is interest in microbiome and FPIES.
- Epidemiology of FPIES is needed to study its natural history

NIH, National Institutes of Health.

Slide 29 — Unmet Needs-I

In terms of the more basic [unmet needs], we would like to know the genetics of FPIES to identify risk factors and develop some good effective prevention strategies, as well as therapies for acute reactions, and ideally strategies to accelerate resolution of FPIES.

Unmet Needs-II

- Define genetics
- Identify risk factors
- Prevention strategies
- Therapies for acute reactions and to accelerate resolution

Slide 30 — Unmet Needs-II

The research in FPIES has been slow or was limited because there was no federal funding for research. We are hoping this will change. The first NIH workshop [is] to take place in June of 2022, which means the NIH is recognizing FPIES as a public health problem. So, hopefully there will be some specific requests for applications following that meeting.

Slide 31 — Federal-Funded Research Is Lacking

Takeaways: suspect acute FPIES in infants with projectile emesis starting 1 to 4 hours after food ingestion. Acute FPIES is more dramatic than chronic FPIES, which develops over time. Suspect chronic FPIES in young infants with dramatic presentation, such as dehydration, metabolic acidosis, and shock that develops over days to weeks. And empower caregivers to introduce new foods without delay. Pay attention to nutritional status; provide a clearly outlined plan for managing acute reactions and monitor for tolerance development.

Key Takeaways

- ★ Suspect acute FPIES in infants with projectile emesis starting 1–4 hours after food ingestion. Acute FPIES typically is more dramatic than chronic FPIES, which develops over time.
- ★ Suspect chronic FPIES in young infants with dramatic presentation (dehydration, metabolic acidosis, shock).
- ★
 - Empower caregivers to introduce new foods without delay.
 - Pay attention to nutritional status.
 - Provide clearly outlined plan for managing acute reactions.
 - Monitor for tolerance development.

Slide 32 — Key Takeaways

Here are some key free resources. I would like to encourage you to use the ICD-10 code K52.2, when you see patients to help us track the prevalence of this disease.

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome



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.*

That's a great question. I don't know. I think it's important, just the timing with the food introduction, because FPIES can start within days or weeks after you introduce the food. I'm not sure whether it makes a difference. I have never had a patient who was a premature infant who was fed with calcium formula or soy formula for 5 months and then started having symptoms. I think it's the timing of the introduction of the food in the diet. So, you wouldn't be adjusting for the prematurity.

As a general practitioner or NICU provider, if we suspected FPIES but want to refer to a subspecialist, is it better to be diagnosed, managed by a pediatric gastroenterologist or allergy immunologist?

It depends on your resources, on the environment you are in. FPIES is a food allergy. We don't perform endoscopies and biopsies for those infants. I think they should be seen. If it's a clear-cut situation, and you have a high suspicion, I would refer to the allergist. But if you have very strong relationship with your gastroenterologist, and they are familiar with the management, and they would be able to introduce the food, guide the patient with the interaction of the food, I don't think there's any contraindication for that. But it is a food allergy, and keep in mind that those infants will likely develop some other allergic conditions as they get older. It might not be a bad idea to establish a relationship with an allergist for them.

Do you know if there's a maximum amount of a FPIES food trigger that children can tolerate? You mentioned a case where a young girl could tolerate traces amounts of soy, and that parents do not need to worry about foods that say, "may contain."

Yes, so you would have to do a challenge, right? You would have to do a... to determine what is the threshold for that individual child. Usually go by the history, right? If you have a history that the child reacted to a lick of the food from a spoon, I would

QUESTION & ANSWER

Editor's Note: This is a transcript of audience questions together with presenter responses from the May 26, 2022, webcast.

Can an older child have both an IgE allergy to cow's milk and an FPIES reaction? For example, I've had a patient 5-years old experiencing acute vomiting FPIES reaction about 8 hours after ingestion compared to the 2-hour mark as an infant.

Anna Nowak-Węgrzyn, MD, PhD: It's more common to have FPIES to 1 food and an IgE food allergy to another food, but there are some reports in literature that there could be a back and forth, oscillating between the FPIES phenotype and the IgE-mediated food allergy in patients with atypical FPIES. So, it is possible, although it is very rare.

Is there a higher risk for siblings to develop FPIES?

There is. It's not 10-fold, but definitely, if there's FPIES in an older sibling, there is a slightly increased risk for FPIES. I think it's maybe 5-fold increase over the general population, so definitely you should be watching for that.

How can we relate FPIES to infants born prematurely? Would a diagnosis need to be delayed until they are 2 to 3 months corrected or is chronological age still applicable?

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

say that this child has a very low threshold. You would be worried about even very small amounts of the food. But let's say in [a] case of cow's milk FPIES, the typical amount is about 1 oz before the child develops a reaction.

There was a study from Israel, which challenged children in an incremental way. They found that the vast majority reacted after drinking about 30 mL, 1 oz of liquid milk. It's not a trace for sure, unless you have that compelling and convincing history of a serious reaction with a tiny amount. Most children don't need to avoid food with their precautionary labeling.

How do I encourage families to offer age- and skill-appropriate textures to prevent development of food difficulties?

You could use the guidelines and utilize the table,⁷ which says, those are the appropriate foods. You start with the foods that are blended and thin. Then

as they get older, you will start with foods that are more coarse and not mashed up. If the child or the parents are having concerns, I would refer them to a registered dietician for consultation. Obviously, pediatricians and allergists or gastroenterologists may not have that much time to go over the mechanics of the feeding, but keep in mind that even in a child that has, let's say, 5 foods in their diet, you can vary the texture.

That's another consideration when you choose foods for introduction. For instance, if you introduce apple, you could have an apple sauce. You can have apple chips in older children. If you introduce potato, it could be mashed potato. It could be French fries. It could be potato chips that you can make. So, it requires some creativity, but once you sort of show the parents that this can be done, they can follow, but if you have a registered dietician, they're also very, very helpful with that.

Abbreviations

EoE	Eosinophilic esophagitis	IgE	Immunoglobulin E
FPE	Food protein-induced enteropathy	NEC	Necrotizing enterocolitis
FPIAP	Food protein-induced allergic proctocolitis	NPO	Nothing by mouth
FPIES	Food protein-induced enterocolitis syndrome		

References

1. 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
2. Nowak-Węgrzyn A, Berin MC, Mehr S. Food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol Pract*. 2020 Jan;8(1):24-35. doi:10.1016/j.jaip.2019.08.020. PMID: 31950904
3. Lee E, Barnes EH, Mehr S, Campbell DE. An exploration of factors associated with food protein-induced enterocolitis syndrome: Birth, infant feeding and food triggers. *Pediatr Allergy Immunol*. 2021;32(4):742-749. doi:10.1111/pai.13448

Guideline-Based Care of Infants With Food Protein-Induced Enterocolitis Syndrome

4. Alonso SB, Ezquiaga JG, Berzal PT, et al. Food protein-induced enterocolitis syndrome: increased prevalence of this great unknown—results of the PREVALE study. *J Allergy Clin Immunol.* 2019;143(1):430-433. doi:10.1016/j.jaci.2018.08.045
5. Lemoine A, Colas AS, Le S, Delacourt C, Tounian P, Lezmi G. Food protein-induced enterocolitis syndrome: A large French multicentric experience. *Clin Transl Allergy.* 2022;12(2):e12112. doi:10.1002/ct2.12112
6. Blackman AC, Anvari S, Davis CM, Anagnostou A. Emerging triggers of food protein-induced enterocolitis syndrome: Lessons from a pediatric cohort of 74 children in the United States. *Ann Allergy Asthma Immunol.* 2019;122(4):407-411. doi:10.1016/j.anai.2019.01.022
7. 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. 28167094
8. Nicolaides R, Bird JA, Cianferoni A, Brown-Whitehorn T, Nowak-Węgrzyn A. Oral Food Challenge for FPIES in Practice-A Survey: Report from the Work Group on FPIES Within the Adverse Reactions to Foods Committee, FAED IS, AAAAI. *J Allergy Clin Immunol Pract.* 2021;9(10):3608-3614.e1. doi:10.1016/j.jaip.2021.06.061
9. Leonard SA, Miceli Sopo S, Baker MG, Fiocchi A, Wood RA, Nowak-Węgrzyn A. Management of acute food protein-induced enterocolitis syndrome emergencies at home and in a medical facility. *Ann Allergy Asthma Immunol.* 2021;126(5):482-488.e1. doi:10.1016/j.anai.2021.01.020
10. Maciag MC, Bartnikas LM, Sicherer SH, et al. A slice of food protein-induced enterocolitis syndrome (FPIES): Insights from 441 children with FPIES as provided by caregivers in the International FPIES Association. *J Allergy Clin Immunol Pract.* 2020;8(5):1702-1709. doi:10.1016/j.jaip.2020.01.030
11. Bartnikas LM, Nowak-Węgrzyn A, Schultz F, Phipatanakul W, Bingemann TA. The evolution of food protein-induced enterocolitis syndrome: From a diagnosis that did not exist to a condition in need of answers. *Ann Allergy Asthma Immunol.* 2021;126(5):489-497. doi:10.1016/j.anai.2021.01.001
12. Su KW, Patil SU, Stockbridge JL, et al. Food aversion and poor weight gain in food protein-induced enterocolitis syndrome: A retrospective study. *J Allergy Clin Immunol.* 2020;145(5):1430-1437.e11. doi:10.1016/j.jaci.2020.01.001
13. Groetch M, Durban R, Meyer R, Venter C, Nowak-Węgrzyn A. Dietary management of food protein-induced enterocolitis syndrome during the coronavirus disease 2019 pandemic. *Ann Allergy Asthma Immunol.* 2021;126(2):124-126. doi:10.1016/j.anai.2020.05.005
14. Ruffner MA, Wang KY, Dudley JW, et al. Elevated atopic comorbidity in patients with food protein-induced enterocolitis. *J Allergy Clin Immunol Pract.* 2020;8(3):1039-1046. doi:10.1016/j.jaip.2019.10.047
15. Lopes JP, Cox AL, Baker MG, et al. Peanut-induced food protein-induced enterocolitis syndrome (FPIES) in infants with early peanut introduction. *J Allergy Clin Immunol Pract.* 2021;9(5):2117-2119. doi:10.1016/j.jaip.2020.12.023
16. Wu V, Vakaljan SL, Scheffler SA, Ohayon JA. Could early peanut introduction in atopic infants increase the risk of peanut induced FPIES? *J Allergy Clin Immunol.* 2019; Abstract only 143(2) suppl AB263 <https://doi.org/10.1016/j.jaci.2018.12.803>
17. Li DH, Wong-Pack A, Macikunas AL, Kim H. Adults with possible food protein-induced enterocolitis syndrome with crustacean ingestion. *Allergy Asthma Clin Immunol.* 2020;16(1):99. doi:10.1186/s13223-020-00497-z