

Food Protein–Induced Enterocolitis Syndrome

Nowak–Węgrzyn A¹, Jarocka–Cyrta E², Moschione Castro APB³

¹Jaffe Food Allergy Institute, Department of Pediatrics, Division of Allergy and Immunology, Kravis Children's Hospital, Icahn School of Medicine at Mount Sinai, New York, New York, USA

²Department of Pediatrics, Gastroenterology and Nutrition, Children's Hospital, University of Warmia and Masuria, Olsztyn, Poland

³Unidade de Alergia e Imunologia do Instituto da Criança, HC Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil

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■ Abstract

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-, cell-mediated food allergy of unknown prevalence and pathophysiology. Onset is typically during the first year of life; seafood-induced FPIES may start in adulthood. Acute FPIES manifests within 1-4 hours after ingestion with repetitive emesis, pallor, and lethargy progressing to dehydration and hypovolemic shock in 15% of cases. Chronic FPIES manifests with intermittent emesis, watery diarrhea, and poor growth progressing to dehydration and hypovolemic shock over a period of days to weeks. Chronic FPIES has been only reported in infants aged less than 3 months fed with cow milk (CM) or soy formula. The most common triggers are CM, soy, rice, and oat. Diagnosis of FPIES relies on recognition of a pattern of clinical symptoms and may be missed owing to the absence of typical allergic symptoms (eg, urticaria, wheezing) and delayed onset in relation to food ingestion. Physician-supervised food challenge is recommended if diagnosis or the trigger food is not clear and to evaluate for resolution. Testing for food-specific IgE is usually negative, although a subset of patients, usually with CM-induced FPIES may develop sensitization to foods. Such atypical FPIES tends to have a more prolonged course. Despite the potential severity of the reactions, no fatalities have been reported, and FPIES has a favorable prognosis. In most cases, FPIES resolves by age 3-5 years, although persistence of CM-induced FPIES and soy FPIES into adulthood has been reported. The first international consensus guidelines on diagnosis and management of FPIES were published in 2017. Given that the pathophysiology of FPIES is poorly understood, there are no diagnostic biomarkers and no therapies to accelerate resolution. These unmet needs warrant future investigations to improve the care of patients with FPIES.

Key words: FPIES. Food protein-induced enterocolitis syndrome. Non–IgE-mediated food allergy. Food allergy. Cow milk allergy.

■ Resumen

SEIOA es una alergia alimentaria con patofisiología y prevalencia desconocidas, que típicamente comienza en el primer año de vida, mientras que la producida por pescado suele tener su comienzo en adultos. La forma aguda se manifiesta entre la hora y 4 horas tras la ingesta del alimento con emesis, palidez, letargia progresiva por deshidratación y shock hipovolémico en el 15% de los casos. La forma crónica se manifiesta con emesis intermitente, diarreas y crecimiento pobre con progresión hacia la deshidratación y shock hipovolémico en un periodo de días o semanas. La forma crónica se ha podido observar únicamente en niños menores de 3 años alimentados con leche de vaca o fórmula de soja. Los desencadenantes más frecuentes son la leche de vaca, la soja, el arroz y avena. El diagnóstico es clínico y puede ser difícil debido a la ausencia de síntomas alérgicos típicos (urticaria, asma...) y a la relación retardada con la ingesta. Es recomendable la provocación controlada si el diagnóstico clínico o el alimento implicado no son claros y también para evaluar la evolución. La IgE específica suele ser negativa, aunque una parte de los pacientes puede desarrollar alergia mediada por IgE. Estos pacientes manifiestan un curso más prolongado. A pesar de la potencial severidad de las reacciones, no se han reportado casos fatales y tiene un pronóstico favorable. La mayoría de los niños consiguen la resolución entre los 3 y 5 años aunque existen casos de persistencia en adultos. Las guías del primer consenso internacional sobre el diagnóstico y tratamiento de esta enfermedad se publicarán en el 2017. Debido a la poco conocida patofisiología, no existen biomarcadores ni terapia que acelere su resolución. Son necesarios estudios que permitan investigar y mejorar la clínica de estos pacientes.

Palabras clave: SEIOA. Síndrome de enterocolitis producida por proteínas alimentarias. Alergia alimentaria no mediada por IgE. Alergia alimentaria. Alergia a leche de vaca.

Introduction

Allergic reactions to foods affecting the gastrointestinal (GI) tract were reported by Hippocrates, who observed that cow milk (CM) could cause urticaria, prolonged diarrhea, vomiting, and failure to thrive in infants that resolved when CM was removed from their diet [1]. At present, GI immune reactions to CM proteins that are mediated by T lymphocytes with or without the contribution of specific IgE antibody are estimated to account for up to 40% of CM protein allergy in infants and young children [2].

Food protein-induced enterocolitis syndrome (FPIES) is a type of non-IgE-mediated GI food allergy (non-IgE-GI-FA) [3-5]. Little is known about the prevalence of FPIES, although the disease is a well-established and distinct clinical entity [2]. The pathophysiology of FPIES requires further investigation; current evidence indicates that cell-mediated responses may play an important role, whereas IgE antibodies to the offending foods have minimal or no significance in pathophysiology [6]. In the absence of definitive laboratory tests, diagnosis relies predominantly on clinical responses to elimination diets with resolution of symptoms, oral food challenges with reappearance of symptoms following ingestion of the offending food, endoscopy and biopsy findings, and exclusion of causes such as infections, inflammatory bowel disease, ischemia, and metabolic disorders.

Historical Perspective

In 1940, Rubin [7] described intestinal bleeding due to CM allergy in newborns. Gryboski et al [8] and Powell [9] reported infants presenting in the first 6 weeks of life with recurrent vomiting, bloody diarrhea, and abdominal distension while being fed with CM-based formula. Many were dehydrated and appeared severely ill. Although evaluations for infectious etiologies were negative, improvement was observed with intravenous fluids or feeding with hydrolyzed casein-based formula, but not with soy-based formula. Upon reintroduction of CM-based formula, recurrence of severe emesis and elevation of the peripheral blood neutrophil count was observed within 1-4 hours. Subsequently, Powell characterized the major features of the disorder, and established criteria for the diagnosis of CM-induced enterocolitis and a standard challenge protocol [10]. Reports of a series of infants with food protein-induced enterocolitis by Sicherer et al [11] (16 patients) and Burks et al [12] (43 patients) further characterized clinical features and refined food challenge protocols. More recent reports have identified various solid foods as triggers for FPIES [13-18]. Prior to implementation of the *International Classification of Diseases, Tenth Revision (ICD-10)* code for FPIES (K52.2) in October 2015, no uniform ICD code existed [19]. The first international consensus guidelines on diagnosis and management of FPIES are to be published in 2017 [20].

Epidemiology

Prevalence

The prevalence of FPIES is unknown. Data from the only FPIES prospective birth cohort were reported by Katz

et al [21], who noted a cumulative incidence of CM-induced FPIES (CM-FPIES) of 3 per 1000 newborns at a single hospital over 2 years (0.34%).

Risk Factors

Data on risk factors are scarce. In an Israeli population-based birth cohort, FPIES was more frequent in infants delivered by cesarean section and of Jewish ethnicity; there was no association with gestational age, maternal age, number of siblings, maternal dairy product consumption, or age at introduction of CM [21]. There was a slight male predominance (60:40), although no data regarding the familial recurrence risk for FPIES were reported. A family history of atopy is common among children with FPIES (20%-77%); to date, only 3 cases of siblings with FPIES have been published. All 3 cases involved twins (1 identical and 2 fraternal twins) [22,23].

Manifestations

The manifestations and severity of FPIES depend on the frequency and quantity of exposure to the offending food (dose of food allergen). Expression of FPIES is also affected by the phenotype of an individual patient, which may vary over time [10-12,15].

Acute FPIES

Acute FPIES is characterized by repetitive, projectile emesis associated with pallor and lethargy within 1-4 hours (usually 2 hours) after ingestion and has been observed when the offending food is ingested on an intermittent basis or following a longer period of avoidance (days-years). Watery diarrhea (rarely with blood or mucus) develops in a subset of patients within 5-10 hours of ingestion and may last for up to 24 hours after exposure. Diarrhea is more common in infants and young children, and more commonly reported in Japan and Korea than in the US, UK, Australia, and Italy [15,18,21,24-26]. Acute FPIES reactions usually resolve within 24 hours following ingestion, provided the offending food is eliminated from the diet. Most children with acute FPIES thrive and have normal longitudinal growth (Table 1).

Chronic FPIES

Chronic FPIES is less well characterized than acute FPIES and has only been reported in infants younger than 4 months of age who were fed with CM- or soy-based formula and developed intermittent emesis, chronic watery diarrhea, and failure to thrive over a period of days-weeks. It is unclear whether chronic FPIES would develop upon prolonged feeding with a low dose of food allergen. Severe chronic FPIES may culminate in dehydration and hypovolemic shock [9,10]. Hypoalbuminemia and poor weight gain (<10 g/d) have been identified as independent predictors of chronic FPIES caused by CM in young infants with chronic GI symptoms and may help differentiate chronic FPIES from the other forms of non-IgE-GI-FA [24]. The defining features of chronic FPIES are that elimination of the offending food leads to resolution of symptoms within days to weeks and that reintroduction of

Table 1. Defining Features for Acute and Chronic Phenotype of FPIES

FPIES Phenotype	Defining Clinical Features	Laboratory Findings
Acute	Occurs with intermittent food exposures, emesis usually starts within 1-4 hours and is accompanied by lethargy and pallor, occasionally hypothermia; diarrhea may follow within 24 hours (usual onset 5-10 hours). Symptoms usually resolve within 24 hours following elimination of the food from the diet. Growth is normal, and the child is asymptomatic during elimination of the food trigger.	<i>Peripheral blood</i> Elevated white blood count with neutrophil predominance Elevated eosinophils Elevated platelets Metabolic acidosis Methemoglobinemia <i>Cerebrospinal fluid and gastric lavage fluid</i> Elevated white blood count with neutrophil predominance <i>Stool</i> Fecal leukocytes, eosinophils Detectable eosinophil-derived neurotoxin Visible or occult blood
Chronic	Occurs with daily ingestion of the food (eg, feeding with cow milk or soy-based formula in an infant). Symptoms include intermittent emesis, chronic diarrhea, poor weight gain, and failure to thrive. Infants with chronic FPIES usually return to their usual state of health within 3 to 10 days of switching to a hypoallergenic formula, although in severe cases, temporary bowel rest and intravenous fluids may be necessary. Subsequent feeding of the offending food following a period of avoidance results in the acute symptoms.	<i>Peripheral blood</i> Elevated white blood count with neutrophil predominance Elevated eosinophils Elevated platelets Metabolic acidosis Methemoglobinemia Hypoalbuminemia Hypoproteinemia Anemia <i>Stool</i> Visible or occult blood

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.

the food following a period of elimination (eg, during an oral food challenge [OFC] to evaluate for acquisition of tolerance) induces an acute FPIES reaction (repetitive projectile emesis, lethargy, pallor) 1-4 hours following food ingestion (Table 1). The appearance of acute symptoms upon reintroduction of the food after a period of avoidance is specific to chronic FPIES and is not seen in food protein–induced enteropathy, proctocolitis, eosinophilic gastroenteritis, or celiac disease. Chronic FPIES is more commonly reported in Asian countries, primarily Japan and Korea, than in the US, Europe, or Australia [24,26,27].

Confusion Regarding the Chronic FPIES Phenotype

There is some confusion among the parents of children with chronic non-IgE-GI-FA and health care providers that any chronic GI symptoms involving vomiting and/or diarrhea in infants indicate chronic FPIES. However, such a diagnosis is presumptive and may be incorrect without a supervised OFC or evidence of accidental food ingestion resulting in a convincing acute FPIES episode. In contrast to other non-IgE-GI-FA disorders and eosinophilic gastroenteropathies, in which food is typically reintroduced at home, diagnosis of chronic FPIES implies that the offending food should be reintroduced under the supervision of a physician. Additionally, chronic GI symptoms have been associated with mast cell activation syndrome and with Ehlers-Danlos syndrome and are sometimes referred to as FPIES, although they likely represent the underlying GI tract disease associated with these disorders.

Triggers of FPIES

Although any food can cause FPIES, the most common foods are CM, soy (in the US but not in Australia or Israel), rice, and oat. Most infants and children with FPIES (60%-70%) react to a single food (mainly CM), approximately 20%-30% react to 2-3 foods, and about 10% react to 4 or more foods. In older children and adults, shellfish (shrimp, scallop), fish, and egg have been reported as possible triggers [28-30].

FPIES Caused by CM/Soy

FPIES is commonly caused by CM or soy proteins in formula-fed infants, with many (up to 40%) reacting to both foods, especially if aged younger than 6 months when formula is introduced [21,25,26]. Typical onset of CM-FPIES/soy FPIES is from the first days to 12 months of life, with the median time to onset being about 3-5 months; later onset is associated with delayed introduction of direct feeding with CM or soy protein in previously breastfed infants. FPIES attributed to the food protein in maternal milk is very rare in exclusively breastfed infants (less than 5% in most reports), suggesting a protective role of breastfeeding in FPIES. Symptoms during breastfeeding are more commonly reported from Japan, where up to 30% of infants were reported to have developed FPIES, suggesting potential genetic predisposition [27].

In the most severe cases, symptoms may manifest within the first days of life with severe bloody diarrhea, lethargy, abdominal distension, hypoactive bowel sounds, weight loss, failure to thrive, dehydration, hypothermia, metabolic acidosis,

electrolyte abnormalities, anemia, elevated white blood count with eosinophilia, and hypoalbuminemia [31,32]. Elevated C-reactive protein peaking at 24 hours after food ingestion has been reported in Japanese infants, especially those with fever; however, it is unclear whether the phenotype of these patients is consistent with FPIES, as only 66.7% developed emesis, 55.6% diarrhea, and 33.3% fever during OFC [33,34]. Intramural gas may be observed on abdominal radiographs, thus prompting a diagnosis of necrotizing enterocolitis, evaluation of sepsis, and treatment with antibiotics. Ileus requiring laparoscopy has been reported [35]. Overall, 75% of infants with FPIES appear acutely ill, including 15% who are hypotensive and require hospitalization and extensive evaluation before the diagnosis of FPIES is established. Methemoglobinemia has also been reported, and when present, is typically associated with severe reactions and profound acidemia [36].

FPIES Caused by Solid Food

FPIES can be caused by solid foods, such as cereal grains (rice, oat, wheat, barley), egg, fruits (apples, pears, banana, peaches), vegetables (sweet potato, squash, white potato), meats (poultry, beef, pork), legumes (soy green pea peanut), seafood (fish, shrimp and mollusks), and nuts. The onset of solid food FPIES occurs later than CM-FPIES, usually between 4 and 7 months, when solids are introduced into the diet. FPIES may develop de novo in older children and adults in association with crustacean shellfish (shrimp, crab, and lobster), mollusks (scallop), finned fish, and egg [8].

Diagnosis of solid food FPIES tends to be later than for CM-FPIES [13,15,18,37,38]. Infants often present with a history of multiple reactions and have undergone extensive evaluations for alternative etiologies (infectious, toxic, metabolic) before diagnosis is confirmed [15,38]. Delayed diagnosis may be explained by delayed onset of symptoms in relation to food ingestion, lack of skin or respiratory symptoms (eg, urticaria, wheezing), low index of suspicion that grains (eg, rice) and vegetables have low allergenic potential and are not considered a cause of severe food allergic reaction, and lack of a definitive diagnostic test.

FPIES Caused by Fish

FPIES caused by finned fish (eg, codfish, salmon, tuna) has been described as one of the most common triggers in infants and toddlers in Spain and Italy, likely reflecting the importance of fish in the diet and the relatively earlier age of introduction compared with other countries [14-16,39-44]. Table 2 presents the characteristics of fish-induced FPIES. The typical age of onset is older than for cereals or other solid foods, likely reflecting later introduction of fish into infant's diet.

Geographical Differences in FPIES Triggers

The Figure displays the geographic differences in the relevance of the individual foods as FPIES triggers. It is unclear to what extent this geographic variability is determined by genetic factors as compared with dietary habits or other environmental factors.

	US	AU	UK	Israel	S. Korea	Spain	Italy
CM	Red	Red	Red	Red	Red	Red	Red
Soy	Red	Yellow	Yellow	Yellow	Red	Yellow	Yellow
Rice	Red	Red	Orange	Yellow	Yellow	Yellow	Yellow
Fish	Yellow	Yellow	Orange	Yellow	Yellow	Red	Red

Figure. Geographic differences in FPIES triggers. Red, most common trigger foods; orange, less common trigger foods; yellow: the least common trigger foods. FPIES indicates food protein–induced enterocolitis syndrome. AU, Australia.

Natural History of FPIES

FPIES is a self-limiting disorder with a favorable natural history. The spontaneous development of tolerance in patients with CM-FPIES and soy FPIES has been reported to occur earlier than with FPIES induced by solid foods.

FPIES Caused by CM/Soy

In a large population-based cohort study from Israel, 75% developed tolerance to CM by 1 year, 89% by 2 years, and 94% by 3 years [21]. In contrast, in a large US case series, the median age of resolution was 6.7 years [18]. For soy-induced FPIES, the average reported age for tolerance is approximately 12 months, although this ranges from 6 months to >22 years [45]. Data from a challenge-based study in Korea show that CM-FPIES and soy FPIES may resolve significantly more rapidly than previously assumed [25]. In pooling data from multiple small cohorts, patients seem to be able to tolerate CM at around 3 years of age, although results from 2 recent large cohorts showed that tolerance developed later [13,15,21,24,25,37,38,45-58]. In a large US case series, the median age of resolution for CM-FPIES was 5.1 years, and in the UK, 25% of the patients had persistent CM-FPIES at 8 years of age [59]. In contrast, data from the same large US case series showed that the median ages of resolution were 4.7 years for rice and 4.0 years for oat [18]. Patients with positive skin prick test results to CM and/or detectable serum CM-IgE (so called atypical CM-FPIES) are older at resolution (median, 13.8 years) than patients with a negative skin test [18]. It is unclear whether sIgE to other foods has a similar effect on natural history.

FPIES Caused by Solid Foods

The average reported age for developing tolerance to grains is 35 months; tolerance to other solids (vegetables, fruits, meats) develops at 42 months. Spanish and Italian studies reported that fish-induced FPIES resolved at 5.5 years (Table 2).

Table 2. Fish-Induced FPIES

Author	Country	No. of Patients	Mean Age at Onset, mo	Range, mo	Fish	Inclusion Criteria	Diagnosis Confirmed by Challenge, No.	Mean Age at Resolution, y (No.)	Atopy, Personal	Atopy Family	Other Food Reaction
Zapatero et al [40]	Spain	14	10.6	9-12	H, S, CF, SF	Clinical criteria and OFC in 9 patients	9	4-5 (4 patients total, 3 patients reacted to a single fish)	4	NR	NR
Ruiz-Garcia et al [39]	Spain	5	15.6	7-30	S, H, W	Clinical findings (Powel/Sicherer criteria) and OFC	5	7.0 (2)	NR	NR	FPIES (1 patient) legume - lentil
Vila et al [16]	Spain	17	17.3	5-120	H, M, SH, G, Me, S, T, Sw, Ma, Sa	Clinical findings (Powel/Sicherer criteria) and OFC	2	4.8 (5)	NR	NR	FPIES (2 patients) banana
Gonzalez-Delgado et al [41]	Spain	16	10	9-17	H, W, S, P, An, M	Powell criteria; not clear if challenge was performed	No	4.5 (3) 8 positive OFC at 6 y	NR	NR	NR
Miceli Sopo et al [14]	Italy	57	28	NR	S, C, G, Se	Clinical findings (Sicherer clinical criteria and Sopo criteria at Rome center)	12	8.1 (22 patients tested-14 tolerant)	35 ^a	15 ^a	NR
Vasilopoulou et al [42]	Greece	1	12	NA	NR	Clinical findings	No	NR	NR	NR	NR
Ludman et al [43]	UK	8	NR	NR	NR	Clinical findings (Powell criteria)	NR	5.5 (7)	NR	NR	NR
Karefylaki and Dan Gustafsson [44]	Sweden	10	18	9-30	C	Clinical findings	No	4-8 (5 patients), 11-12 (2 patients)	NR	NR	NR
Mehr et al [15]	Australia	1	6	NA	NR	OFC	1	NR	NR	NR	No

Abbreviations: An, anchovy; C, cod; CF, cork float; F, flatfish; FPIES, food protein–induced enterocolitis syndrome; G, gilthead; H, hake; Ma, mackerel; Me, megrim; M, monkfish; NA: not applicable; NR: not reported; OFC, oral food challenge; P, perch; S, sole; Se, seabass; SH, small hake; Sw, swordfish; Sa, salmon; T, tuna; W, whiting; Wh, whiff.

^aMixed fish and shellfish.

Diagnosis

Diagnosis of FPIES relies on the clinical history, recognition of clinical symptoms, exclusion of other etiologies, and a physician-supervised OFC. Although OFC is the gold standard, most infants do not need to undergo confirmatory OFC, especially if they have a history of severe reactions and become asymptomatic following elimination of the suspected food. However, OFCs are necessary to determine resolution of FPIES or to confirm chronic FPIES. The revised diagnostic criteria for FPIES are presented in Table 3.

Differential Diagnosis

The differential diagnosis of FPIES is extensive and includes infectious diseases, other food allergies, and intestinal obstruction, as well as neurologic and metabolic diseases (Table 4). The initial episodes are often misdiagnosed as acute viral gastroenteritis or are evaluated for sepsis, especially if patients present with profound lethargy, hypotension, and have an elevated white cell count with a left shift [10,15].

A variety of other conditions may also be considered in the differential diagnosis, especially in infants with repeated episodes of severe or protracted vomiting. Metabolic disorders

frequently present with episodic vomiting, dehydration, and lethargy, as well as metabolic acidosis but are not associated with specific food intake. Other associated features include hyperammonemia, hypoglycemia, hyperpnea, hematologic abnormalities, elevated liver enzymes, renal disease, and developmental delay not seen in adverse food reactions [60].

OFC in FPIES

OFC should be used to confirm the initial diagnosis if the history is unclear and to evaluate for resolution. OFC in FPIES is considered a high-risk procedure; up to 50% of patients undergoing positive challenges require treatment with intravenous fluids owing to the possibility of severe reaction [61]. Similarly, home challenge with suspected food triggers is generally not recommended because of the potential for severe adverse reactions. One recent study reported successful management of physician-supervised OFC reactions with oral rehydration and treatment of anecdotally mild reactions with oral rehydration [21].

Several OFC protocols for FPIES have been published and vary in dosing regimens, laboratory assessment, and treatment [10,61-64]. All OFCs require close supervision with immediate access to intravenous fluids. The peripheral intravenous line

Table 3. Diagnostic Criteria for Patients Presenting With Possible FPIES

Acute FPIES	
Major Criterion	Minor Criteria
Vomiting in the 1-4 hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms	<ol style="list-style-type: none"> 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Episode of repetitive vomiting 1-4 hours after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency room visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea within 24 hours (usually 5-10 hours) 8. Hypotension 9. Hypothermia

The diagnosis of FPIES requires that a patient meets the major criterion and at least 3 minor criteria. If only a single episode has occurred, a diagnostic oral food challenge should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group. Further, while not a criterion for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours, compared to with the usual several-day course required for resolution of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.

Chronic FPIES

Severe presentation: when the offending food is ingested in on a regular basis (eg, infant formula)

Intermittent but progressive vomiting and diarrhea (occasionally with blood) can develop, sometimes with dehydration and metabolic acidosis.

Milder presentation: lower doses of the culprit food (eg solid foods or food allergens in breast milk) lead to intermittent vomiting, and/or diarrhea, usually with poor weight gain/ failure to thrive, but without dehydration or metabolic acidosis.

The most important criterion for diagnosis of chronic FPIES 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, and diarrhea in 24 hours (usually 5-10 hours). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

Abbreviation: FPIES, food protein-induced enterocolitis syndrome.
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Table 4. Differential Diagnosis of FPIES

Condition	Features That May Distinguish From FPIES
Infectious gastroenteritis (eg, viral, bacterial)	Single episode of illness, fever, sick contacts
Sepsis	Fluid resuscitation alone not effective
Necrotizing enterocolitis	Newborns and younger infants, rapid escalation of symptoms, bloody stools, shock, intramural gas on abdominal radiographs
Anaphylaxis	Symptoms begin within minutes to 2 hours of exposure, positive IgE testing, usually other manifestations (eg, urticaria)
Food aversion	Clamping mouth shut and turning head away from the breast, bottle, spoon, or food; taking a few sips or a small portion of the milk or food offered, and pulling away or arching back and crying
Inborn errors of metabolism: urea cycle defects, hereditary fructose intolerance, hyperammonemic syndromes, propionic /methylmalonic aciduria, β -oxidation defects, hyperinsulinism-hyperammonemia syndrome, pyruvate dehydrogenase deficiency, mitochondrial disorders, maple syrup urine disease, ketothiolase deficiency	Developmental delay, neurologic manifestations, organomegaly, reaction to fruits and sugars (saccharose, fructose)
Lactose intolerance	In severe form, gas, bloating, cramps, diarrhea, borborygmi, and vomiting following ingestion of liquid milk and large doses of dairy products with lactose
Neurologic disorders (eg, cyclic vomiting)	No relation to specific food intake
Gastroesophageal reflux disease	Emesis more chronic and not usually severe (ie, does not lead to dehydration), only upper gastrointestinal symptoms present
Hirschsprung disease	Delay in passage of the first meconium, marked abdominal distension
Food protein-induced enteropathy	Symptoms usually not temporarily associated with specific food intake, symptoms more chronic than episodic, vomiting less severe; most commonly implicated foods are cow milk, soy, wheat, egg white
Eosinophilic gastroenteropathies (eg, eosinophilic esophagitis, eosinophilic gastroenteritis)	Usually not associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, more likely to have positive IgE tests
Celiac disease	No temporal relationship between symptoms and specific food intake; progressive malabsorption; celiac serology is positive
Immune enteropathies (eg, autoimmune enteropathy, immunodeficiency) and inflammatory bowel disease	Rare in infancy, not related to specific food intake
Obstructive problems (eg, malrotation, Ladd bands, volvulus)	Not related to specific food intake, evidence of obstruction on radiological studies
Coagulation defects	No relation to specific food intake
α 1-antitrypsin deficiency	No relation to specific food intake; hepatic involvement, pruritus, white stools, splenomegaly
Primary immunodeficiencies	No relation to specific food intake; frequent infections
Mast cell activation syndrome	Recurrent abdominal pain, diarrhea, flushing, itching, nasal congestion, coughing, chest tightness, wheezing, light-headedness (usually a combination of some of these symptoms is present), and laboratory evidence of mast cell mediator (eg, N-methyl histamine, prostaglandin D2 or 11- β -prostaglandin F2 α , leukotriene E4)
Ehlers-Danlos syndrome	Positive family history, prematurity, hypotonia, joint hypermobility, hip dislocation, smooth velvety skin, easy bruising, poor wound healing

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.
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should be secured prior to the OFC in patients with a history of severe reactions and/or anticipated difficult access. A baseline complete blood count with differential is recommended in the research setting (as a comparator with a postchallenge complete blood count), although this is optional in OFCs performed for clinical indications. Some OFC protocols provide the entire dose in a single serving; however, the current consensus is to administer the challenge food at a dose of 0.06 g to 0.6 g—usually 0.3 grams of the food protein per kilogram of body weight in 3 equal doses over 30 minutes in order not to exceed a total of 3 grams of protein or 10 grams of total food (100 mL of liquid) for an initial feeding (which aims to approximate a serving size)—and observe the patient for 4-6 hours [63]. A lower starting dose and longer observation period between doses should be considered in patients with a history of severe reactions [61]. When a very low dose of food protein is administered and there is no reaction after 2-3 hours of observation, some experts advocate that the patient should ingest a full age-appropriate serving of the food followed by observation for an additional 4 hours. In patients with detectable sIgE to the challenge food, more gradual administration according to the protocol for IgE-mediated food allergy is recommended, with a longer postchallenge observation period, which is typical for FPIES [63]. The total dose and the dosing regimen used in OFC for FPIES have not been systematically studied, and it is at the discretion of the treating physician to potentially modify the regimen as per the individual patient's circumstances [20].

During a positive (ie, failed) OFC, typical FPIES symptoms (repetitive emesis, pallor, and lethargy) begin within 1-4 hours after ingestion. Diarrhea may also occur in about 5-10 hours and is more common in infants aged under 12 months. OFC outcomes are usually unequivocal based on the clinical symptoms, but some clinicians obtain laboratory tests to help confirm the clinical impression. This most often includes a complete blood count immediately before and 4-6 hours after

the onset of the OFC, which in the case of positive results typically reveals a rise in the neutrophil count (>1500 cells/mL) peaking about 6 hours after food ingestion [9,10,18]. In addition, in patients who develop diarrhea, a stool sample can be assessed for the presence of occult blood, leukocytes, and red blood cells. The current revised criteria for interpretation of OFC results are presented in Table 5.

First-line treatment for a positive OFC is aggressive fluid resuscitation with IV boluses of normal saline (20 mL/kg). Findings from case series suggest that intravenous or intramuscular ondansetron (0.1 to 0.15 mg/kg, maximum single dose 16 mg) may be effective in shortening the duration of emesis [55,65,66]. Corticosteroids (eg, intravenous methylprednisolone, 1 mg/kg) are also commonly recommended but have not been systematically studied for efficacy [67].

Laboratory Testing

Food-Specific IgE Testing

Most patients in large series have negative skin prick test results and undetectable sIgE to the offending foods. Negative food sIgE test results do not exclude FPIES to that food [16,17,28,29]. However, some patients with classic FPIES manifestations have detectable CM-specific IgE (by serology or skin prick test) at the initial diagnosis or during follow-up. These patients are considered to have “atypical CM-FPIES,” and FPIES tends to take longer to resolve; a subset may transition to the IgE-mediated CM allergy phenotype during follow-up. In addition, up to 30% of children with FPIES have IgE-mediated allergy to other foods [13,18]. Testing for CM sIgE is recommended prior to undertaking an OFC, and if positive, the OFC protocol should be modified to include more gradual administration of increasing doses of food combined with a longer observation period of about 4 hours, as recommended for FPIES [20].

Table 5. Diagnostic Criteria for the Interpretation of Oral Food Challenges in Patients With a History of Possible or Confirmed FPIES

Major Criterion	Minor Criteria
Vomiting in the 1-4 hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms	<ol style="list-style-type: none"> 1. Lethargy 2. Pallor 3. Diarrhea 5-10 hours after food ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of at least 1500 neutrophils above the baseline count

The OFC will be considered diagnostic of FPIES, ie, positive, if the major criterion is met with at least 2 minor criteria. However, we would suggest 2 important caveats to these criteria: (1) With the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor, and lethargy may be averted; and (2) Not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore, the treating physician may decide that a challenge be considered diagnostic in some instances, even if only the major criterion was met.

However, in challenges performed for research purposes, stringent criteria for challenge positivity should be adhered to.

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.
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Atopy Patch Test

The atopy patch test has been evaluated in 2 studies with conflicting results regarding its accuracy; at present, the atopy patch test is not recommended for diagnosing FPIES [49,51].

Blood Testing

Patients with chronic FPIES may have anemia, hypoalbuminemia, an elevated white blood cell count with left shift, and eosinophilia [24,32]. Patients with acute FPIES may have elevated peripheral blood neutrophil counts and CSF neutrophils requiring a complete sepsis workup in the emergency department [22]. Thrombocytosis was reported in one acute FPIES series in 65% of patients [15]. Metabolic acidosis and methemoglobinemia have also been reported in both acute and chronic FPIES due to hemodynamic shifts [36]. These tests are not pathognomonic of FPIES but may support the diagnosis [20].

Stool Testing

The results of stool analyses may be abnormal in both acute and chronic FPIES. Carbohydrate content may be increased in acute FPIES, with diarrhea, frank or occult blood, mucus, and elevated leukocyte counts [10]. Stool examination may reveal neutrophils, eosinophils, Charcot-Leyden crystals, and/or reducing substances [24]. Assessment of gastric aspirates in one series before and 3 hours after OFC revealed >10 leukocytes/hpf in 15 of 16 patients with positive OFC results to FPIES and 0 of 8 patients with negative OFC results; however, none of these evaluations are performed routinely [68].

Endoscopy and Biopsy

Considering the description of the typical constellation of clinical symptoms and strict criteria for a positive OFC results, endoscopy is not performed routinely in patients with suspected FPIES. However, prior to establishment of diagnostic criteria, endoscopy was performed in infants with CM and/or soy FPIES and rectal bleeding. Rectal ulceration and bleeding with friability of the mucosa was observed in most patients; endoscopy findings were normal in a minority of children. Plain radiological imaging or imaging with barium contrast in infants with ongoing chronic symptoms of diarrhea, rectal bleeding, and/or failure to thrive revealed air-fluid levels consistent with intestinal obstruction, nonspecific narrowing, and thumbprinting of the rectum and sigmoid, as well as thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid. Striking, ribbon-like jejunum with loss of plicae circulares and separation of bowel loops suggestive of thickening of the bowel wall has also been reported [69,70]. Distension of small bowel loops and marked jejunal wall thickening distal to the Treitz ligament with diffuse subserosal bleeding has been observed in extreme cases of ileus treated via laparotomy [69,71]. However, the bowel may appear grossly normal in FPIES without ileus [35]. Follow-up studies with a restricted diet in asymptomatic patients documented resolution of radiological abnormalities.

Management

Emergency Management

Acute FPIES can lead to hypovolemic shock; therefore, the priority in management is restoration of stable hemodynamics through aggressive isotonic fluid resuscitation (eg, 10–20–mL/kg boluses of normal saline), repeated as needed, and dextrose saline as a continuous maintenance infusion. A single dose of intravenous methylprednisolone (at 1 mg/kg, with a maximum of 60 to 80 mg) may decrease presumed cell-mediated inflammation, although no studies support this recommendation [62]. In severe reactions, patients may require supplemental oxygen, mechanical ventilation or noninvasive positive pressure ventilation for respiratory insufficiency or failure, vasopressors for hypotension, bicarbonate for acidemia, and methylene blue for methemoglobinemia [28,36,61,64,65,72,73]. Epinephrine autoinjectors are not routinely recommended/prescribed for FPIES, although those with concomitant IgE-mediated allergy should be prescribed an epinephrine autoinjector at the discretion of the treating physician if deemed at risk of food-induced anaphylaxis [3,74]. Mild-moderate acute FPIES may resolve with oral rehydration, including breastfeeding, at home (Table 6).

Ondansetron is a serotonin 5-HT₃ receptor antagonist approved for prophylaxis and treatment of nausea and vomiting induced by chemotherapy but also commonly used in viral gastroenteritis. Small case series have reported that intravenous ondansetron was helpful in stopping emesis during OFC for FPIES [55,65,75]. Double-blind placebo-controlled trials are needed to determine the role of ondansetron in the management of acute FPIES and better define its efficacy. This intervention is potentially promising, although its use has received little attention to date.

Long-term Management

The long-term management of FPIES involves elimination of the culprit food/s, alterations to diet, treatment of symptoms at presentation or upon re-exposure (including emergency treatment planning), and a plan for supervised OFC to assess for resolution. Nutritional consultation should be strongly considered for any patient, irrespective of the number of foods that should be avoided. However, this is particularly crucial in patients with multiple food–induced FPIES to ensure adherence to dietary avoidance and adequate nutrition within the constraints of the limited diet.

Dietary Avoidance

Elimination of the trigger food is the cornerstone of long-term management. Following elimination of the trigger food, acute FPIES usually resolves within 4–12 hours, whereas chronic FPIES usually resolves within 3 to 10 days of switching to a hypoallergenic formula; however, in severe cases, temporary bowel rest and intravenous fluids may be necessary [9,10].

No systematic studies have evaluated the threshold dose in FPIES. In general, while strict avoidance of the trigger food is recommended, avoidance of products with precautionary labeling statements is not necessary unless there is a history of a severe FPIES reaction to trace amounts [21,37,40,47,49,76].

Table 6. Management of Acute FPIES Episodes

			Medical Facility	
	Mild	Moderate	Severe	
Symptoms				
	1-2 episodes of emesis No lethargy	>3 episodes of emesis and mild lethargy	>3 episodes of emesis, with severe lethargy, hypotonia, ashen or cyanotic appearance	
Management				
	1. Attempt oral re-hydration (eg, breastfeeding or clear fluids) 2. If age 6 months and older: Consider intramuscular ondansetron ^a (0.15 mg/kg/dose, maximum 16 mg/dose) 3. Monitor for resolution about 4-6 hours after the onset of a reaction	1. If age older than 6 months: administer intramuscular ondansetron ^a (0.15 mg/kg/dose, maximum 16 mg/dose) 2. Consider placing a peripheral intravenous line for normal saline bolus 20 mL/kg, repeat as needed 3. Transfer the patient to the emergency department or intensive care unit in case of persistent or severe hypotension, shock, extreme lethargy, or respiratory distress 4. Monitor vital signs 5. Monitor for resolution at least 4-6 hours after the onset of a reaction 6. Discharge home if patient is able to tolerate clear liquids	1. Place a peripheral intravenous line and administer normal saline bolus (20 mL/kg) rapidly, repeat as needed to correct hypotension 2. If age 6 months and older: administer intravenous ondansetron (0.15 mg/kg/dose, maximum 16 mg/dose) 3. If placement of intravenous line is delayed due to difficult access and age is 6 months or older administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 4. Consider administering intravenous methylprednisolone 1 mg/kg, maximum 60 to 80 mg/dose 5. Monitor and correct acid base and electrolyte abnormalities 6. Correct methemoglobinemia if present 7. Monitor vital signs 8. Discharge after 4-6 hours from the onset of a reaction when the patient is back to baseline and is tolerating oral fluids 9. Transfer the patient to the emergency department or intensive care unit for further management in case of persistent or severe hypotension, shock, extreme lethargy, or respiratory distress	
Home				
	History of severe FPIES reaction	Call an ambulance or go to the emergency department if the triggering food was definitely ingested, regardless of the severity or presence/absence of symptoms		
	No history of severe FPIES reaction	1-2 episodes of emesis No or mild lethargy	Attempt oral rehydration at home (eg, breastfeeding or clear fluids)	
		More than 3 episodes of emesis and moderate-severe lethargy	Call an ambulance or go to the emergency room	

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.

^aOndansetron is not approved for infants younger than 6 months.

Food challenges should be performed in children with a history of severe FPIES in the hospital or other monitored setting with immediate availability of intravenous resuscitation.

Oral challenges in the physician's office can be considered in patients with no history of severe FPIES reaction, although caution is advised, as there are no biomarkers that can predict future severity of FPIES reactions

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Infants with suspected CM-FPIES and soy FPIES are generally recommended to avoid all forms of the culprit food, including baked and processed foods, unless they are already tolerating baked foods [20]. There are no conclusive studies to date on tolerance to the baked-milk and egg proteins in children with FPIES; small case series have reported tolerance of baked milk and egg in some patients with FPIES. Baked milk and egg should be reintroduced under the physician's supervision, as the long-term outcomes associated with this practice remain unclear [77,81,82].

Infant Formula

Infants with CM-FPIES/soy FPIES may be breastfed or use a hypoallergenic formula approved for infants with milk allergy, such as extensively hydrolyzed casein-based formula. Whenever possible, continuation of breastfeeding should be encouraged, consistent with current American Academy of Pediatrics recommendations for infant feeding [83]. About 10%-40% of infants may not tolerate extensively hydrolyzed casein-based formula and require an amino acid–based

formula [22,18]. In infants with CM-FPIES, especially those younger than 6 months, introduction of soy formula under the physician's supervision should be considered.

Other Animal Milks

It is unknown whether children with CM-FPIES can tolerate goat and sheep milk. Based on the high homology of the protein sequences in these animal milks, goat and sheep milk are not recommended in CM-FPIES [84]. Milk from donkey and/or camel might be tolerated in CM-FPIES, as they are usually well tolerated in IgE-mediated CM allergy [85-87].

Breastfeeding

Acute and chronic FPIES attributed to breast milk are rare (except for reports from Japan, where symptoms are reported in up to 30% of infants during breastfeeding [3,74,88,89]). In the case of symptomatic FPIES occurring in an exclusively breastfed infant, the mother should eliminate the suspected trigger food(s) from her diet if the reactions occur after breastfeeding or the infant is failing to thrive. The mother should seek immediate consultation with an allergy specialist for evaluation [27,88,89]. Nutritional advice should also be sought to design the elimination diet for the breastfeeding mother. If symptoms do not resolve with a maternal elimination diet, discontinuation of breastfeeding and introduction of feeding with a hypoallergenic formula (extensively hydrolyzed casein-based or amino acid–based) should be considered.

Introduction of New Foods

Most children (65%-80%) have FPIES to a single food, mainly CM [13,15,18]. However, referral centers in the US

reported that about 5%-10% of children reacted to more than 3 foods and that some reacted to as many as 6 or more foods [13,18]. Children with CM-FPIES or soy FPIES may react to both foods; this seems to be more likely among infants in the first 3-6 months of life [10,56,18]. Clinical experts generally recommend that infants with early onset FPIES are breastfed or receive a hypoallergenic formula in the first 12 months of life. In infants with CM-FPIES or soy FPIES, it is prudent to introduce the other food under the supervision of a physician. Table 7 presents current data regarding potential co-allergy in FPIES.

Infants and children with CM-FPIES or soy FPIES may also be at increased risk of reacting to a solid food, most often rice or oat. It is not recommended to delay introduction of complementary foods past 6 months of life because of FPIES [4,20,67,90]. A practical sequence for introducing solid foods at about 6 months of age at home could start with fruits and vegetables, followed by other complementary foods, for example, red meats and then cereal grains, as shown in Table 8. If an infant tolerates a variety of the early food proteins, subsequent introduction may be more liberal. Tolerance to one food from the food group is considered as a favorable prognostic indicator for tolerance of other foods from the same group [61].

In an infant with severe CM-FPIES/soy FPIES, supervised introduction of solid foods (eg, in-office) may be considered to promote a normal varied diet and to prevent unnecessary avoidance due to parental apprehension.

Testing for Resolution

Foods that triggered FPIES reactions in the past should generally be reintroduced under medical supervision during a formal OFC. The ideal timing of the OFC to determine resolution of FPIES has not been systematically studied and varies considerably by geographic location and by individual provider preference. In the US, OFC is usually attempted within 12-24 months following the most recent reaction [61,64]. However, Korean data suggest children may be ready within a year of diagnosis, with tolerance rates to CM and soy, respectively, of 27% and 75% at 6 months, 42% and 91% and 8 months, and 64% and 92% at 10 months [25]. In Israel, 75% of cases of CM-FPIES resolved within the first year of life, 89% by age 2 years, and 94% by age 3 years [21]. However, retrospective series from the US report lower rates of resolution of FPIES to milk or soy, namely, 35% by age 2 years, 70% by age 3 years, and 85% by age 5 years, likely reflecting selection bias towards more severe and persistent phenotypes among children evaluated at the referral allergy centers than among those those identified from the general population [13,18]. There are no data on resolution of seafood FPIES in older children and adults. Periodic re-evaluations should be considered in adult patients.

Emergency Treatment Planning

A patient with a confirmed or suspected FPIES should be provided with an emergency treatment plan describing the condition and providing treatment guidance for the emergency department physician. An example of an emergency

Table 7. Common Food Co-allergies in Children With FPIES

FPIES to	Clinical Cross-reactivity/ Co-allergy	Observed Occurrence ^a
Cow milk	Soy	<30%-40%
	Any solid food	<16%
Soy	Cow milk	<30%-40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow milk or soy	<25%
Legumes ^a	Soy	<80%
Grains (eg, rice, oats) ^a	Other grains (including rice)	About 50%
Poultry ^a	Other poultry	<40%

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.

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

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Table 8. Empiric Guidelines for Selecting Weaning Foods in Infants With FPIES^a

Ages and Stages	Low-Risk Foods ^b	Moderate-Risk Foods ^b	High-Risk Foods ^b
4-6 months (as per AAP CoN) If developmentally appropriate, safe and nutritious foods are available. – Begin with smooth, thin purees and progress to thicker purees. – Choose foods that are high in iron. – Add vegetables and fruits.	Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
	Fruits		
	Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
6 months (as per WHO) Complementary feeding should begin no later than 6 months of age. – In the breastfed infant, high-iron foods or supplemental iron (1 mg/kg/d) is suggested by 6 months of age. – Continue to expand variety of fruits, vegetables, legumes, grains, meats, and other foods as tolerated.	High-Iron Foods		
	Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Fortified infant rice and oat cereals.
8 months of age or when developmentally appropriate – Offer soft-cooked and bite-and-dissolve textures from around 8 months of age or as tolerated by the infant.	Other		
	Tree nuts and seed butters ^b (sesame, sunflower, etc) Thinned with water or infant puree for appropriate texture and to prevent choking ^b	Peanut, legumes other than green pea	Milk, soy, poultry, egg, fish
12 months of age or when developmentally appropriate – Offer modified tolerated foods from the family table-chopped meats, soft cooked vegetables, grains, and fruits.			

Abbreviations: AAP CoN, American Academy of Pediatrics, Committee on Nutrition; FPIES, food protein–induced enterocolitis syndrome; WHO, World Health Organization.

^aExclusive breast feeding until 4-6 months of age and continuing breastfeeding through the first year of life or longer as long as mutually desired by both mother and child [98]. If an infant tolerates a variety of foods early, subsequent introduction may be more liberal. Additionally, tolerance to 1 food in a food group (green pea) is considered as a favorable prognostic indicator for tolerance of other foods from the same group (legumes) [61].

^bRisk assessment is based on the clinical experience and the published reports of FPIES triggers.

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treatment letter can be accessed at http://fpies.org/images/PDF/ER_Letter.pdf. Antihistamines and epinephrine are not recommended for first-line management; epinephrine autoinjectors are not routinely prescribed for patients with classic (seronegative) FPIES, although they may be prescribed for patients with atypical FPIES or those at risk for anaphylaxis due to concomitant IgE-mediated food allergy.

Pathophysiology

The mechanisms underlying FPIES remain poorly characterized, and further studies are needed for a better understanding of this disease. FPIES is classified as a cell-mediated disorder presumed to involve antigen-specific T lymphocytes, monocytes, antibodies, and cytokines as a cause of inflammation in the colon and, with variable degrees, the ileum [70,91-97]. This inflammation is hypothesized to result in increased intestinal permeability leading to a fluid shift into the gastrointestinal lumen. In acute FPIES, the effect of ondansetron on resolution of emesis suggests a potential neuroimmune mechanism and serotonin pathway involvement [57]. Current evidence regarding potential

immunologic pathogenic mechanisms is summarized in Table 9.

Conclusions

FPIES is a non-IgE-, cell-mediated food allergy of unknown prevalence and pathophysiology. Onset is typically in the first year of life; seafood FPIES may start in adulthood. Acute FPIES manifests within 1-4 hours following food ingestion with repetitive emesis, pallor, and lethargy progressing to dehydration and hypovolemic shock in 15% of cases. Chronic FPIES manifests with intermittent, progressive emesis, watery diarrhea, and poor growth progressing to dehydration and hypovolemic shock over a period of days to weeks. Chronic FPIES has been only reported in infants less than 3 months old fed with CM or soy formula. The most common triggers are CM, soy, rice, and oat. Diagnosis of FPIES relies on recognition of a specific pattern of clinical symptoms and may be missed owing to the absence of typical allergic symptoms (eg, urticaria, wheezing) and delayed onset in relation to food ingestion. Physician-supervised OFC is recommended if the diagnosis or the trigger food is not clear

Table 9. Putative Pathophysiology of FPIES

Cell Type/Mechanism	Evidence	Comments
<i>Cellular Mechanisms</i>		
CD4 ⁺ T lymphocytes	Older studies reported proliferation of PBMCs upon stimulation with food allergen [49,50,58,99-103].	More recent study found no difference in proliferation of T cells and production of T _H 2 cytokines after casein stimulation in children with CM-FPIES and controls [6].
Monocytes	Profiling of whole blood by mass cytometry demonstrated profound activation of cells of the innate immune system, including monocytes, neutrophils, NK cells, and eosinophils, in children with active but unresolved FPIES. Pan T–cell activation and redistribution from the bloodstream was noted after a positive OFC, but not in those who had outgrown FPIES [104].	These data show systemic innate immune activation in adverse reactions elicited by foods in FPIES. Further investigation is needed to identify the mechanism of antigen specificity in reactions to foods [104].
Eosinophils	Peripheral blood eosinophilia with increased expression of CD69, clusters of eosinophils in intestinal biopsies, and eosinophils and Charcot-Leyden crystals in stool samples have been nonspecifically noted in a subset of infants with FPIES. Fecal eosinophil-derived neurotoxin is elevated following a positive challenge [97,105,106].	Gastrointestinal eosinophil accumulation may overlap with other disorders such as eosinophilic gastroenteropathies, food-induced proctocolitis, IgE-mediated food allergy, inflammatory bowel diseases, and gastroesophageal reflux [105].
Neutrophils	Peripheral blood neutrophilia and leukocytosis are present in patients with acute FPIES, peaking approximately 6 hours after trigger food ingestion and returning to baseline within 24 hours [9,10,12,15,107]. Neutrophils have been found in the gastric juice aspirate and in stool mucus of FPIES patients [25].	Neutrophilia may result from secretion of TNF or IL-8 by the local inflammatory cells [108]. The potential active contribution of neutrophils and platelets to the pathophysiology of FPIES requires further study [9,26,58,100].
Platelets	Thrombocytosis is found in acute and chronic FPIES [15], likely as an acute phase reactant (eg, owing to stress-induced demargination of platelets from the spleen into the circulation) [109].	The potential active contribution of neutrophils and platelets in the pathophysiology of FPIES requires further study [9,26,58,100].
Mast cells	Higher baseline tryptase levels (although within normal range for age) were found in children with active CM-FPIES compared with those who had outgrown CM-FPIES, as documented by OFC; there was no change in tryptase after OFC	Elevated baseline serum tryptase levels in active FPIES suggest low-grade intestinal mast cell activation or increased mast cell load.
<i>Cytokines</i>		
TNF- α /IFN- γ /TGF- β imbalance	Increased TNF- α and decreased expression of TGF- β receptors, known to protect the intestinal barrier from the penetration of foreign antigen have been found in the intestinal mucosa of FPIES patients [97,100,110,111].	Release of proinflammatory cytokines (TNF- α , IFN- γ) by activated PBMCs has been suggested to induce local intestinal inflammation [101,112]. High levels of TNF- α released by antigen-specific T cells could act synergistically with IFN- γ to increase intestinal permeability and then increase the amount of antigen flux into the submucosa, with further activation of antigen-specific T cells [101].
IP-10	There was a trend toward an increase of serum level of IP-10 in patients with active CM-FPIES and a positive OFC result [6].	In response to IFN- γ , IP-10 is secreted by several cell types (such as monocytes, endothelial cells and fibroblasts) and has been attributed several roles, particularly as a chemoattractant for activated T cells and monocytes/macrophages [113]. An increase of IP-10 and IL-8 levels was recently demonstrated in patients with IgE-mediated food allergy, thus highlighting the importance of these cytokines in this disorder [113].

Table 9. Putative Pathophysiology of FPIES (continuation)

Cell Type/Mechanism	Evidence	Comments
<i>Cytokines</i>		
TGF- β	Children with active CM-FPIES have deficient T cell-mediated TGF- β responses to casein [114].	TGF- β might be a promising biomarker in identifying children who are likely to experience FPIES reactions to CM [114].
IL-10	Significant increase in serum IL-10 was observed in children with CM-FPIES following a positive OFC to CM but not after a negative OFC. However, IL-10 in the supernatant from the PBMC culture stimulated with casein was lower in children with active CM-FPIES compared with those whose CM-FPIES had resolved [6].	IL-10 may play a key role in the acquisition of tolerance in CM-FPIES but it seems to be produced by cell types other than T lymphocytes [6].
IL-8	Serum level of IL-8 was significantly higher in CM-FPIES patients following a positive OFC compared to those with a negative OFC.	IL-8 is a potent chemoattractant of neutrophils from peripheral blood into tissues, and is involved in the initiation and amplification of inflammatory processes [115]. IL-8 is also secreted by neutrophils. The functional role of neutrophils in IgE-mediated diseases has been demonstrated [116]. Antigen-dependent IL-8 release has been suggested to occur through IgE-dependent mechanisms [116]. The role of neutrophils, and particularly that of IL-8, in the pathogenesis of FPIES requires further investigation.
IL-9	Casein-specific production of IL-9 was significantly higher in children with CM-FPIES compared to children with IgE-CM allergy ($P < 0.05$) [6].	A recent study suggested that mast cell-derived IL-9 is essential in intestinal anaphylaxis [117]. The data raise the possibility of mast cell involvement in FPIES, which could be a variant of intestinal anaphylaxis.
<i>Humoral Mechanisms</i>		
IgE, IgG, IgG4, IgA to casein	Children with active CM-FPIES have lower levels of CM, casein-IgG, and casein-IgG4 than patients who tolerate CM ($P < 0.05$) [6,114].	The overall paucity of humoral responses may be caused by lack of help from T lymphocytes, unresponsiveness of B cells, or inadequate antigen processing.

Abbreviation: CM, cow milk; FPIES, food protein-induced enterocolitis syndrome; OFC, oral food challenge; PBMC, peripheral blood mononuclear cell.

and to evaluate the steps necessary for resolution. Testing for food-specific IgE is usually negative, although a subset of patients, usually with CM-FPIES, may develop sensitization to food IgE. Such atypical FPIES tends to have a more prolonged course. Despite the potential severity of the reactions, no fatalities have been reported, and FPIES has a favorable prognosis. FPIES resolves in most cases by age 3-5 years, although persistence of CM-FPIES and soy FPIES into adulthood has been reported. The first international consensus guidelines on diagnosis and management of FPIES are to be published in 2017. The pathophysiology of FPIES remains obscure. Consequently, there are no diagnostic biomarkers and no therapies to accelerate resolution. These unmet needs

warrant future investigations to improve the care of patients with FPIES.

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Conflicts of Interest

Anna Nowak-Węgrzyn is Chair of the Medical Advisory Board for the International FPIES Organization. The remaining authors declare that they have no conflicts of interest.

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■ Anna Nowak-Węgrzyn

Icahn School of Medicine at Mount Sinai
 Kravis Children's Hospital
 Division of Allergy and Immunology
 Jaffe Food Allergy Institute
 New York City, New York, USA
 E-mail: anna.nowak-wegrzyn@mssm.edu