Clinical Commentary Review

Food Protein-Induced Enterocolitis Syndrome

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Learning objectives:

1. To describe the clinical characteristics of food protein-induced enterocolitis syndrome (FPIES) phenotypes.
2. To identify the potential role of innate immunity and IgE in FPIES.
3. To identify criteria for FPIES diagnosis.
4. To describe the management of acute FPIES episodes as well as long-term management, recognizing the potential co-reactivity between food triggers.

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Food protein-induced enterocolitis syndrome (FPIES) is a non−IgE-mediated food allergy that manifests with projectile, repetitive emesis that can be followed by diarrhea and may be accompanied by lethargy, hypotonia, hypothermia, hypotension, and metabolic derangements. FPIES usually starts in infancy although onset at older ages is being increasingly recognized. FPIES is not rare, with the cumulative incidence of FPIES in infants estimated to be 0.015% to 0.7%, whereas the population prevalence in the US infants was 0.51%. FPIES diagnosis is challenging and might be missed because of later (1-4 hours) onset of symptoms after food ingestion, lack of typical allergic skin and respiratory symptoms, and food triggers that are perceived to be hypoallergenic. Diagnosis is based on the recognition of symptoms because there are no biomarkers of FPIES. The pathophysiology remains obscure although activation of the innate immune compartment has been detected. Management relies of avoidance of food triggers, treatment of accidental exposures, and periodic re-evaluations with supervised oral food challenges to monitor for resolution. There are no strategies to accelerate development of tolerance in FPIES. Here we review the most important current concepts in epidemiology, pathophysiology, diagnosis, and management of FPIES. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:24-35)

Key words: *Food allergy; Food protein-induced enterocolitis syndrome; FPIES; Food challenge; Cow milk allergy; Rice allergy; Shellfish allergy*

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Abbreviations used
CM- Cow's milk
CRP- C-reactive protein
FPIES- Food protein-induced enterocolitis syndrome
OFC- Oral food challenge

Food protein-induced enterocolitis syndrome (FPIES) is a non−IgE-mediated food allergic disorder that can manifest with symptoms of projectile, repetitive emesis that can be followed by diarrhea and may be accompanied by lethargy, hypotonia, hypotension, hypothermia, and metabolic derangements.[1] FPIES usually starts in infancy although onset at older ages is being increasingly recognized. FPIES is not rare, with the cumulative incidence of FPIES in infants estimated to be 0.015% to 0.7%, whereas the population prevalence in the US infants was 0.51%.[2-5]

FPIES diagnosis is challenging and might be missed because of delayed (1-4 hours) onset of symptoms after food ingestion and lack of typical allergic skin and respiratory symptoms, as well as food triggers that are perceived to be hypoallergenic.[6-8] Diagnosis is based on the recognition of symptom constellation because there are no biomarkers of FPIES. The pathophysiology remains obscure although activation of the innate immune compartment has been detected.[9,10] Management relies of avoidance of food triggers, treatment of accidental exposures, and periodic re-evaluations with supervised oral food challenges (OFCs) to monitor for resolution. There are no strategies to accelerate development of tolerance in FPIES.

In this article, we will review the most important current concepts in epidemiology, pathophysiology, diagnosis, and management of FPIES.

FPIES EPIDEMIOLOGY

Phenotypes: acute, chronic, adult, atypical, during exclusive breastfeeding

Clinical presentation of FPIES is determined by the frequency and the dose of the food allergen in the diet.

Acute FPIES. If food is ingested on an intermittent basis and at a lower dose, acute symptoms emerge. Acute FPIES is characterized by repetitive, projectile emesis, within 1 to 4 hours (typically 2 hours) of food ingestion, and may be associated with concurrent lethargy, hypotonia, pallor, and/or hypothermia. Diarrhea may follow within 6 to 8 hours. Symptoms usually resolve within 24 hours. Anecdotally, very severe reactions during an acute episode or an OFC may be associated with more persistent abdominal pain and diarrhea lasting for few days or weeks. Reports from Japan describe fever in the setting of acute FPIES but has not been reported in other ethnic groups.[11,12] Infants with acute FPIES are well in between the episodes and are growing and developing well.

Chronic FPIES. If food is ingested frequently, such as daily feedings with cow's milk (CM)-based or soy-based formula in young infants, chronic FPIES emerges. Chronic FPIES is characterized by frequent watery diarrhea (occasionally with blood or mucous) accompanied by intermittent and progressively worsening emesis over days to weeks that are associated with poor weight gain or weight loss.[13] Both acute and chronic FPIES may culminate in dehydration, metabolic acidosis, hypotension, and hypovolemic shock necessitating admission for emergent medical management. Child with CM or soy FPIES may present initially with chronic symptoms in infancy and with acute symptoms after a period of avoidance and then early reintroduction.[13] Table I compares clinical and laboratory features of acute and chronic FPIES.

A clinical vignette (Figure 1) illustrates this phenotypic fluidity. Chronic FPIES symptoms may take days to weeks to fully resolve, and occasionally require a temporary bowel rest and parenteral feeding.

Adult FPIES. FPIES in older children and adults usually presents as acute symptoms within 1 to 4 hours of food ingestion, and typically triggered by seafood.[15,16] Patients report tolerating the food regularly beforehand although no clear inciting event has been identified leading to the development of FPIES. The most commonly reported symptoms include severe abdominal pain, followed by emesis, and diarrhea.[17] In extreme cases, loss of consciousness has been reported.[16] In adults, FPIES is more common in females than in males, whereas in children there is no female predominance.[16,17]

Atypical FPIES. A subset of infants with FPIES develop positive skin test and/or serum food-specific IgE to the FPIES food trigger, referred to as atypical FPIES.[18] The frequency of atypical FPIES varies by population, between 5% and 30% of infants with CM-FPIES, but atypical FPIES has also been rarely reported with foods other than CM.[7,8,19] The majority of infants with atypical FPIES retain FPIES phenotype; however, a subset of approximately 25% may over time switch to classic IgE-mediated food allergic reactions.[7,20,21] Limited data suggest that atypical CM-FPIES is more persistent and resolves at an older age than classic FPIES.[7,18] Some reports describe a classic IgE-mediated food allergy switching to FPIES phenotype, highlighting phenotypic fluidity and the shared underlying dysfunction of the immune responses in FPIES and IgE-mediated food allergy (Figure 1).[14]

FPIES during exclusive breastfeeding. Infants who are exclusively breastfed are usually asymptomatic and protected from a full expression of the FPIES phenotype when the offending food is present in the maternal diet. They react on the direct feeding of that food only. Reports from Japan describe symptoms in up to 30% of infants with CM-FPIES, whereas other studies report less than 5% suggesting variable genetic susceptibility to expressing FPIES symptoms during exclusive breastfeeding.[2,7,19] It is possible that milder gastrointestinal symptoms of colic, gastroesophageal reflux, diarrhea, and irritability may represent an incomplete expression of FPIES during exclusive breastfeeding.

Food triggers

Any food can induce FPIES, but the most common FPIES food triggers vary by age and phenotype. In acute FPIES in infants and children, rice and oat have emerged as the most common triggers, followed by CM, soy, egg, fish, fruits, and vegetables.[7,8,22,23] In Spain and Italy, fish are the most common solid food triggers in infantile acute FPIES, likely reflecting the local dietary patterns.[24-27] In chronic FPIES, CM and soy (in countries that use soy-based infant formula) are the most common triggers.[28,29] In older children and adults, fish and shellfish are most common, although wheat, egg, and dairy have also been reported.[16,17,30,31] The majority (60%) of infants with FPIES react to a single food, 1 in 3 may react to 2 to 3 foods, and 1 in 10 to multiple foods.[7,8] In adults with seafood-FPIES, overall 60% react to a single food group, either fish or shellfish. Fifty

TABLE I. Clinical and laboratory characteristics of acute and chronic FPIES

	Clinical symptoms	Laboratory values that may be present
Acute FPIES	• Repetitive projectile vomiting 1-4 h after food ingestion	• Leukocytosis with neutrophilia
	• Diarrhea within 24 h	• Thrombocytosis
	• Lethargy	• Metabolic acidosis
	• Pallor	• Electrolyte derangements
	• Hypotonia	• Methemoglobinemia
	• Dehydration	• Stool leukocytes, eosinophils
	• Hypovolemia ± shock	• Stool reducing substances
	• Hypothermia	• Stool occult or frank blood
	• Symptoms resolve within 24 h	
	• Normal growth	
Chronic FPIES	• Frequent watery diarrhea	• Leukocytosis with neutrophilia
	• Intermittent but progressive emesis	• Anemia
	• Abdominal distension	• Thrombocytosis
	• Lethargy	• Metabolic acidosis
	• Pallor	• Electrolyte derangements
	• Hypotonia	• Methemoglobinemia
	• Dehydration	• Hypoalbuminemia and hypoproteinemia
	• Hypovolemia ± shock	• Stool leukocytes, eosinophils
	• Hypothermia	• Stool reducing substances
	• Fever (rare, only in Asian infants)	• Stool occult or frank blood
	• Failure to thrive/poor growth	
	• Symptoms resolution over days to weeks, may require bowel rest and parenteral nutrition	

FPIES, Food protein-induced enterocolitis syndrome.
Adapted with permission from Nowak-Wegrzyn et al;[1] the differentiating features are marked in bold.

percent fish-FPIES react to a shellfish (crustacean or mollusk), 40% of crustaceans react to a mollusk, and 55% of mollusks react to crustacean and/or fish.[16]

Prevalence and natural history

Infantile FPIES typically starts in the first year of life, usually within days or weeks of introducing the food into the diet. Frequently, an infant tolerates initial feedings with a small amount of food without any or with minimal symptoms but subsequently develops an acute FPIES when a larger serving of the food is ingested and/or the feeding is interrupted for days-weeks and subsequently resumed. There is no information regarding the events leading to onset of adult FPIES.

The population-based estimates of infantile FPIES cumulative incidence range between 0.015% (Australia) and 0.7% (Spain).[2,3,5] A recent population-based survey of American households described parent-reported, physician-diagnosed FPIES in 0.51% of pediatric population younger than 18 years and in 0.22% of adults.[4] In one study, 20% of US adults reporting allergic reactions to shrimp had no detectable shrimp-specific IgE and presented with exclusive gastrointestinal symptoms.[17]

The natural history of infantile FPIES is generally favorable, as in the majority of patients, FPIES resolves by school age.[3,7,8,32-34] However, in the more persistent phenotype, resolution may be delayed into adulthood. The characteristics of the persistent phenotype are not clearly described but may involve more severe reactions, FPIES to seafood and/or multiple foods. The natural history of adult-onset FPIES is not known; the limited data suggests that it persists for years.[16,17] Table II summarizes selected studies providing insights into the natural history of infantile FPIES caused by various foods.[3,7,8,25,29,33,37,35,36]

IMMUNE PATHOPHYSIOLOGY OF FPIES

Food-specific immunoglobulins and FPIES

FPIES is a non−IgE-mediated food allergy; however, as described above, 5% to 30% of individuals with FPIES have low levels of IgE against the food,[18,19,38] the presence of IgE was found to be associated with persistent FPIES,[7] and there is reported fluidity between FPIES and IgE-mediated food allergy.[7,14,39] The implications of this association with IgE for the pathophysiology of FPIES are not well understood (Table III).

There are conflicting reports of other immunoglobulin isotypes in FPIES, as highlighted in Table III. Two studies have compared children defined with strict criteria as reactive or not by OFC, with one finding elevated food-specific IgA before challenge in reactive infants,[40] and the other finding no difference in milk-specific antibody levels (IgA, IgG, IgD) between reactive and resolved FPIES when measured before challenge.[43] The first cohort was younger (all infants less than 1 year of age vs median 2-4 years of age), and differences in antibody production could reflect a shorter period of time of food avoidance before evaluation. There are some data demonstrating that antigen-specific immunoglobulin responses increase after food challenge in FPIES.[40] This is consistent with older studies in CM enteropathy where mucosal IgA responses were highly responsive to food challenge, rising and falling with exposure and elimination, respectively.[44]

Food-specific T cells and FPIES

The lack of role for IgE led to the hypothesis that FPIES was a type IV hypersensitivity reaction and several groups have investigated antigen-specific T cells. As with immunoglobulin studies, there are mixed results (Table IV). Most studies are able to detect T-cell responses to food antigens by proliferation or activation markers.[9,19,43,45,46] The cytokine profile includes a proinflammatory Th2-skewed immune response including TNFα, IL-5, IL-13, and IL-9.[19,43] IFN-γ production has been reported to be induced[43] or not[9,19] in an antigen-specific manner in FPIES, but there is no evidence that Th1 responses differ between active and resolved FPIES. There are similarly variable results when examining IL-10,[9,19,43] with a trend of increased IL-10 in resolved compared with active FPIES.[43] Two studies show increased antigen-specific T-cell responses in active

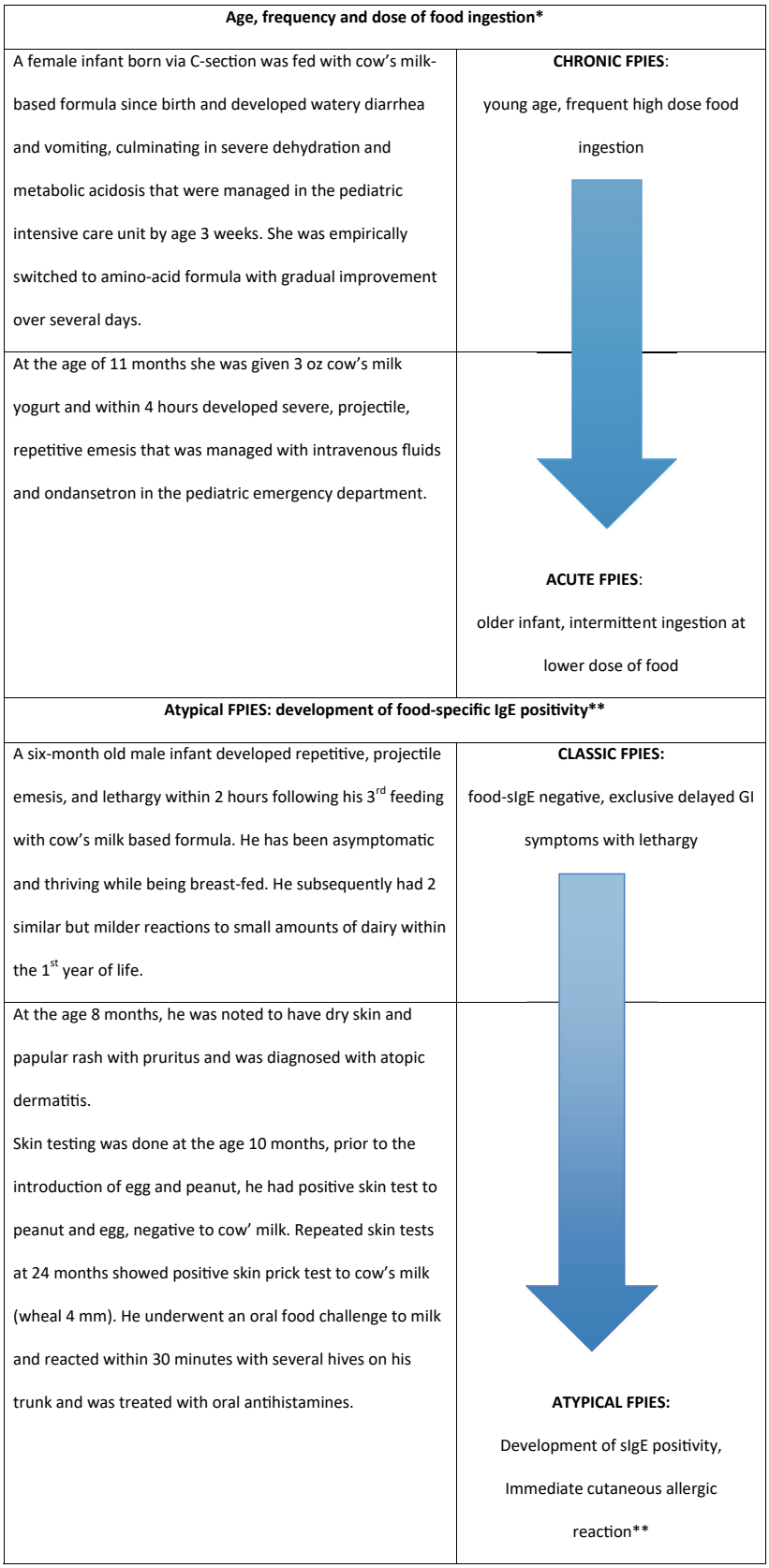

FIGURE 1. Clinical vignette illustrating fluidity of FPIES phenotypes in an individual infant. *This case scenario is based on our clinical experience in which chronic FPIES manifests in young infants who subsequently, after food avoidance in the diet, react with acute FPIES

compared with resolved FPIES.[9,45] However, 2 studies show no difference in antigen-specific T-cell responses when comparing FPIES with healthy controls.[9,46] When taken all together, the data support the conclusion that FPIES is associated with a detectable food-specific T-cell response, but there is a lack of compelling evidence that either the frequency or phenotype of the CD4+ T-cell response is unique to FPIES (Th2-biased immunity is also observed in IgE-mediated food allergy) or can explain the acute reactions to foods in FPIES.

The impact of antigen exposure on the T-cell response in FPIES has not been directly addressed. In the context of celiac disease, gluten challenge is associated with a rise in detectable gluten-specific CD4+ and CD8+ T cells in the peripheral blood in approximately 6 days, and commencement of a gluten-free diet results in a gradual decline of gluten-specific T cells.[47,48] Similar longitudinal studies are needed in FPIES. T-cell activation and expansion after antigen exposure may contribute to gastrointestinal inflammation during chronic FPIES.

INNATE IMMUNITY IN FPIES

One of the diagnostic criteria of FPIES reactions is an increase in circulating neutrophils as measured 4 to 6 hours after symptom onset.[18,49] There is also evidence for eosinophil activation in FPIES, with elevation of stool eosinophil-derived neurotoxin compared with baseline in those reacting to food challenge, and baseline samples slightly but significantly elevated compared with age-matched healthy infants.[50] Circulating eosinophils were also found to have elevated expression of the activation marker CD69.[51]

Two studies that took a data-driven approach have highlighted the major innate immune activation that occurs during an FPIES reaction. Goswami et al[9] used transcriptional profiling by RNAseq and CyTOF analysis of whole blood to study changes associated with positive or negative reactions during FPIES food challenge. The dominant feature of positive FPIES food challenges was monocyte activation, identified by the pathway analysis of differentially expressed genes such as Arg2 and CEACAM1 and upregulation of CD163 at the protein level. Activation was not restricted to monocytes, and was observed by activation marker expression on eosinophils, neutrophils, and natural killer cells. Furthermore, there was a significant loss of circulating of lymphocytes from the circulation and upregulation of CD69 on those remaining, suggesting activation-induced extravasation.

Mehr et al[10] extended these findings using transcriptional profiling of blood from 36 children undergoing a food challenge for FPIES, resulting in data from 10 reactors and 26 nonreactors. Using weighted gene coexpression network analysis, they identified a module of genes that was associated with positive reactions. This module was enriched for genes associated with granulocytes and innate signaling (IL-10, TREM1), and analysis of hub genes identified matrix metalloproteinase 9, IL-β, and STAT3 as central to the positive FPIES challenge response. The finding of hub genes such as IL-1β is exciting because it points to a potential target for intervention (ie, anakinra). STAT3 as a central hub is also interesting, as IL-10 that uses STAT3 to signal was previously found to be elevated in the circulation during positive FPIES challenges.[43] As IL-10 is considered to be regulatory, it is not clear if IL-10 is playing a role in disease or is rather a marker of monocyte activation. Figure 2 summarizes the innate immune activation observed during FPIES reactions.

The mechanism of food recognition by the immune system in FPIES remains unexplained and challenges our understanding of immune recognition. Antigen specificity is typically encoded by the T-cell receptors or B-cell receptors, but there is a lack of evidence for an antibody or T-cell response that deviates significantly from normal in FPIES. Speculated mechanisms that could mediate food recognition include: (1) local antibody or T-cell recognition that is not reflected in the blood, (2) the activation of innate-type receptors that have some differential recognition to different foods, or (3) the processing of food antigens *in vivo* into ligands that can bind or activate TCR or antibody. Lack of access to the gastrointestinal mucosa and lack of animal models hampers our understanding of the immune mechanisms of FPIES.

FPIES diagnosis

The diagnosis of FPIES remains a clinical one. Although the presence of neutrophilia and/or thrombocytosis supports the diagnosis of acute FPIES, these laboratory features are only present in up to 50% of cases, may also be present in sepsis or gastroenteritis, and magnitude of the elevation in the neutrophil count can be as high as that seen in bacterial sepsis.[52] International consensus guidelines published in 2017 aimed to assist in standardizing the diagnosis of acute FPIES by using a system of major and minor criteria (Table V).[1] No such criteria exist for chronic FPIES. Given that profuse vomiting is a common pediatric presentation, the criteria ensure that those presenting only once with profuse vomiting or with milder reactions (eg, vomiting and pallor alone) are not inappropriately diagnosed with FPIES. The criteria strongly suggest for a diagnostic OFC in those with a single reaction (even if all diagnostic major and minor criteria are met). The criteria also ensure standardization of patient cohorts in those conducting research into FPIES. But the accuracy of these criteria has not been evaluated (being based on expert opinion only), access to timely medically supervised OFC in those with single reactions may not be always possible, and ultimately clinical judgment should prevail if a diagnostic OFC is warranted in those with single presentations (eg, FPIES is still the most likely diagnosis in an infant presenting once with profuse vomiting, pallor, and lethargy a couple hours after eating rice for the first time, who then quickly recovers within hours).

A recent study of children with profuse vomiting and subsequently diagnosed with either acute FPIES, infectious gastroenteritis or bacterial sepsis, determined floppiness, pallor without fever, and a normal C-reactive protein (CRP) should alert clinicians to the diagnosis of acute FPIES.[52] An alternative diagnosis must be sought in those presenting with a highly elevated CRP (in this cohort, no infant with FPIES had a CRP value on presentation >20 mg/dL). Although others have reported

symptoms on food ingestion. **This case scenario describes progression to atypical FPIES with clinical symptoms switching from FPIES to immediate IgE-mediated reaction. Please note that the majority of infants/children with atypical FPIES continue to manifest FPIES phenotype with delayed gastrointestinal symptoms. Several case reports also highlighted the possibility of IgE-mediated food allergy switching to FPIES phenotype at an older age.[14] *FPIES*, Food protein-induced enterocolitis syndrome; *GI*, gastrointestinal.

TABLE II. Natural history of infantile FPIES-selected studies

Study, country	Study design, no. of patients	Study population	Food	Rates of resolution by age
Hwang et al, 2009,[28] South Korea	Prospective; n = 23; OFCs were performed at 6 mo of age and every 2 mo thereafter	Cohort of infants with FPIES evaluated by pediatric gastroenterologist practice	Cow's milk, soy	CM: 27.3% by age 6 mo, 100% by age 2 y
				Soy: 75% by age 6 mo, 100% by age 14 mo
Katz et al, 2011,[3] Israel	Prospective, FPIES diagnosed by an OFC in 44 infants	Unselected population-based cohort (n = 13,019), single center	CM	90% resolution rate by age 3 y
Caubet et al, 2014,[7] USA	Retrospective, single-center, n = 160	Cohort of patients evaluated in a referral allergy center	CM, soy, rice, oat, other	Median age (y) at resolution was: CM 5.1; soy 6.7; rice 4.7; oat 4.0
Ruffner et al, 2013,[8] USA	Retrospective, single center, n = 462	Cohort of patients evaluated in a referral allergy center	CM, soy, cereal grains, fruits, and vegetables	Resolution rates:
				By age 2 y: 35%
				3 y: 70%
				4 y: 80%
				5 y: 85%
Lee et al, 2017,[32] Australia	Retrospective, single center, n = 69	Cohort of patients evaluated in a referral allergy center	CM, egg, rice, fish, other	Resolution rates by age 3 y:
				CM: 88%
				Rice: 87%
				Egg: 12.5%
				Fish: 25%
Vila et al, 2015,[35] Spain	Retrospective, single center, n = 21	Cohort of patients evaluated in a referral allergy center	Fish, other	Median age of tolerance:
				Fish: 30% by a median age 4 y (range, 1-17 y)
				Other solid foods (fruit, rice, corn): 3 y (range, 1-4 y)
Gonzalez-Delgado et al, 2016,[25] Spain	Retrospective, single center, n = 16	Cohort of patients evaluated in a referral allergy center	Fish	Fish: 18.75% resolution by a mean age 4.5 y
Sopo et al, 2012,[36] Italy	Retrospective, multicenter, n = 66	Cohort of patients evaluated in a referral allergy centers	CM, other foods*	Overall 48% resolved by a mean age 29 mo (SD, 17 mo)
				Age of resolution:
				CM: 24 ± 8 mo
				Other foods: 53 ± 17 mo ($P < .0006$)

CM, Cow's milk; *FPIES*, food protein-induced enterocolitis syndrome; *OFC*, oral food challenge.
*Other foods: fish, egg, rice, soy, corn, poultry, and goat's milk.

TABLE III. Food-specific immunoglobulins in FPIES

Citation	Comparison	IgA	IgG	IgG_4	IgD
McDonald et al, 1984[40]	Reactive vs nonreactive (CM, soy, egg, by OFC)	Increased in reactive	Increased in reactive (egg and soy, not milk)		
Shek et al, 2005[41]	FPIES vs controls	Increased		Decreased	
Konstantinou et al, 2014[42]	Reactive vs nonreactive (CM, by OFC)	Not different			
Caubet et al, 2017[43]	Reactive vs nonreactive (CM, by OFC)		Not different	Not different	Not different

CM, Cow's milk; *FPIES*, food protein-induced enterocolitis syndrome; *OFC*, oral food challenge.

TABLE IV. Food-specific T-cell responses in FPIES

Citation	Comparison	Method	Finding
Van Sickle et al, 1985[45]	Reactive vs nonreactive (milk, soy, egg by OFC)	Proliferation (^{3}H thymidine)	Increased in reactive vs nonreactive
Hoffman et al, 1997[46]	Milk FPIES vs control	Proliferation (^{3}H thymidine)	Stimulation index not significantly different in FPIES vs controls
Morita et al, 2013[19]	GI food allergy (including FPIES) vs controls	Proliferation (^{3}H thymidine)	Increased proliferation in FPIES vs controls
		Secreted cytokines	Increased TNFα, IL-2, IL-3, IL-6, IL-5, IL-10, IL-13
Caubet et al, 2017[43]	FPIES (casein vs unstimulated)	Proliferation (CFSE)	Proliferative response to casein detected
	FPIES (casein vs unstimulated)	Secreted cytokines	Increased TNFα, IL-5, IL-6, IL-13, IFN-g, IL-9
	FPIES casein vs IgE milk allergy casein	Secreted cytokines	FPIES: increased IL-9, decreased IL-10
Goswami et al, 2017[9]	Reactive vs nonreactive (milk, rice, soy by OFC)	CD154-based detection	Decreased antigen-responsive CD4+ T cells in nonreactive
	Reactive vs healthy controls	CD154-based detection	No difference in antigen-responsive CD4+ T cells

CFSE, Staining with carboxyfluorescein succinimidyl ester; *FPIES*, food protein-induced enterocolitis syndrome; *GI*, gastrointestinal; *OFC*, oral food challenge.

elevations in CRP in some children with acute FPIES, the elevations have been mild (and based on cutoffs used in most laboratories, such reported elevations would have be deemed to fall within the normal range).[11] Febrile FPIES has also been reported in the literature, but appears to be rare outside of Asia.[12] In Asian cohorts, up to 30% of acute FPIES can present with fever, but even in these cases, CRP was only marginally elevated (median of 5-13 mg/dL).[12] The rapid resolution of profuse vomiting and pallor/lethargy within hours of initial presentation should alert the clinician to a potential diagnosis of FPIES. This is a useful distinguishing feature of acute FPIES, compared with infants with sepsis or gastroenteritis,[12] who often have more prolonged symptoms and often require longer admissions in hospital.

Metabolic syndromes, multiple food protein intolerance, immunodeficiency/dysregulation syndromes, and early onset inflammatory bowel disease must be considered in those presenting with suspected FPIES.[1] This is especially the case if the child has coassociated failure to thrive, organomegaly, persistent diarrhea (particularly if bloody) despite appropriate food elimination, persistently elevated inflammatory markers, and reactions to multiple different food proteins (eg, children with lysurinic protein intolerance can initially present with FPIES-like reactions after eating large protein loads, and thus may be misdiagnosed as having multiple food FPIES).[53] Table VI presents differential diagnosis of FPIES.

FPIES management

Community and hospital management of an acute FPIES reaction involves appropriate fluid rehydration and potentially the administration of ondansetron. Adrenaline has no place in the management of acute FPIES reaction (and as such infants do not need to be prescribed adrenaline autoinjectors unless required for a concomitant IgE-mediated food allergy). Ondansetron appears to reduce the severity of frequency of profuse vomiting in acute mild-moderate FPIES based on retrospective cohorts (with no randomized control trial evidence currently available), but must be avoided in infants <6 months of age (due to the lack of safety data) and those with a history of heart defects/arrhythmias (due to the risk of prolonged QT).[20]

Infants already diagnosed with FPIES who have another reaction in the community are encouraged to seek medical attention if they are lethargic, floppy/hypotonic, or hypothermic. FPIES action plans are available in some countries to assist child cares/schools to determine when to seek medical care, and FPIES emergency letters are available for parents if emergency care is required; the letters provide the attending physician with basic information about acute FPIES. Templates of FPIES emergency letters can be found online (eg, https://www.fpies.org/wp-content/uploads/2018/08/IFPIES-ER-Letter-2018.pdf; https://www.allergy.org.au/patients/food-other-adverse-reactions/fpies-action-plan).

Long-term management of acute FPIES revolves around providing reassurance that the majority of children will only have 1 trigger, foods with precautionary labeling are safe, exclusion of the triggering food in the maternal diet while breastfeeding is not required unless the infant is symptomatic, and the prognosis is excellent in the majority of children. Long-term management of chronic FPIES involves removing the triggering food(s) from the diet, and then reintroducing it

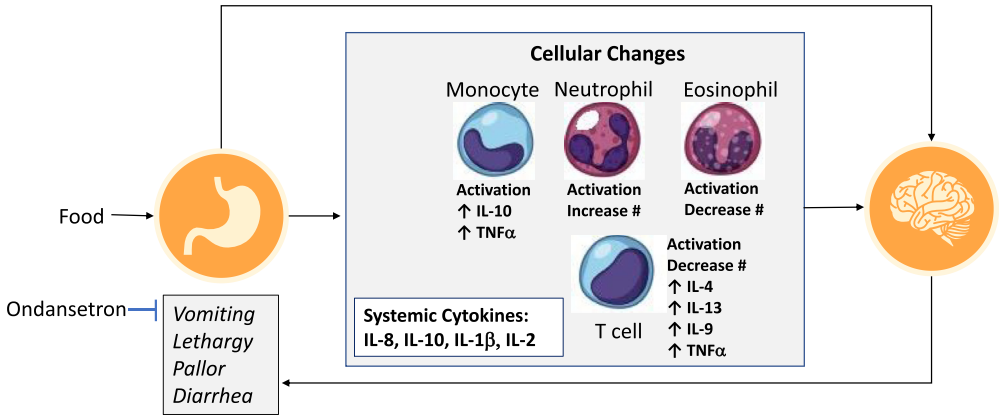

FIGURE 2. Pathogenesis of food protein-induced enterocolitis syndrome (FPIES). Ingestion of foods results in repetitive vomiting, pallor, and lethargy within approximately 2 hours ± delayed diarrhea symptoms in children with FPIES. Immune characteristics of FPIES reactions include broad systemic innate immune activation of monocytes, eosinophils, neutrophils, and release of cytokines into the systemic circulation. It is not yet clear if triggering of neuronal vomiting pathways is independent or downstream of local or systemic immune activation, but administration of the 5HT3 receptor antagonist ondansetron effectively terminates FPIES symptoms.

TABLE V. Diagnostic criteria for patients presenting with acute FPIES in the community setting*

Major criterion
Vomiting (1-4 h after ingestion of the suspect food) and absence of classic IgE-mediated allergic skin or respiratory symptoms
Minor criteria (3 or more)
• A second (or more) episode of repetitive vomiting after eating the same suspect food
• Repetitive vomiting episode 1-4 h after eating a different food
• Extreme lethargy with any suspected reaction
• Marked pallor with any suspected reaction
• Need for emergency department visit with any suspected reaction
• Need for intravenous fluid support with any suspected reaction
• Diarrhea in 24 h (usually 5-10 h)
• Hypotension
• Hypothermia

FPIES, Food protein-induced enterocolitis syndrome.
The diagnosis of acute FPIES reactions requires the major criterion and 3 or more of the minor criteria. If only a single FPIES reaction has occurred, it is strongly recommended that a diagnostic food challenge be performed.
*Adapted with permission from Nowak-Wegrzyn et al.[1]

(often >12 months since their initial presentation). Because of the risk of transformation into acute FPIES or IgE-mediated reaction, such challenges should be performed under physician supervision in a medical facility.[1]

Guidelines are available to assist in new food introduction in those presenting with acute FPIES. These guidelines, based only on expert opinion, in essence promote the introduction of foods less likely to cause FPIES first before more commonly reported triggers of FPIES (eg, sweet potato, banana, legumes, dairy, soy, egg, rice, oats, chicken, and fish).[1] The guidelines attempt to provide a framework for parents to follow, who are often worried about what food to try next. Table VII summarizes dietary advice in those who present with specific FPIES triggers. Limited data[54] are available regarding rates of tolerance to modified food allergens. Some centers offer OFC to foods where coallergy is more likely (eg, if CM-FPIES, then soy may be challenged under medical observation). However, it is important to note that coassociation between food allergens is not absolute (eg, CM/soy coreactivity is approximately 40% to 60%; rice and oats is approximately 40% to 50%), and that infants with FPIES may react after a few times of initially tolerating a food.[2]

Many infants appear to outgrow FPIES 12 months after their last reaction, and the timing of the OFC to evaluate for FPIES resolution depends on the dietary and social importance of the food as well as patients and family preferences. Considering the natural history of FPIES to specific food, OFC to determine tolerance to common triggers such as rice, CM, and egg may be considered by 18 to 24 months of age (and if the child's last reaction has been >12 months ago), whereas challenges to fish could be deferred until 5 years of age or older.

Currently, OFCs should be conducted in a medical facility equipped for fluid resuscitation. How FPIES OFCs are conducted will vary between centers, but the overriding principles of FPIES challenges are: (1) the patient is observed for at least 4 to 6 hours after the last ingested dose and an age appropriate amount is eaten (either as a single dose or as split doses), (2) for determination of tolerance an ssIgE or skin prick test should be considered at the time of the OFC due to the risk of IgE-mediated transformation (particularly to CM or egg; IgE transformation to rice/oats has not yet been reported), (3) intravenous access should be at least available if required, and (4) ondansetron (oral, intravenous, intramuscular) may be effective in reducing the severity of a reaction; there is a lack of any evidence about the efficacy of corticosteroids for acute reactions.[6,7,20,55,56] Although there have been no reported cases of fatality from FPIES, acute reactions can induce hypotension and hypothermia.[7,55] The safety of conducting FPIES challenges at home has not been studied. Nevertheless, there is a move in some centers toward making FPIES challenges shorter (eg, single dose or abbreviated challenges with a 4-hour observation time instead of whole day OFCs or splitting challenges over 2 days) and not inserting intravenous lines beforehand in all cases.[3,55,56] At one center an initial test serve is given in hospital with an intravenous line

TABLE VI. Differential diagnosis of FPIES

Condition	Similarities with FPIES	Differentiating features from FPIES
Allergic disorders		
Food protein-induced allergic proctocolitis (FPIAP)	Stool with blood or mucous, associated with feeding with cow's milk formula	Well-appearing, thriving infant; no vomiting, resolution sooner (approximately 1 y of age)
Food protein-induced enteropathy (FPE)	Failure to thrive, intermittent vomiting or diarrhea with ingestion of specific food (eg, cow's milk, soy, egg, wheat, etc.)	Small bowel injury and malabsorption. No lethargy, pallor, or dehydration, and no metabolic derangements. Diagnosis confirmed with endoscopy and biopsy
Anaphylaxis	Vomiting, diarrhea with ingestion of specific food, reproducible	Immediate symptoms with ingestion of food (minutes to 1 h), positive SPT and food-ssIgE, other systemic symptoms (ie, urticaria, angioedema, wheezing, etc.)
Eosinophilic esophagitis (EoE)	Triggered by specific food, vomiting, failure to thrive	Vomiting less profuse, nonprojectile, early satiety, older children-dysphagia/food impaction, chronic
Gastrointestinal disorders		
Celiac disease	Failure to thrive, chronic diarrhea, vomiting, anemia	Small bowel injury and malabsorption; celiac serology and generic markers positive, confirmation with biopsy
Gastrointestinal reflux	Intermittent vomiting	No diarrhea, no dehydration, vomiting usually minimal
Lactose intolerance	Diarrhea with ingestion of specific food (lactose)	Symptoms with liquid cow's milk/large amounts of cheese or cream/lactose; bloating, flatulence, low prevalence under 5-6 years of age; frequently positive family history of lactose intolerance
Cyclic vomiting	Repetitive recurrent vomiting, lethargy	Vomiting not associated with food, typically early in the day; prodrome: headache, photophobia
Anatomical GI obstruction		
Malrotation/volvulus	Bilious vomiting in an infant, bloody stool (bowel ischemia), dehydration and shock, failure to thrive, distended loops of bowel on X-ray	Not associated with a specific food; sepsis from necrotic bowel, fluid resuscitation alone does not improve symptoms
Intussusception	Intermittent, vomiting, bloody diarrhea, lethargy, and pallor	Severe cramping abdominal pain-intermittent, not associated with specific food, abdominal mass on examination, detectable on ultrasound
Hirschsprung's disease	Vomiting, failure to thrive in infant/young child	Abdominal distension, constipation, delayed passage of meconium, bilious emesis
Pyloric stenosis	Recurrent projectile vomiting leading to dehydration	No diarrhea, diagnosis with ultrasound
Necrotizing enterocolitis	Lethargy, vomiting, bloody diarrhea, neutrophilia	Higher risk in premature low birth weight infants, formula-fed infants. Requires parental nutrition, IV antibiotics, pneumatosis intestinalis on X-ray
Very early onset inflammatory bowel disease	Failure to thrive, diarrhea, blood or mucus in stool, vomiting	Symptoms are not often linked to specific food; family history may be positive for IBD; confirmation by biopsy findings
Infections		
Sepsis	Sudden lethargy, vomiting, hypotension, hypothermia, neutrophilia	Fever present, treatment with fluid resuscitation alone does not improve
Acute viral gastroenteritis	Vomiting, watery diarrhea	Fever present, slower course over days, no specific food trigger
Bacterial gastroenteritis (*Shigella*, *Salmonella*, *Campylobacter*, *Escherichia coli*)	Vomiting, abdominal pain	Watery or bloody diarrhea, fever, positive stool culture, responds to antibiotics
Inborn errors of metabolism: galactosemia, fructose intolerance, methylmalonic acidemia, ornithine transcarbamylase deficiency	Intermittent vomiting/lethargy	Inability to process sugars, amino acids, and organic acids; many patients may self-avoid food that cannot be metabolized (avoidance of fruit in fructose intolerance and dairy in galactosemia)

(continued)

TABLE VI. *(Continued)*

Condition	Similarities with FPIES	Differentiating features from FPIES
Inadequate energy production: mitochondrial, fatty acid oxidation disorders, glycogen storage disorder	Intermittent vomiting/lethargy	Failure to thrive, heart and muscle involvement, splenomegaly, hypoglycemia
		No diarrhea or food avoidance
Disorders of complex molecules		
Lysosomal storage disorders	Poor growth, feeding swallowing difficulties	Hepatosplenomegaly, developmental delay, short stature, chronic pain
Congenital disorder of glycosylation	Vomiting, diarrhea	Low tone, seizures, dysmorphic features
Congenital methemoglobinemia (type I)	Methemoglobinemia	Mostly asymptomatic, no vomiting or diarrhea, general fatigue, dyspnea
Primary immunodeficiency	Chronic diarrhea (due to frequent or persistent GI infections, eg, enterovirus)	Not specific to food, abnormality in lymphocyte counts, immunoglobulins, etc.
Immune enteropathy	Chronic diarrhea	Diarrhea frequently with blood or mucous, severe diarrhea with no food association, rare in infants and toddlers
Mast cell activation syndrome	Chronic/intermittent watery diarrhea	Symptoms food nonspecific, other organ systems, eg, skin, respiratory, cardiovascular; elevated serum tryptase and/or urinary histamine metabolites or PGD2 or 11-b-PGF2-alpha during at least 2 acute episodes

FPIES, Food protein-induced enterocolitis syndrome; *GI*, gastrointestinal; *IBD*, inflammatory bowel disease; *IV*, intravenous; *PGD2*, prostaglandin D2; *SPT*, skin prick test. Adapted with permission from Nowak-Wegrzyn et al.[1]

TABLE VII. Suggested dietary advice after FPIES to a specific food trigger

Triggering food	Dietary advice
Cow's milk	If a formula required, extensively hydrolyzed formula (EHF) remains the first choice (10% to 20% reactivity) over soy (40% to 60% coreactivity) and amino acid formulas for those who react to EHF.[2] Rice formulas are available, but the rate of coreactivity has not been examined*
Rice	Corn (1% coreactivity) and wheat (5% coreactivity) are often tolerated in those with rice FPIES, whereas there appears to be a higher rate of coreaction to oats (40% coreactivity)[2]
Chicken	Avoid all poultry
Egg/cow's milk	Case reports of tolerance to baked egg/milk (but rate or markers of tolerance to baked goods has not been examined)[3,54]
Fish	Currently suggest avoid all fish, although reports of some children tolerating other fish species.† If a new fish species is desired, an OFC is required[27]
	Approximately 50% those with fish FPIES may react to shellfish

FPIES, Food protein-induced enterocolitis syndrome; *OFC*, oral food challenge.
*In one study of the 33 children who presented with cow's milk FPIES, 22 had a coassociated FPIES reaction to a grain (of which 14 were due to rice).
†In one study, 37 children reacted only to 1 fish species (but 22 had not eaten another species of fish to determine if they were tolerant to other fish).

inserted (approximately one-third of a serve size), and if no reaction occurs, then a gradual updosing is done at home. In this study, 13 of the 30 positive challenges occurred in children who initially passed the challenge in hospital but then reacted at home. However, only 3 presented with profuse vomiting (diarrhea was more common), and only 1 child presented to the emergency department.[55] This shortened hospital approach may be a better way to conduct FPIES challenges, allowing more challenges to be conducted, and potentially improves the chance of the toddler eating a serving size of the foods in the comfort of their own home.

CONCLUSIONS

Over the past 2 decades, big strides were made in our understanding of FPIES epidemiology and characterization of clinical phenotypes. First international consensus guidelines were published in 2017 to improve diagnosis and management of FPIES. However, FPIES remains an enigma with incompletely understood pathophysiology, lack of diagnostic biomarkers, incomplete understanding of its natural history, and no therapeutic strategies to accelerate resolution. These are the biggest unmet needs in FPIES that must be addressed to improve patient care. In addition, the long-term follow-up of infants, children, and adults is needed to understand the potential long-term consequences of FPIES.

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