

REVIEW

Food protein-induced enterocolitis syndrome

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Abstract

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food allergic disorder that has gained a major interest the past decade. FPIES prevalence, which still needs to be accurately determine in different populations, appears to be higher than previously thought (ie up to 0.7% in infants in the 1st year of life). FPIES to seafood in adults is also increasingly reported; limited data suggest that adult FPIES is most commonly triggered by shellfish, tends to affect females more than men, is characterized by a significant delay in diagnosis and a prolonged course. The first international consensus guidelines on diagnosis and management of FPIES have been published in 2017, proposing new diagnostic criteria as well as new criteria for a positive oral food challenge. However, there is a need to develop new biomarkers to improve the diagnosis and management of FPIES patients, and this requires a better understanding of the pathophysiology. Recently, the role of T cells has been questioned and a major role of innate immune cells has been suggested in acute FPIES. Regarding the treatment of acute FPIES reaction, ondansetron has emerged as an adjunct to intravenous rehydration in moderate-severe reactions and as a first-line treatment in mild reactions. Important information regarding the nutritional management of FPIES patients that might be complex has also been provided in the international guidelines. In this review, we discuss recent advances regarding all those different aspects.

KEYWORDS

children, food allergy, food protein-induced enterocolitis syndrome, guidelines

1 | INTRODUCTION

The clinical characteristics of the food protein-induced enterocolitis syndrome (FPIES) were initially described by Powell in 1978 (chronic FPIES) and in 1986 (acute FPIES).^{1,2} Although FPIES was rarely recognized during the following 20 years, with only few publications on this topic, it has been attracting a steadily increasing attention in the past decade. Several large studies provided important insights regarding FPIES epidemiology. Based on those data, first international consensus guidelines were published in 2017 to improve diagnosis and management of FPIES.³ New diagnostic

criteria, as well as revised criteria for interpreting oral food challenge (OFC) outcome, were proposed. Important practical advice addressing the challenges in nutritional management of infants and young children with FPIES was also included. However, major gaps in knowledge remain regarding FPIES pathophysiology. The role of T cells, which are traditionally incriminated in this non-IgE-mediated disorder, was questioned, and a major role of mast cells, neutrophils and other innate immune cells was suggested, but needs to be confirmed.^{4,5}

This review discusses major advances regarding our understanding of FPIES, an emerging non-IgE-mediated food allergic disorder.

2 | EPIDEMIOLOGY

Epidemiology remains ill-defined as only few studies have evaluated the cumulative incidence of FPIES. In 2011, based on a single-centre, unselected Israeli birth cohort, Katz et al reported a cumulative incidence for cow's milk (CM)-FPIES of 0.34% (44/13 019 patients) over a 2-year period.⁶ In the same population, the incidence of IgE-mediated allergy to CM was 0.5%, suggesting strongly that FPIES is probably less rare than previously thought. Bellón et al⁷ recently reported a similar cumulative incidence of 0.7% in the first year of life, based on a birth cohort of 1142 children in Spain. Strict diagnostic criteria were applied, and OFC was performed in the majority of the patients to confirm FPIES diagnosis. The most common food trigger was CM, followed by fish and egg yolk. An Australian study based on a national reporting system with utilization of a questionnaire, and a strict case definition estimated a lower cumulative incidence of 15.4/100 000/y in children under 2 years.⁸ Based on the same national paediatric reporting system, the estimated cumulative incidence of FPIES surpassed the estimated incidence of eosinophilic esophagitis in all children younger than 18 years and that of inflammatory bowel disease under the age 2 years. Underestimation of the true cumulative incidence is possible, due to the limitations of the voluntary reporting system, potential lack of familiarity with FPIES among primary

care physicians, as well as parental underreporting of milder symptoms to the paediatricians.^{9,10} However, there is clearly an improvement of medical community awareness as shown by the significant increase in the publication rate with over 100 publications since 2010, in contrast to fewer than 20 articles published between 1986 and 2010 (PubMed search on "food protein induced enterocolitis syndrome and FPIES," 1986-2010; 2010-2018). There is clearly a lack of data and accurate epidemiologic data in different countries are needed to estimate the true prevalence of FPIES. With the increased awareness, increased reporting is anticipated

Globally, CM is the most common reported FPIES trigger, whereas among solids, rice and oat are predominant.^{11,12} In countries that utilize soya infant formulas, soya-FPIES is also commonly reported.¹³ In Spain and Italy, fish and shellfish are the most commonly reported solid foods, probably reflecting the earlier introduction of seafood into the infant diet.^{7,14,15} Additional solid food FPIES triggers include poultry meats (chicken and turkey), egg yolk, cereal grains (barley, wheat), fruits (apple, peach, banana) and vegetables (sweet potato, pea, carrot).^{3,16,17} It should be recognized that any food can trigger FPIES, including additional fruits and vegetables, peanut, avocado and other legumes.^{18,19} Since acute FPIES typically starts within the first year of life (commonly within the first 6 months), usually following few feedings with the food, the common reported triggers reflect the first few foods introduced into the infant diet. Of note,

Treatment Algorithm for Food Protein Induced Enterocolitis Syndrome

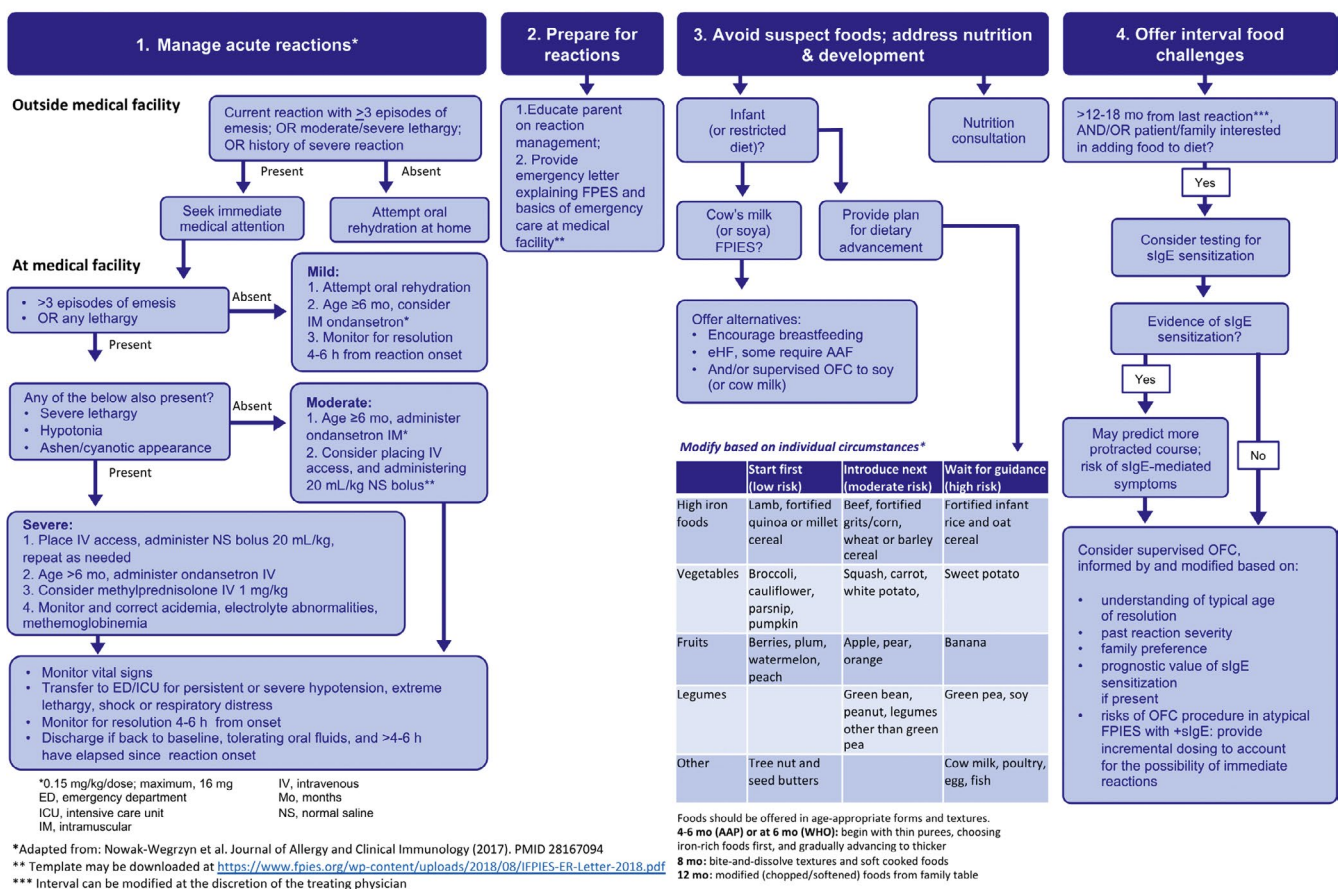


FIGURE 1 Treatment algorithm for food protein-induced enterocolitis syndrome reprinted with permission from Ref. ⁷⁶

new onset of FPIES is rare if the food is introduced into the diet after the 1st birthday.^{11,20}

3 | DIFFERENT PHENOTYPES OF FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

3.1 | Acute food protein-induced enterocolitis syndrome

The most often reported is the acute form of FPIES, which is characterized by profuse, repetitive vomiting, lethargy and pallor, occurring 1 to 4 hours (usually 2 hours) after food ingestion.³ Vomiting is the most frequent reported manifestation, occurring in more than 95% of the patients.^{6,12,13,16,21-23} Lethargy and pallor are found in up to 40%-100% of the FPIES patients, while only a minority of patients (20%-50%) reports diarrhoea several hours later (and even less frequently during diagnostic OFC).^{6,12,13,16,21-23} Diarrhoea seems to be more common in infants younger than 6 months and with more severe reactions. Acute FPIES can present with different degrees of severity. Severity criteria have been proposed based on symptoms intensity in the international consensus guidelines.³ Thus, the mild form is characterized by 1-2 episodes of vomiting with or without mild lethargy, while the more severe form includes patients with 3 or more episodes of vomiting, lethargy, hypotonia, and ashen, dusky or cyanotic appearance. These criteria need to be validated in prospective studies.

3.2 | Chronic food protein-induced enterocolitis syndrome

Chronic FPIES in young infants fed with CM or soya-based infant formulas was the first reported phenotype of FPIES.¹ There is much overlap between symptoms of chronic FPIES and other non-IgE-mediated gastrointestinal food allergy (non-IgE-GI-FA). The symptoms of chronic FPIES emerge within days to few weeks following the initiation of the formula feedings. Chronic FPIES refers to frequent watery diarrhoea, occasionally with blood or mucus, chronic intermittent emesis, abdominal distension and/or lethargy, poor weight gain or weight loss.^{1,2} With continued feeding, chronic symptoms worsen progressively and in severe cases may culminate in dehydration and admission to the emergency department for management. As with other, non-IgE-GI-FA, elimination of the incriminated food(s) lead to resolution of symptoms; however, the defining feature of chronic FPIES is that subsequent reintroduction induces acute FPIES rather than chronic symptoms.³ Nevertheless, confusion regarding the definition of chronic FPIES is pervasive and can be attributed to the non-specific symptoms. In clinical practice, chronic FPIES sometimes is used as a default diagnosis for any chronic gastrointestinal symptoms of unknown origin that seem to respond to dietary manipulations.

Chronic FPIES has been exclusively reported in infants younger than 4 months continuously exposed to the offending food, mainly milk or soya formula, and has been rarely reported in exclusively

breastfed infants.¹ The literature regarding chronic FPIES is extremely limited, potentially due to the widespread availability of hypoallergenic infant formulas that may interrupt the progression to severe manifestations with continued feeding of CM- or soya-based infant formulas. In addition, most of the published studies did not include an OFC to confirm diagnosis. In recent years, chronic FPIES has been mainly reported from Asian countries.²³⁻²⁵ To date, chronic FPIES has not been described after the age 4 months and in association with solid foods.

3.3 | Atypical food protein-induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome is classified as non-IgE-GI-FA, but FPIES patients with detectable systemic food-specific IgE (by skin prick or serologic testing) referred to as "atypical FPIES" have been described since a long time.^{6,26-28} Based on a small number of patients, it has been suggested that these patients might have a more protracted course, and an increased risk to switch to an IgE-mediated phenotype (5%-40%).^{11,12} Controlled multi-centre trials need to be performed to evaluate the degree of this risk in different population. However, it is important to take into account this potential risk, particularly when a challenge is indicated, to adapt the protocol to a more gradual administration of the dose. Interestingly, children with a previous IgE-mediated phenotype and developing symptoms of a non-IgE-mediated allergy to the incriminated food have been reported.^{29,30}

3.4 | Adult food protein-induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome in adults has been reported anecdotally for many years; however, only recently adult case series have been published in the peer-reviewed literature.³¹⁻³⁵ The dramatic symptoms of acute FPIES are usually triggered by shellfish and fish, whereas more chronic gastrointestinal symptoms have been attributed to CM, wheat/gluten and hen's egg. While the prevalence and natural history of adult FPIES remain unknown, the recent report from Spain provided interesting insights.³⁵ Twenty-five patients with exclusively gastrointestinal symptoms following ingestion of seafood and negative skin and food-specific IgE were reported. Delay to diagnosis was median 8 years, median number of past episodes was 8, highlighting the under-recognition of this disorder in the adult population. The majority of patients reported reactions to crustacean shellfish (60%), followed by fish (48%), cephalods (20%) and bivalves (20%); 60% reported reaction to a single food group. Physician-supervised OFCs were conducted in 11 patients, six were positive, five were negative. The predominance of female adult patients with FPIES (88%) is striking and has been also reported by other reports.³²⁻³⁴ This is contrast to infantile FPIES, which is slightly more common in males. Further large multi-centre studies are needed to better characterize adult FPIES.

3.5 | Pathophysiology of food protein-induced enterocolitis syndrome

Food protein-induced enterocolitis syndrome is classified as a non-IgE-GI-FA. The pathophysiology of FPIES remains largely unknown and most of the available data are based on small number of patients. A local inflammation induced by food proteins is supposed to lead to increase intestinal permeability and fluid shift.³⁶⁻⁴⁴ Powell et al did not confirm the hypothesis of an increased gastrointestinal absorption of intact antigen leading to systemic immunization, as she found a normal baseline intestinal absorption in a group of infants with FPIES.³⁷ Anecdotally, there seems to be an association between FPIES and Down syndrome. Wakiguchi et al⁴⁵ reported prolonged CM-FPIES in two children with Down syndrome. Immune dysregulation increased levels of TNF- α and reduced levels of IL-10 have been described in Down syndrome.⁴⁶ Considering the potential role of IL-10 in acquisition of tolerance, the defect in IL-10 might contribute to delay in FPIES resolution. Increased TNF- α in Down syndrome patients might confer predisposition to FPIES.^{46,47}

T cells have long been incriminated in the FPIES pathophysiology.^{48,49} However, although higher proliferation of peripheral mononuclear cells (PBMCs) after stimulation with the causal antigen has been found in CM-FPIES patients compared to controls, a large overlap was found between the groups. More recently, a high CD4⁺ T cell-proliferative response and T_H2 cytokines production have been found in CM-FPIES children after casein stimulation, but these results were similar to children with IgE-mediated CM allergy, and children who outgrow their CM-FPIES.⁴ Morita et al⁵⁰ reported a T_H2-skewed cytokines profile from antigen-restimulated PBMCs in FPIES patients. Thus, the primary role of T cells is being questioned and needs to be elucidated, particularly T cell I role in the unique gastrointestinal manifestations compared to IgE-mediated allergy.⁵ Regulatory T cells (CD4⁺CD25⁺) have been incriminated in the mechanism of tolerance acquisition in FPIES, with a potential key role of IL-10, but these data still need to be confirmed in a larger sample of patients.^{4,51,52} Humoral responses have been investigated in FPIES. Lower levels of specific IgE, IgA and IgG4 have been found in FPIES patients, compared to controls. The overall paucity of humoral responses might reflect the lack of help from T lymphocytes.

Other cells types may participate in the inflammation induced in FPIES patients, particularly innate immune cells. A potential role of neutrophils has been particularly suggested (ie increase the absolute count and increase of IL-8 after a positive challenge, presence of these cells in biopsies as well as gastric aspirate and stool mucus).^{1,2,4,13,52,53} Recently, it has been found that CRP increases in the first 6 hours after an FPIES reaction, paralleling the neutrophils increase.⁵⁴ The dynamics of these changes mirror those found during acute foodborne infection, suggesting that abnormalities of the host innate immune response could induce a misrecognition of specific foods in FPIES patients.⁵⁴ Similarly, thrombocytosis is typically found in acute and chronic FPIES, potentially reflecting involvement of platelets in the pathomechanism.^{1,2} However, both the rise of peripheral platelets and neutrophils might also be linked to the

associated stress and their active contribution needs to be determined. Non-specific presence of eosinophils have also been reported in FPIES patients (increase expression of CD69, clusters of eosinophils in intestinal biopsies and eosinophils/Charcot-Leyden crystals in stool samples).^{55,56} A potential role of mast cells was suggested, as higher baseline tryptase levels within the normal range were found in children with CM-FPIES compared to controls.⁴ These data need to be confirmed by further studies. In addition, an increase of IL-9 after a positive OFC in FPIES patients was found, while this activation was not observed in children who had outgrown FPIES.⁴ IL-9 has been shown to be essential in intestinal anaphylaxis, suggesting that FPIES could be a variant of intestinal anaphylaxis.^{4,5}

3.6 | Diagnosis and role of oral food challenge

Food protein-induced enterocolitis syndrome diagnosis is based on a recognition of typical clinical features. Powell proposed the first diagnostic criteria in 1978 mainly for the chronic FPIES to CM and soya.¹ These criteria were modified successively by Powell in 1986 and by Sicherer in 2005 to include the acute FPIES.^{2,26} Recently, new diagnostic criteria for acute FPIES were proposed in the international guidelines, including major modification in light of current knowledge (Table 1).³ It should be noted that none of the FPIES diagnostic criteria have been systematically validated in prospective studies. Vomiting was recognized as the most important clinical feature and constitutes the major criterion, in the absence of classic IgE-mediated allergic skin or respiratory symptoms. The age limit was removed, as FPIES is increasingly described in older children, and even in adults.³³ Lethargy and pallor were included as minor criteria. The importance of diarrhoea, occurring only in a minority of patients, decreased and constitutes now a minor criterion. Finally, while the OFC remains the gold standard, OFC is not mandatory to confirm the diagnosis of acute FPIES. However, "if only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group."³ Thus, a patient presenting with two typical reactions does not need an OFC, but if the clinical presentation is not typical or the trigger food remains unknown, an OFC should be strongly considered.³ Although these new criteria will hopefully improve diagnosis of acute FPIES, it is important to note that they need to be validated by multi-centre studies including large numbers of patients.⁵⁷

Chronic FPIES is likely over-diagnosed due to the non-specific symptoms. Indeed, chronic gastrointestinal manifestations resolving under a restrictive diet are often called "chronic FPIES." In order to decrease the over-diagnosis of FPIES, new diagnostic criteria have been proposed.³ Thus, typical symptoms should be resolved within days (usually 3-10 days) upon elimination of the incriminated food, and an OFC is mandatory to confirm the diagnosis (Table 1).³

Oral food challenge to the documented FPIES food triggers should be performed in a safe medical environment, by a trained team with emergency drugs available. FPIES international guidelines recommend to administer the food in three equal doses over a period of 30 minutes.³ A single dose is proposed as an alternative in

TABLE 1 Diagnostic criteria for food protein-induced enterocolitis syndrome (FPIES) and diagnostic criteria for interpretation of positive oral food challenge (OFC) in FPIES patients Adapted with authorization from Nowak-Węgrzyn et al³

Acute FPIES	
1 Major criterion + Vomiting in the 1-4 h after ingestion of the suspect food and absence of IgE-mediated allergic symptoms	≥3 Minor criteria: • One episode to the same food • Repetitive vomiting to a different food • Lethargy • Pallor • Emergency department visit • Need for intravenous fluid support • Diarrhoea in 24 h • Hypotension • Hypothermia
Chronic FPIES	
Milder: intermittent vomiting and/or diarrhoea, with FTT, without dehydration. Severe: intermittent vomiting and diarrhoea (possible with blood), lead to potential dehydration, when the offending food is regularly consumed.	Resolution of symptoms within days after elimination of the offending food(s), with acute symptoms upon reintroduction, is the most important criterion. OFC is required to confirm diagnosis.
Positive criteria for OFC	
1 Major criterion + Vomiting in the 1-4 h after ingestion of the suspect food and absence of IgE-mediated allergic symptoms	≥ 2 Minor criteria • Lethargy • Pallor • Diarrhoea 5-10 h • Hypotension • Hypothermia • Increase of neutrophils levels of ≥1500 above the baseline level

several references centres. Data from large multi-centre studies are needed to standardize and determine the optimal protocol for the OFC in FPIES patients. Another controversial point is the utility of intravenous access in all FPIES patients during OFC.⁵⁸ Indeed, FPIES is considered a high-risk procedure as a large proportion of patients will need intravenous fluid administration, and some develop severe reaction with hypotension.^{11,20,26} Data from a population-based birth cohort (with a spectrum of severity), suggested that mild reactions could be treated with oral rehydration.⁶ Risk factors predicting a severe reaction during OFC has not been well defined.²⁰ Thus, in the international guidelines, home OFC is not recommended in patients with prior severe reactions, and secure peripheral intravenous access is advisable to provide intravenous hydration in case of severe reactions.³ We propose that in patients with prior mild reactions to large amounts of food (eg regular serving for age, few episodes of vomiting, no or minimal lethargy, recovered without treatment at home) or in case of introducing potentially co-reactive foods (eg soya in an infant with CM-FPIES or wheat in an infant with rice-FPIES), gradual home introduction might be considered, based on the comfort level of the physician and the caregivers (shared decision making). It should be recognized that the risk of developing FPIES to a newly introduced food decreases significantly after 12 months of age. Due to the possibility of atypical FPIES characterized by the presence of specific IgE to the incriminated food and the possible switch to an IgE-mediated allergy, testing (skin prick tests and/or

specific IgE) is recommended before the OFC.³ If positive, the protocol should be adapted to include a more gradual administration of the food combined with a prolonged observation for 4 hours, as recommended for FPIES.³ New criteria for a positive OFC were proposed (Table 1). Vomiting was emphasized as the most important symptom and stool tests, included in the previous criteria, were removed.^{3,53} These criteria differ in the degree of neutrophilia, which has been decreased arbitrary to 1500 cell/mm³. These criteria also need validation in large multi-centre studies.

In vitro biomarkers of FPIES are lacking. Blood testing may reveal anaemia, thrombocytosis, eosinophilia and/or an elevated white blood cell count with left shift.^{24,59} All these parameters are non-specific, but might support diagnosis of FPIES. In more severe case, acidosis and methemoglobinemia have been reported in both acute and chronic FPIES.^{60,61} Patch tests in a small study were reported to have a negative predictive value of 100% and a positive predictive value of 75%; however, another more recent study based on 38 OFC reported a sensitivity of only 11.8% and a specificity of 85.7%.^{49,62} Based on these conflicting results, patch tests are not currently recommended for diagnosing FPIES.³

Endoscopy is not routinely performed in FPIES, but might be helpful to exclude other aetiologies in case of chronic symptoms with unclear triggers.³ Stool testing is not routinely recommended, although non-specific findings (ie presence of neutrophils, eosinophils, Charcot-Leyden crystals and/or reducing substances) can

TABLE 2 Food protein-induced enterocolitis syndrome (FPIES) differential diagnosis

	Similarities	Differences
Allergic disorders		
Anaphylaxis	Vomiting, diarrhoea with ingestion of specific food, reproducible	Immediate symptoms with ingestion of food (minutes to 1 h), positive SPT and food-sIgE, other systemic symptoms (eg urticaria, angioedema), vomiting responsive to intramuscular epinephrine
Food protein-induced allergic proctocolitis (FPIAP)	Stool with blood or mucous, associated with cow's milk (CM) formula intake	No failure to thrive, no vomiting, resolution sooner (~1 y of age), patients appearing well
Food protein-induced enteropathy (FPE)	Failure to thrive, intermittent vomiting or diarrhoea with ingestion of specific food (eg CM, egg)	Small bowel injury and malabsorption. No lethargy, pallor or dehydration, no methemoglobinemia or acidemia; confirm diagnosis with endoscopy and biopsy
Eosinophilic esophagitis (EoE)	Triggered by specific food, vomiting, failure to thrive	Vomiting less profuse, non-projectile, early satiety, older children-dysphagia/ food impaction sensation, chronic
Gastrointestinal disorders		
Very early onset inflammatory bowel disease	Failure to thrive, diarrhoea, blood or mucus in stool, vomiting	Symptoms are not often linked to specific food; family history may be positive for IBD
Coeliac disease	Failure to thrive, chronic diarrhoea, vomiting, anaemia	Coeliac serology positive and confirmed with biopsy, malabsorption
Gastrointestinal reflux	Intermittent vomiting	No diarrhoea, no dehydration, vomiting usually minimal
Lactose intolerance	Diarrhoea with ingestion of specific food (lactose)	Symptoms with liquid CM/large amounts of cheese or cream/lactose; bloating, flatulence, low prevalence under 5-6 y of age; frequently positive family history of lactose intolerance
Cyclic vomiting	Repetitive recurrent vomiting, lethargy	Not associated with food, stereotypical vomiting typically early in the day, associated with prodrome (can be associated with headache, photophobia)
Anatomical GI obstruction		
Malrotation/volvulus	Vomiting in an infant, bloody stool (bowel ischaemia), dehydration and shock, failure to thrive, distended loops of bowel on X-ray	Bilious vomiting, abdominal distension, sepsis from necrotic bowel, fluid resuscitation alone does not improve symptoms
Intussusception	Intermittent, vomiting, bloody diarrhoea, 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 diarrhoea, diagnosis with ultrasound
Necrotizing enterocolitis (NEC)	Lethargy, vomiting, bloody diarrhoea, neutrophilia	Higher risk in premature low birth weight infants, formula-fed infants. Requires parental nutrition, IV antibiotics, pneumatosis intestinalis on X-ray
Infections		
Acute viral gastroenteritis	Vomiting, watery diarrhoea	Fever present, slower course over days, no specific food trigger
Sepsis	Sudden lethargy, vomiting, hypotension, hypothermia, neutrophilia	Fever present, treatment with fluid resuscitation alone does not improve
Bacterial gastroenteritis (Shigella, Salmonella, Campylobacter, Escherichia coli)	Vomiting, abdominal pain	Watery or bloody diarrhoea, fever, positive stool culture, responds to antibiotics
Inborn errors of metabolism		
Enzyme deficiencies: 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)

(Continues)

TABLE 2 (Continued)

	Similarities	Differences
Inadequate energy production: Mitochondrial, fatty acid oxidation disorders, glycogen storage disorder	Intermittent vomiting/lethargy	Failure to thrive, heart and muscle involvement, splenomegaly, hypoglycaemia; No diarrhoea or food avoidance
Disorders of complex molecules		
Lysosomal storage disorders Congenital disorder of glycosylation	Poor growth, feeding swallowing difficulties Vomiting, diarrhoea	Hepatosplenomegaly, developmental delay, short stature, chronic pain Low tone, seizures, dysmorphic features
Congenital methemoglobinemia (type I)	Methemoglobinemia, dusky appearance	Mostly asymptomatic, no vomiting or diarrhoea, general fatigue, dyspnoea
Other disorders		
Primary immunodeficiency	Chronic diarrhoea (due to frequent or persistent GI infections, eg enterovirus)	Not specific to food, abnormality in lymphocyte counts, immunoglobulins, etc
Immune enteropathy	Chronic diarrhoea	Diarrhoea frequently with blood or mucous, severe diarrhoea with no food association, rare in infants and toddlers
Mast cell activation syndrome	Chronic/intermittent watery diarrhoea	Symptoms from other organ systems, for example, skin, respiratory, cardiovascular, not specific to food; elevated serum tryptase and or urinary histamine metabolites or PGD2 or 11-b-PGF2-alpha during at least two acute episodes
Congenital adrenal hypoplasia (CAH)—classic phenotype	Vomiting, dehydration, diarrhoea, shock	Symptoms usually present from birth, no association with feeding, females-ambiguous genitalia, virilization
Intracranial mass	Vomiting, difficulty feeding and swallowing, dehydration	Unrelated to feeding, progressive, usually associated with additional symptoms such as headaches, seizures, vision impairment
Adapted from Nowak, WG, 2017 ³		

support the diagnosis.^{1,24} Fecal calprotectin has been as suggested as a useful marker for non-IgE-GI-FA, including FPIES.⁶³ Data are very limited and further studies, including control groups, are needed particularly in infants since in this age group, levels of fecal calprotectin vary widely in asymptomatic infants and normal values of fecal calprotectin have not been established.

4 | FPIES ON A SPECTRUM OF GI FOOD ALLERGIC DISORDER-DIFFERENTIAL DIAGNOSIS

Several conditions either related or unrelated to food allergy can present with symptoms similar to FPIES, as summarized in Table 2.⁶⁴

Acute viral gastroenteritis is the most common diagnosis of exclusion for acute FPIES; it is not associated with a specific food trigger and vomiting is often accompanied by diarrhoea and fever.⁶⁵ History of sick contacts may help differentiate infectious gastroenteritis from FPIES.³ Other cause of vomiting/diarrhoea in young infants not related to food allergies can be anatomical disorders, such as intestinal atresia, necrotizing enterocolitis (NEC), Hirschsprung disease, pyloric stenosis, malrotation with volvulus and intussusception. Presence of bilious vomiting, severe abdominal pain, abdominal distension, failure to pass the meconium may help to differentiate from FPIES

and abdominal X-ray, upper gastrointestinal series and abdominal ultrasound may be necessary to establish proper care (Table 2).^{3,66,67} Intracranial mass and acute adrenal insufficiency (eg congenital adrenal hyperplasia (CAH)),⁶⁸ present with vomiting, dehydration, hyponatremia and hyperkalaemia and can mimic acute FPIES.^{68,69}

Chronic FPIES with intermittent vomiting and/or diarrhoea leading to failure to thrive has a broader differential diagnosis. Indeed, several other non-IgE-GI-FA, such as food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enteropathy (FPE), as well as the eosinophilic oesophagitis (EoE) can present with similar symptoms to chronic FPIES. However, in those diseases reintroduction of the offending food is not associated with acute FPIES symptoms. EoE is increasingly more prevalent world-wide, can affect any age and is associated with chronic persistent symptoms due to oesophageal dysfunction such as intermittent vomiting, decreased appetite, early satiety, feeding difficulties, chest or abdominal pain and dysphagia.⁷⁰ CM, wheat, soya and egg are the most frequent triggers of EoE.⁷¹ The diagnosis is made by performing an esophagogastroduodenoscopy (EGD) if at least one oesophageal biopsy shows 15 eosinophils per high power field (eos/hpf).⁷¹ Non-EoE eosinophilic gastroenteropathies (non-EoE EGID) are rare severe diseases that can present acutely or sub-acutely with vomiting, diarrhoea, failure to thrive, weight loss, hypoproteinaemia.⁷² They are associated with eosinophilic infiltration in one or more part of the gastrointestinal

tract, and often significant peripheral eosinophilia is present.⁷² They are almost never responsive to diet and remission is often induced by use of oral steroids. Diagnosis requires an endoscopy and accurate reading of the biopsy by an expert pathologist.⁷²

Other non-food allergic diseases that can mimic chronic FPIES but are not food allergy related are gastroesophageal reflux, congenital diarrhoea disorders (CDD), primary immunodeficiency and very early onset inflammatory bowel diseases (VEO-IBD).^{65,73-75.}

5 | MANAGEMENT

5.1 | Emergencies

Treatment of acute FPIES reaction includes rehydration with normal saline bolus (10-20 mL/kg repeated as needed) and dextrose saline as a continuous maintenance infusion if required for the most severe reactions.³ Figure 1 additional supportive treatment (oxygen,

TABLE 3 Resolution rates of Food protein-induced enterocolitis syndrome (FPIES) by country and age. Reproduced with authorization from Graham et al in press

Food	Country	Study	n	6 mo (%)	8 mo (%)	10 mo (%)	1 y (%)	2 y (%)	3 y (%)	4 y (%)	5 y (%)
Cow's milk	USA	Nowak-Wegrzyn ¹⁶	25						60		
		Caubet ¹¹	70						20		53 ^a
	Italy	Miceli Sopo ²²	44					63			
	ROK	Hwang ¹³	23	27	42	64					
	Spain	Vazquez-Ortiz ⁹⁴	21					50 ^b		75 ^b	
	Israel	Katz ⁶	36				50	89	94 ^b		
	Australia	Lee ⁹⁵	25				12	56	88	96	96
Soya	USA	Nowak-Wegrzyn ¹⁶	22						27		
		Caubet ¹¹	66						20		32 ^a
	Australia	Mehr ²¹	6						83		
	ROK	Hwang ¹³	23	75	91	92					
Grains	USA	Caubet ¹¹	70								65.5
Rice	USA	Nowak-Wegrzyn ¹⁶	10						40		
		Caubet ¹¹	13						28 ^a		
	Australia	Mehr ²¹	5						80		
		Lee ⁹⁵	27				0	63	87	100	
Oat	USA	Caubet ¹¹	14						30 ^a		
		Nowak-Wegrzyn ¹⁶	6						66		
Barley	USA	Nowak-Wegrzyn ¹⁶	2						100		
Egg	Italy	Miceli Sopo ²²	2								100 ^c
	Spain	Vazquez-Ortiz ⁹⁴	8						50 ^b		75 ^b
	Australia	Lee ⁹⁵	8				0	12.5	12.5	12.5	25
		Hsu ⁹⁶	2					50			
Meats/	USA	Nowak-Wegrzyn ¹⁶	1						0		
Poultry		Caubet ¹¹	6								50
Fish/	USA	Caubet ¹¹	1								0
Shellfish	Spain	Ruiz-Garcia ⁹⁷	5						20		
		Gonzalez-Delgado ⁹⁸	16								19
		Vazquez-Ortiz ⁹⁴	44							25 ^b	75
	Australia	Lee ⁹⁵	4				0	25	25	25	25
V	USA	Nowak-Wegrzyn ¹⁶	3						67		
L + S	USA	Ruffner ¹²	462					35	70	80	
	Spain	Vazquez-Ortiz ⁹⁴	81						25 ^b	50 ^b	75

Note: Data taken from studies where specific resolution rates by age are mentioned.

Abbreviations: L, liquids; mo, months; n, number of patients with FPIES to specified food; ROK, Republic of Korea; S, solids; V, vegetables; y, year.

^aExtrapolated from Kaplan-Meier survival curves (figure 2) in study.¹¹

^bRounded to the nearest year (ex: 25% resolution rate at 3.8 y placed in the 4 y column).

^cExtrapolated from figure 6 in study.²²

TABLE 4 Common food co-allergies in children with Food protein-induced enterocolitis syndrome (FPIES)

FPIES to	Clinical cross-reactivity/ co-allergy	Observed Occurrence ^a
Cow's milk	Soya	<30%-40%
	Any solid food	<16%
Soya	Cow's milk	<30%-40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow's milk or soya	<25%
Legumes ^a	Soya	<80%
Grains: rice, oats, etc ^a	Other grains (including rice)	About 50%
Poultry ^a	Other poultry	<40%

^aWhere a child already tolerates a food type in a particular group (eg beans), clinical reactions to other members of the same group (eg other legumes) are unlikely. Caution is warranted in interpreting these data as they were derived from single centres and from patient populations skewed towards the more severe phenotype of FPIES and may overestimate the actual risk of co-allergy.

mechanical ventilation, vasopressors, bicarbonate and/or methylene blue) should be provided if needed. Intravenous corticosteroids (methylprednisolone 1 mg/kg, maximum 80 mg) can be used, although no evidence supports this recommendation.⁷⁶ Ondansetron, serotonin 5-HT₃ receptor antagonist, has been proposed as adjunctive management of emesis in acute FPIES, based on results from small case series and experts experience.⁷⁷⁻⁷⁹ Large placebo-controlled studies are needed to determine ondansetron efficacy to treat acute FPIES reactions. For mild reactions (1-2 episodes of vomiting), oral rehydration, including breastfeeding, might be sufficient at home.³ An emergency treatment plan should be provided for the emergency department physician (<https://www.fpies.org/wp-content/uploads/2018/08/IFPIES-ER-Letter-2018.pdf>). Epinephrine autoinjectors and oral antihistamines are not recommended as first-line management, except for patients with atypical FPIES or those with concomitant IgE-mediated food allergy to other foods.

5.2 | Long-term

Avoidance of the incriminated food remains the cornerstone of FPIES management. Elimination leads to resolutions of the symptoms within 4-12 hours and 3-10 days, for the acute- and chronic FPIES, respectively. Based on the natural history data (Table 3), OFC could be repeated every 12-24 months to evaluate for resolution.³ However, this timing should be adapted according to the food incriminated and to the specific population, as major differences have been found regarding the age of resolution (Table 3).³

Although strict avoidance of the trigger food is recommended, there are no data to reliably identify the degree of avoidance required.

Both, higher and lower threshold doses of 0.15 g of protein/kg body weight were reported.^{22,49} The lower threshold amount of allergen is not likely to be present in products with precautionary allergen labels (PAL) in amounts typically eaten by infants and young children, and therefore, avoidance of products with PAL is not recommended routinely.³ FPIES reactions in infants triggered by food allergen in breast milk are also rare. In a recent Australian population-based survey, 5% of parents reported reactions in exclusively breastfed infants but these reactions were not confirmed by an OFC.⁸⁰ Since the vast majority of infants do not appear to react to breast milk from an unrestricted maternal diet, routine avoidance of offending triggers while breastfeeding is not recommended while the infant is thriving and asymptomatic.³ Infants with CM-FPIES who are not breastfeeding should be fed a hypoallergenic formula.⁸¹ The majority of infants with FPIES tolerate extensively hydrolysed formula, whereas a small subset needs an amino acid-based formula as first-line treatment. Soya formula is not recommended due to the greater risk of co-reactivity between CM and soya in FPIES in the US and UK, especially under 6 months of age^{11,17} (Table 4). In addition, patients with CV- and/or soya-FPIES have an increased risk of reacting to solid food(s)^{82,83} (Table 4). Similarly, children with solid food-FPIES have a higher risk to react to other solid foods^{11,16,21} (Table 4). Thus, these foods should be introduced carefully, usually under medical supervision, especially in children with severe initial reactions. Miceli et al⁸⁴ demonstrated tolerance to baked egg (77%) at a mean age of 30.2 months in a cohort of children (n = 66) with egg-induced FPIES, suggesting that baked egg-OFC may be beneficial. There is no evidence at this time that baked milk is tolerated in those with CM-FPIES and anecdotally baked milk OFC were not successful. Introduction of any trigger food (regardless of the method of cooking) should be conducted under physician supervision during an OFC.

In addition to avoidance education, it is common practice to delay the introduction of other related foods that may trigger FPIES during the complementary feeding period, particularly in patients with the most severe forms.³ Foods that are commonly delayed are milk, soya, grains and certain fruits (eg banana, avocado) and vegetables (eg sweet potato, green peas).^{3,18} To support infant nutrition, growth and development, advice on complementary feeding should be provided (Table 5). The delayed introduction of iron-rich grains, milk, soya and other nutritionally dense foods may impact the nutritional adequacy of the infant diet. Iron-rich foods are recommended by the American Academy of Pediatrics as one of the early complementary weaning foods in the breastfed infant as iron needs are high after 6 months of age (11 mg/d), healthy infant iron stores are diminished by 4-6 months of age, and breast milk provides only an estimated 0.35mg/L, with the average intake of breast milk in the exclusively breastfed infant <1 L/d.⁸⁵ Exclusive breastfeeding for more than 6 months has been associated with increased risk of iron deficiency anaemia at 9 months of age and an infant diet that has only low-iron fruits, vegetables and breast milk will likely present the same risk. Some high iron foods include meats, iron-fortified grains, beans, peas and lentils, greens such as spinach and dried fruits such as prunes.

TABLE 5 Empiric guidelines for selecting weaning foods in infants with Food protein-induced enterocolitis syndrome (FPIES)

Lower risk foods ^a	Moderate risk foods ^a	Higher risk foods ^a
Vegetables		
Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
Fruits		
Blueberries, strawberries, plum, watermelon, peach	Apple, pear, orange, avocado	Banana
High iron foods		
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.
Other		
Tree nuts and seed butters ^a (sesame, sunflower, etc) ^a Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Cow's milk/dairy, soya, poultry, egg, fish

Note: Revised from Nowak-Węgrzyn et al.³

Abbreviations: AAP, CoN, American Academy of Pediatrics, Committee on Nutrition; WHO, World Health Organization.

This table should be considered in the context of the following notes:

a. Exclusive breastfeeding until 4–6 mo of age and continuing breastfeeding through the first year of life or longer as long as mutually desired by both mother and child

b. If an infant tolerates a variety of early foods, subsequent introduction may be more liberal.

Additionally, tolerance to one food in a food group (green pea) is considered as a favourable prognostic indicator for tolerance of other foods from the same group (legumes).

^aRisk assessment is based on the clinical experience and the published reports of FPIES triggers. Any food has the potential to trigger FPIES.

The impact on paediatric growth as a result of dietary elimination for food allergies has been well documented.^{86–91} A recent international survey on growth indices in children with food allergies ($n = 430$) found that children with non-IgE-mediated allergies or mixed IgE- and non-IgE-mediated food allergy had lowered height-for-age Z scores than those with IgE-mediated food allergy alone, confirming findings from other studies.^{86,87,92,93} Children with FPIES should have their growth closely monitored including measurements of both weight and length.

Nutritional guidance is required to ensure appropriate food avoidance, adequate intake of alternative foods and introduction of nutritionally appropriate and timely complementary foods to ensure growth and development in the paediatric patient.

6 | CONCLUSION

Over the past decade, it has become apparent that FPIES is more common than previously appreciated. FPIES is a heterogeneous disorder, with a wide range of clinical features. Recently, the first international evidence-based guidelines have been published, providing important clinical recommendations for the diagnosis and management of FPIES patients. Large multi-centre studies are needed to validate the proposed diagnostic criteria and criteria for a positive

OFC, to standardize the OFC protocol, to better characterize chronic FPIES, to decipher pathophysiology to develop new biomarkers for improved diagnosis and follow-up.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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