

Food Protein–Induced Enterocolitis Syndrome



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KEYWORDS

- Non-IgE-mediated food allergy • Food protein–induced enterocolitis syndrome
- FPIES • Gastrointestinal food allergy

KEY POINTS

- Food protein–induced enterocolitis syndrome (FPIES) is a rare, non-immunoglobulin E–mediated gastrointestinal food allergy that continues to be misdiagnosed, contributing to delays in diagnosis and increased morbidity.
- Varied presentations of FPIES have been reported in different populations, however acute and repetitive vomiting remains the predominant feature.
- Although most cases are diagnosed in infants and resolve by school age, FPIES may present at any age and persist into teenage and adult years.
- Further study into the prevalence, pathophysiology, and natural course of FPIES is warranted.

INTRODUCTION

Food protein–induced enterocolitis syndrome (FPIES) is a rare, non–immunoglobulin E (IgE)-mediated gastrointestinal food allergy primarily diagnosed in infancy. Acute FPIES reactions typically present with delayed, repetitive vomiting, lethargy, and pallor within 1 to 4 hours of food ingestion. Chronic FPIES typically presents with protracted vomiting, diarrhea, or both, accompanied by weight loss or poor growth. Foods regularly included in the diet are thought to induce chronic symptoms, such as cow's milk (CM) or soy formula, while acute reactions are commonly reported after intermittent ingestion of the causative food. The pathophysiology of FPIES is unknown but is thought to be immunologic and cellular in nature.¹

Owing to nonspecific symptoms and the lack of diagnostic testing, FPIES is often initially misdiagnosed, leading to a delay in diagnosis and increased morbidity from

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extensive workups and hospitalizations. Varying clinical manifestations of FPIES in different populations further complicate the picture. An understanding of the various presentations of FPIES along with increased awareness of the condition by general practitioners and emergency room providers will help to improve the management and quality of life of patients with FPIES.

EPIDEMIOLOGY

Large population studies to assess the overall prevalence of FPIES are lacking. In the only such study with more than 13,000 Israeli infants prospectively enrolled, the cumulative incidence of CM FPIES was reported at 0.34%.² IgE-mediated CM allergy, a condition considered more common than FPIES, was diagnosed in 0.5% of the same population.

Several studies have reported an increase in FPIES diagnosis, frequently attributed to increased awareness of the syndrome as separate from other food sensitivities. In an Italian cohort, a significant increase in the number of FPIES cases was noted in 2008, when the diagnostic criteria for FPIES were modified at one of its centers, with a constant level of cases reported thereafter.³ Alternatively, in an Australian cohort, although the number of FPIES cases increased steadily over a 16-year period, the median number of prediagnosis FPIES reactions did not substantially change, suggesting that increased awareness did not play a role.⁴ In a recent large United States cohort, no increase in the number of FPIES cases was observed over a 6 year period.⁵

Although FPIES develops primarily in infancy, reports in older children and adults indicate that it may develop at any age.⁵⁻⁷ There does not seem to be a gender predilection in childhood, however a female predominance in a small cohort of adults with FPIES has been reported, similar to that seen in IgE-mediated food allergy.⁷ In a large United States cohort, 65% of FPIES subjects were Caucasian, mirroring the referral population evaluated their allergy clinic.⁵ In Israel, FPIES was more common in the Jewish population ($P = .03$).⁴ Overall, FPIES has been reported across all races and ethnicities.^{5,8}

Many FPIES patients have an atopic background. Eczema was reported in 9% to 57% of FPIES subjects, similar to or higher than the overall population.³⁻⁶ Wheezing or asthma was reported in 3% to 25% of FPIES subjects, similar to or lower than overall population.⁴⁻⁶ Allergic rhinitis was reported in 38% of FPIES subjects, IgE-mediated food allergy to other foods in 11% to 30%, and eosinophilic esophagitis in 1 FPIES subject.^{4,6} A family history of allergic disease was reported in 20% to 77% of FPIES cases.^{3,6} In one cohort, 34% of FPIES subjects had a family history of food allergy, and 6% ($n = 10$) had a family history of FPIES.⁶

CM FPIES in the Israeli cohort was not found to be associated with gestational age, birth weight, maternal age, number of siblings, dairy consumption by mother, or age of CM introduction.² However, infants with CM FPIES were more likely than healthy infants to have been born by cesarean section (27% vs 15%, respectively) ($P = .003$). Conversely, in a United States FPIES cohort, the rate of cesarean section was 29%, lower than the overall population.⁶ In the Italian FPIES cohort, 95% were breastfed for a median duration of 4 months (range 0.5–12), whereas the breastfeeding rate in a large United States cohort was 47%, similar to the national rate.^{3,5}

CLINICAL PRESENTATION

The rates of FPIES symptoms in different cohorts are presented in [Table 1](#). Vomiting is the predominant FPIES symptom, while diarrhea is typically reported in 50% or fewer FPIES cases. Isolated vomiting and isolated diarrhea have been reported.³ It has been

Table 1
Most common symptoms of FPIES in cohort studies (%)

	Mehr et al ⁴ (N = 35; 66 Episodes)	Katz et al ² (N = 44 CM FPIES)	Sopo et al ³ (N = 66)	Ruiz-García et al ¹¹ (N = 16)	Tan & Smith ⁷ (N = 31 Adults)	Ludman et al ⁸ (n = 50 Acute, n = 4 Chronic)	Caubet et al ⁶ (N = 74 Positive OFCs)
Vomiting	100 (66)	100 (44)	98 (65)	100 (16)	71 (24)	81 (44)	96 (70)
Diarrhea	24 (16)	25 (11)	54 (36)	56 (9)	58 (18)	37 (20)	7 (5)
Lethargy	85 (55)	77 (34)	—	25 (4)	—	17 (9) ^a	7 (5)
Pallor	67 (44)	14 (6)	80 (53)	19 (3)	—	15 (8) ^b	—
Abdominal pain	—	—	—	—	77.4 (24)	6 (3)	80 (59)
Hypotension	—	—	77 (51)	—	—	—	19 (14)

Values are percent (no. of subjects).

Abbreviation: CM, cow's milk.

^a "Listless".

^b "Gray appearance".

suggested that diarrhea is likely associated with more severe cases, exacerbating fluid loss, and infancy.⁴ In the study by Sopo and colleagues,³ 47% versus 27% of acute reactions with and without diarrhea, respectively, required hospitalization and were treated with intravenous fluids (IVF). However, diarrhea was reported in only 7% of a large United States cohort of oral food challenges (OFCs), while hypotension was reported in 19%.⁶

Hypotension has been reported in 5% to 77% of different cohorts.^{3,5,6} This large range is likely due to differences in methodology, whether blood pressure was measured, and the number of cases observed during OFCs or treated at a medical facility compared with symptoms reported by parents. Sopo and colleagues³ reported that pallor and hypotension/lethargy never occurred alone. There was no mention of pallor or hypotension in the adult cohort, although these symptoms were reported in an adult case report of scallop FPIES.⁹ In the adult cohort, abdominal pain was reported in 77% of cases, more so than vomiting (71%).⁷

Other reported presenting symptoms included dehydration, lethargy, irritability, loss of consciousness, clamminess, hypotonia, cyanosis, and other stool changes, including bloody diarrhea, melena, and malodorous, pale or sticky stools.^{5,8,10} Mehr and colleagues⁴ reported that 6 of 25 (24%) patients who had body temperature measured were hypothermic (<36°C). Weight loss and poor growth has been reported in chronic FPIES.⁸

The amount ingested that causes FPIES symptoms can be very low, as in the case of a 6-month-old diagnosed with rice FPIES who developed symptoms after chewing on a wrapper from a rice cake.¹² Similarly, Bansal and colleagues¹³ reported 4 cases where increasingly smaller amounts were needed to trigger subsequent FPIES reactions. Conversely, Katz and colleagues² reported that 54% of subjects with CM FPIES tolerated 121 mL or more of CM before having symptoms during OFCs.

Although approximately 60% of FPIES cases occur on first exposure, many cases occur after a period of tolerance.^{2,4} In the study by Mehr and colleagues,⁴ 12% of the cohort developed FPIES symptoms on second exposure, 12% on third, and 15% on fourth. Katz and colleagues² reported that 16% of infants with CM FPIES tolerated CM for more than 4 days and 11% tolerated CM for 14 to 30 days before developing symptoms. FPIES in adults has been reported to be acquired after tolerating the trigger food previously.⁷

The appearance of symptoms after ingestion of trigger foods is typically delayed in comparison with IgE-mediated food allergy.^{2,11} The median reported time from first dose to development of symptoms during OFCs in 2 cohorts was 1.5 to 2 hours, with a range of 0.5 to 4 hours.^{3,4} This is similar to the findings of Katz and colleagues,² who reported a range of 30 minutes to 5.25 hours between ingestion and symptoms, with 60% occurring after 2 hours. In the fish-related FPIES cohort of Zapatero Remón and colleagues,¹⁴ two patients reported symptoms within 5 to 10 minutes and one showed symptoms at 6 hours; during observed OFCs the range of time from ingestion to symptoms was between 30 minutes and 5 hours. The duration of symptoms has been reported to be between 2 and 48 hours.^{3,14} During observed OFCs, the median time to recovery was 50 minutes (interquartile range [IQR] 13–95 minutes) in the cohort of Caubet and colleagues.⁶

The age at onset of FPIES seems to differ according to food trigger (Table 2). Likely because of delays in diagnosis, the overall median age at FPIES diagnosis was 15 months (IQR 9–24 months) in one cohort, and the overall mean age at diagnosis was 14 months in another cohort.^{3,6} Several cohorts report CM or soy FPIES presenting earlier than solid food FPIES, mostly before 6 months of age.^{2,3,5,6} Late-onset fish or shellfish FPIES was diagnosed after infancy in 7% of one cohort with a median age

Table 2
FPIES cohort studies

	Country, Location	Type of Study	No. of Patients; Gender	Age at Onset	No. of Foods
Mehr et al, ⁴ 2009	Sydney, Australia, tertiary	Retrospective, 16 y (1992–2007)	35; 57% male	Mean 5.5 ± 2.4 mo	83% to 1 food, 17% to 2 foods
Sopo et al, ³ 2012	Rome, Benevento, and Florence, Italy, tertiary	Retrospective, 7 y	66; 61% male	Overall mean 5.7 ± 5.1 mo; milk 3.5 ± 2.4 mo; other foods 10.6 ± 6.7 mo	85% to 1 food, 15% to multiple triggers
Hsu & Mehr, ²¹ 2013	Sydney, Australia, tertiary	Retrospective, 4 y (2008–2012)	38; 53% male	Mean 6 mo	66% to 1 food, 34% to multiple triggers
Ruffner et al, ⁵ 2013	Philadelphia, PA, USA, tertiary	Retrospective, 6 y	462; 60.4% male	Overall mean 9.7 ± 10.2 mo; milk/soy 7 ± 0.7 mo; solids 12.1 ± 1.1 mo	70% to 1 or 2 foods, 30% to ≥3 foods; 5% reacted to >6 foods
Ruiz-García et al, ¹¹ 2014	Madrid, Spain, tertiary	Retrospective, 12 y	16; 10 boys, 6 girls	Median 6.5 mo (range, 1–30)	94% to 1 food, 1 (6%) to 2 foods
Ludman et al, ⁸ 2014	London, UK, tertiary	Retrospective, 3 y	54; 59% male	Median 8 mo (range, 0.75–60); milk/soy 6 mo (0.75–36); solid 8 mo (3–60); chronic 5 mo (0.75–12)	70% to 1 food, 30% to multiple triggers
Caubet et al, ⁶ 2014	New York, NY, USA, tertiary	Retrospective and prospective (51%), 11 y	160; 54% male	Milk/soy only: median 5 mo (IQR 2–10); solid food only: median 7 mo (IQR 6–12); milk/soy and solid food: median 4 mo (IQR 2–6)	65% to 1 food, 26% to 2 foods, 9% to ≥3 foods; median 3 foods (range, 3–10 foods)
Tan & Smith, ⁷ 2014	South Australia, Australia, private practice	Retrospective, 8 y	31; 23% male	Median 29 y (IQR 22–45.8)	84% to 1 food, 13% to 2 foods, 3% to 3 foods

at diagnosis of 30 months.⁶ Zapatero Remón and colleagues¹⁴ reported the age of onset of fish FPIES to be between 9 and 12 months.

Ruffner and colleagues⁵ found no significant difference in age at FPIES presentation between breastfed and formula-fed infants. Caubet and colleagues⁶ found that in solid food FPIES, formula was introduced later (median 1.5 months) and breastfeeding lasted longer (median 2.8 months) than in those with CM or soy FPIES, for whom formula was introduced and breastfeeding lasted a median 0.03 months ($P = .0002$). In this cohort, 62% of CM or soy FPIES infants were exposed to CM or soy formula in the first few weeks of life. In addition, most CM or soy FPIES presented with chronic symptoms, such as diarrhea, colitis, reflux, or failure to thrive, occurring shortly after CM or soy formula introduction, which resolved with avoidance. Subsequent acute episodes to CM or soy occurred at a mean age of 7 months (range, 0.3–60 months).⁶

Acute CM or soy FPIES in exclusively breastfed infants is rare.^{3,15–17} Theories about breast milk being protective include the presence of protective immunoglobulin A, that the food is highly processed, or that the threshold dose may not be present in breast milk.¹⁸ Three breastfed infants in one cohort ($N = 160$) had symptoms of chronic FPIES to CM in the maternal diet.⁶ By contrast, in a parent survey ($N = 263$), a surprising proportion (42%) reported reactions through breast milk exposure.¹⁹ This result may be affected by recall bias and may depend on the definition of FPIES symptoms.

The amount ingested that causes FPIES symptoms can be very low, as in the case of a 6-month-old diagnosed with rice FPIES who developed symptoms after chewing on a wrapper from a rice cake.¹² Similarly, Bansal and colleagues¹³ reported 4 cases where increasingly smaller amounts were needed to trigger subsequent FPIES reactions. Conversely, Katz and colleagues² reported that 54% of subjects with CM FPIES tolerated 121 mL or more of CM before having symptoms during OFCs.

CAUSATIVE FOODS

Foods that have been reported in the literature to trigger FPIES are listed in **Table 3**.^{3–14,20–23} The rates of the most common foods causing FPIES in cohorts are presented in **Table 4**. In the two large United States cohorts, CM, soy, rice, and oats are the most common foods.^{5,6} In the study by Caubet and colleagues,⁶ solid food-only FPIES was reported in 31% of subjects, CM only in 22%, soy only in 22%, CM and soy in 13%, and CM and/or soy plus solid food in 11%. In the cohorts from Australia, Israel, and Italy, soy FPIES was not common.^{2–4} Ruffner and

Table 3 Reported food triggers identified in the literature	
Liquids	Cow's milk, soy milk (also a legume), goat's milk
Grains	Rice, oat, barley, wheat
Vegetables	Sweet potatoes, squash, pumpkin, corn, carrots, white potato, spinach, cauliflower, cucumber
Legumes	Green pea, peanut, string bean, green bean, lentil, kidney bean
Fruits	Banana, orange, pineapple, apple, strawberry, blueberry, raspberry, mango, peach, pear, plum, apricot, grape, cherry, kiwi, watermelon, avocado, coconut, tomato
Animal protein	Egg, chicken, turkey, beef, lamb, pork, duck
Seafood	Fish, shellfish, mollusks
Other	Almond, other tree nuts, mushroom, quorn, probiotic <i>Saccharomyces boulardii</i>

Table 4

Most common food triggers of FPIES in cohort studies (%)

	Mehr et al ⁴ (N = 35)	Sopo et al ³ (N = 66)	Hsu and Mehr ²¹ (N = 38)	Ruffner et al ⁵ (N = 462)	Ruiz-García et al ¹¹ (N = 16)	Ludman et al ⁸ (N = 52)	Caubet et al ⁶ (N = 160)
Cow's milk	20 (7)	67 (44)	32 (12)	67 (309)	44 (7)	46 (25)	44 (70)
Soy	34 (12)	4 (3)	13 (5)	41 (189)	6 (1)	11 (6)	41 (66)
Rice	40 (14)	4 (3)	53 (20)	19 (88)	—	4 (2)	23 (36)
Oat	6 (2)	—	18 (7)	16 (74)	—	6 (3)	16 (26)
Wheat	—	—	—	10 (46)	6 (1)	11 (6)	1 (2)
Poultry	3 (1)	3 (2)	—	4.5 (21)	6 (1)	7 (4)	—
Fish	3 (1)	12 (8)	—	—	31 (5)	15 (8)	—
Egg	—	6 (4)	10 (4)	11 (51)	—	13 (7)	—
Peanut	—	—	—	1.9 (9)	—	—	—
Corn	—	2 (1)	—	8 (37)	—	—	—
Banana	3 (1)	—	—	3.5 (16)	—	6 (3)	—
Sweet potato	6 (2)	—	—	4.1 (19)	—	—	—

Values are percent (no. of subjects).

colleagues⁵ reported that the most common fruit was banana (3.5%), while the most common vegetables were sweet potato (4.1%) and pea (3.2%).

Fish was the second most common FPIES trigger after CM in the Italian cohort, and was also reported in the cohorts from Spain.^{3,11,14} Fish is introduced early into children's diets in Spain and Italy, however so is rice, which was not a common FPIES trigger in these populations. Similar to IgE-mediated fish allergy, while some subjects developed FPIES to multiple fish, others in the cohort of Sopo and colleagues³ were able to tolerate some species of fish.

Egg is becoming a more frequently reported trigger of FPIES, for example in the British (13%) and Australian (10%) cohorts.^{8,21} In an adult cohort, egg was the second most common trigger (16%) after seafood.⁷ Whereas chronic FPIES in infants is typically seen with CM or soy, egg was reported as a chronic trigger in one cohort.⁸ There is one case report of FPIES reaction to egg yolk, although challenge to egg white alone was not undertaken so it is not known whether the trigger was small amounts of egg white in the egg yolk.²⁴

There have been reports of tolerance to baked or processed FPIES foods, as is common with IgE-mediated food allergy to CM and egg. Miceli Sopo and colleagues²⁵ reported that 4 of 7 patients with CM or egg FPIES tolerated baked CM or egg. Caution is warranted, as FPIES reactions to baked CM and egg have also been reported.^{21,25} Yasutomi and colleagues²⁶ also reported the case of an 8-month-old female with atypical (detectable specific IgE) rice FPIES who tolerated highly processed retort rice, but developed symptoms with boiled rice. The patient's IgE was found to bind to boiled rice extract, but not the retort rice, on Western blot analysis.

Reactions to Multiple Foods

Reactions to multiple foods in different cohorts are listed in [Table 2](#). In the United States cohorts, Ruffner and colleagues⁵ and Caubet and colleagues⁶ reported that 43.5% and 37% of CM FPIES, respectively, also reacted to soy. Caubet and colleagues⁶ reported that 61.5% of CM and soy FPIES had reactions to both within 2 months of each other. These results differ from those in cohorts outside the United States, where most patients with CM FPIES tolerated soy or had no reported reactions to soy.²⁻⁴ In the CM FPIES cohort of Katz and colleagues,² 35 of 44 tolerated soy milk, and 5 of the remaining 9 added soy to the diet after a negative soy OFC.

In the United States cohorts, most subjects with multiple FPIES triggers reacted to CM and/or soy and solid foods.^{5,6} In these same cohorts, 40% to 50% of subjects with grain FPIES reacted to two or more grains. No solid food FPIES was reported in cases of CM FPIES in several cohorts outside the United States.^{2,10,14} Caubet and colleagues⁶ found no difference in FPIES to one, two or three or more foods and age at diagnosis, age at onset, detectable specific IgE, detectable specific IgE to other foods, family history of atopy, or family history of FPIES.

DIAGNOSIS

Diagnosis of FPIES is usually based on clinical criteria. Because most FPIES patients are young and have a limited diet, an in-depth history is usually enough to elicit the trigger food. Diagnostic OFCs were performed for 53% and 64% of patients in the Sopo and Katz cohorts,^{2,3} respectively. In the study by Caubet and colleagues,⁶ 180 OFCs were performed in 82 subjects, and 30% of the FPIES population had OFCs diagnostic of FPIES.

For most subjects, skin-prick testing (SPT) and specific IgE (sIgE) levels to FPIES trigger foods were negative.^{2-5,8,14} In several cohorts, less than 10% of subjects

tested had a positive SPT to trigger foods, and between 11% and 24% had detectable sIgE levels.^{2–6,8} Most of the detectable sIgE levels were to common foods that cause IgE-mediated allergy, such as CM, soy, egg, peanut, and tree nuts, but a few were also positive to rice and oats.^{5,6}

Subjects with detectable sIgE levels to trigger foods have been noted to have a protracted course. For example, no subjects with CM-sIgE levels in the cohort of Caubet and colleagues⁶ had outgrown CM FPIES, whereas those with undetectable CM-sIgE levels had resolution of FPIES at a median age of 61 months. In addition, 33% of subjects (41% with CM FPIES) with detectable sIgE levels converted to an IgE-mediated phenotype. This transition has been noted in other cohorts.^{2,3,27} Katz and colleagues² noted that transition from FPIES to IgE-mediated food allergy was not associated with average age of onset, mean dose-evoking response, median time from ingestion to response, or SPT results at time of FPIES presentation. There has been one reported case of a 4-month-old with a history of IgE-mediated CM allergy that shifted to FPIES.²⁸

Atopy patch testing (APT) has been suggested as a diagnostic test for FPIES because it is presumably T-cell mediated, and delayed cutaneous responses are thought to represent a cellular mechanism. In a series of 19 FPIES patients, Fogg and colleagues²⁹ reported APT to have sensitivity of 100% and specificity of 71%. In a subsequent study by the same group with a larger cohort, APT was found to have a 45% false-negative rate and was determined not to be useful in the diagnosis of FPIES.⁵ In addition, in a series by Järvinen and Nowak-Węgrzyn³⁰ of 25 FPIES patients, the sensitivity and specificity of APT was only 11.8% and 85.7%, respectively, with a positive predictive value of 40% and a negative predictive value of 54.5%. In a small series ($n = 8$) in yet another population, less than half of those with a positive APT reacted during OFCs.¹⁴

An increased absolute neutrophil count (ANC), typically peaking at 6 hours, is a common finding in acute FPIES reactions.³¹ Caubet and colleagues⁶ reported that the ANC after positive OFCs showed a median increase of 1850 cells/mm³ and a mean increase of 3228 cells/mm³ (IQR 825–4200) 5 to 8 hours after a positive challenge; this is slightly lower than the increase of 3500 cells/mm³ proposed by Powell.³¹ This finding could be confounded by intravenous steroids, which increase ANC. While helpful, an isolated increase in ANC is not enough to diagnosis FPIES and should not be used to exclude foods from the diet.⁶

Two cohorts noted a mild increase in platelets. Caubet and colleagues⁶ reported a median increase of 19,000/mm³ (range, –121,000 to 110,000). Mehr and colleagues⁴ reported thrombocytosis ($>500 \times 10^9$ cells/L) in 63% of FPIES episodes with a median increase of 588×10^9 cells/L (range, $515\text{--}777 \times 10^9$ cells/L). Other laboratory findings, depending on severity and chronicity, have included metabolic acidosis, methemoglobinemia, anemia, hypoalbuminemia, and eosinophilia.¹

Stool studies showing leukocytes and eosinophils have been proposed to support a diagnosis of FPIES.¹ However, as diarrhea is not a major feature in most FPIES cohorts, this may not be useful. In addition, although gastric juice aspirates showing an increase in leukocytes greater than 10 per high-powered field has been associated with positive FPIES OFCs, such a test may not be practical for most patients.³²

Diagnostic Criteria

An OFC remains the gold standard for diagnosis of FPIES; however, OFCs may not be necessary in cases of repeated reactions, especially severe ones with hypotension in young infants.³³ In light of the recent large cohorts from different populations, modifications to the current criteria used to diagnose FPIES may be warranted. The most

commonly used criteria for diagnosing FPIES (Powell’s criteria) and newly proposed criteria are listed in **Table 5**. Some researchers suggest that repetitive vomiting with pallor and lethargy are enough for diagnosis.^{2,3} Given the possibility that older children and adults can develop FPIES, it has also been proposed that the criteria should not include an age limit for age of onset.⁶ Although symptoms are typically delayed, data from OFCs indicate that vomiting may begin as early as 30 minutes, so a delay in symptoms should not be a requirement for diagnosis either. Minor criteria could include pallor, lethargy, hypotension (typically present only in a subpopulation), and positive stool studies, as diarrhea is not as common in acute FPIES as previously thought.⁶

Delay in Diagnosis

Delays in diagnosis were common in most cohorts, and awareness is still lacking.^{2–6,8} In a recent survey of general pediatricians, 24% had never heard of FPIES.³⁴ The likely reasons for this are the: (1) absence of a diagnostic test; (2) delay in onset of symptoms; (3) absence of classic allergy symptoms, such as rash or respiratory distress; and (4) low index of suspicion for grains and vegetables, which are typically considered hypoallergenic.⁶

The median number of FPIES reactions before diagnosis in several cohorts was 2 to 3 (range, 1–10).^{3,4,7,11,14} Unfortunately, the mean number of reactions before diagnosis did not change over 7 years in the cohort of Sopo and colleagues.³ A median delay in diagnosis of 4 to 7 months has been reported.^{6,8} In the study by Ludman and colleagues,⁸ subjects presented a mean of 2 times (range, 1–10) before an allergy or gastrointestinal referral was made. Sopo and colleagues³ reported that 60% of their subjects were self-referred, 30% were referred by a general pediatrician, and 10% were referred by a general practitioner.

Seventy-three percent of general pediatricians in the survey conducted by Menon and colleagues³⁴ reported having FPIES patients in their practice, and 39% reported managing FPIES by themselves. Management included oral steroids and oral rehydration at home followed by evaluation in the ED, while 29% prescribed an epinephrine autoinjector. Similarly, 11% of FPIES patients discharged from the ED in one cohort

Table 5 Proposed old and new FPIES diagnostic criteria for acute reactions	
Powell Criteria ³¹	New Proposed Criteria
<9 mo at initial reaction	Major Criteria
Exposure to food elicits repetitive vomiting and/or diarrhea within 4 h without any other cause for symptoms	1. Repetitive vomiting or diarrhea within 6 h of food ingestion
Symptoms are limited to gastrointestinal tract	2. Absence of cutaneous and respiratory symptoms suggestive of an IgE-mediated allergy
Avoidance of the offending protein from the diet results in resolution of symptoms	3. Removal of causative food results in resolution of symptoms
Reexposure or a food challenge elicits the typical symptoms	4. Reexposure or a food challenge elicits the typical symptoms
	Minor Criteria
	a. Hypotension
	b. Lethargy, pallor, or hypotonia
	c. Negative skin-prick test and undetectable specific IgE level
	d. Absence of fever or hypothermia (<36°C)

were prescribed epinephrine autoinjectors,⁴ and in a parent survey by Green and colleagues,¹⁹ 14% reported carrying epinephrine autoinjectors for FPIES.

Differential Diagnosis and Misdiagnosis

Patients presenting with FPIES symptoms are often misdiagnosed with IgE-mediated food allergy, surgical abnormalities (eg, intussusception, malrotation, obstruction, volvulus), viral gastroenteritis, or sepsis.^{4,8} In the study by Mehr and colleagues,⁴ only 2 of 19 patients presenting to the ED were correctly diagnosed with FPIES. Workups have included abdominal imaging (eg, radiography, barium, ultrasonography), septic evaluation (eg, complete blood count, blood culture, chest radiograph, lumbar puncture), surgical consult, electrocardiogram, echocardiogram, Holter monitoring, brain MRI, electroencephalography, and urine metabolic screening.⁴ Some evaluations have even been invasive, such as intestinal biopsies and laparotomies.^{4,11,35,36} The treatment of patients presenting to the ED with FPIES have included IVF, antibiotics, oxygen, air or barium enema, and intravenous epinephrine.⁴

TREATMENT AND MANAGEMENT

OFCs may be used to assess for disease resolution, if multiple foods were ingested and the trigger food is not known, or to assess whether a food can safely be introduced in light of the high rate of multiple triggers. To decrease the need for OFCs, Sopo and colleagues³ proposed that patients with 2 or more severe reactions be diagnosed clinically. Although OFCs to foods that were being avoided by way of precaution may seem low risk, 11% were positive in one cohort.⁶

Several investigators recommend that OFCs to food triggers be done under medical supervision, regardless of food.⁶ Up to 33% of positive OFCs may require emergency treatment.¹⁴ Ruiz-García and colleagues¹¹ reported one FPIES patient who was treated in the intensive care unit for severe dehydration, hypotension, and loss of consciousness after a fish OFC. Caubet and colleagues⁶ reported 14 severe reactions (19%) with hypotension during OFCs to CM, soy, oat, and wheat. These investigators also reported that 20% of subjects with positive OFCs reported a history of tolerating a small amount of the trigger food. Furthermore, severity of reactions did not correlate with severity of reported reactions, gender, age, food, previous hospitalization due to FPIES, detectable sIgE level to trigger food, or sIgE levels to other foods.⁶

By contrast, some investigators have reported successful oral hydration after positive OFCs without significant hypotension.^{2,14} Sopo and colleagues³ reported 9 subjects who were reintroduced to the food at home by parents at a median 20 months after last FPIES reaction (range, 19–24 months). Over three years of follow-up, Caubet and colleagues⁶ reported 11 patients (32%) who successfully reintroduced foods at home. In a parent survey, more than half of the cohort ($n = 263$) underwent home challenge for initial reintroduction.¹⁹

Several protocols for FPIES OFCs exist at different centers.^{2,3,6} It is recommended that full resuscitation facilities be available, particularly for rapid IVF repletion. Patients are typically treated with IVF; a single dose of intravenous methylprednisolone can be used for more severe reactions, based on the presumed inflammatory pathophysiology.⁶ Monitoring for 3 to 4 hours after ingestion is warranted, owing to the delayed nature of symptoms.⁵ The time to onset of symptoms after ingestion may vary with the amount ingested during OFCs, but usually vomiting starts within 1 to 4 hours.^{2,6} Often two equal doses are given over 30 minutes, so it is difficult to know which dose was the eliciting dose.² Forty percent of subjects in one cohort with symptom onset of less than 120 minutes had detectable sIgE to the trigger food.⁶ If patients have a positive

SPT or detectable sIgE to trigger foods, the OFC procedure should be modified to a more incremental and gradual administration of challenge doses, as per the protocol for IgE-mediated food allergy, and preparation for IgE-mediated reactions must also be considered.

Recently, ondansetron has been reported to successfully shorten the duration of FPIES reactions. Holbrook and colleagues³⁷ reported that the use of intravenous ondansetron for positive OFCs in patients older than 3 years resolved symptoms within 10 to 15 minutes. One patient received oral ondansetron initially with mild improvement, followed by an intravenous dose with complete resolution. A second case series has reported resolution of symptoms within 15 minutes with the use of intramuscular ondansetron in 5 patients (4 of whom were <3 years old).³ Empirically, liquid oral ondansetron has been used for reactions at home, resulting in resolution of symptoms (Leonard, personal communication, 2014). It is still advised that patients seek medical attention for FPIES reactions, even if ondansetron is used.

Close follow-up of young children with FPIES is advised to monitor for additional reactions and to assess for tolerance. Most investigators suggest a minimum of 12 months since the last FPIES reaction before considering an OFC to check for resolution.^{3,5,8,14} Ruffner and colleagues⁵ report normally waiting 18 months. SPT and sIgE levels are recommended at diagnosis and follow-up because those with positive testing tend to have a more protracted course, and the possibility of IgE-mediated reactions should be assessed before an OFC is performed.

Anticipatory Guidance

Patients should be warned of the possibility of multiple triggers. Owing to the high rate of simultaneous CM and soy FPIES in United States cohorts, Ruffner and colleagues⁵ and Caubet and colleagues⁶ do not recommend that infants with CM FPIES ingest soy at home. Breastfeeding is encouraged in these cases, or the use of extensively hydrolyzed casein or elemental formula is recommended.^{1,6} If needed, tolerance of soy formula in a child with CM FPIES should be assessed by OFC. Cohorts from Australia, Italy, and Israel report a much lower rate of simultaneous CM and soy FPIES in infants, suggesting that soy may be an alternative for patients with CM FPIES in these countries.²⁻⁴

Extended dietary restrictions have been suggested for infants with FPIES for higher-risk foods such as CM, soy, grains, legumes, and poultry.³⁸ The theory is that delaying other common FPIES triggers might avoid sensitization/reactions to additional foods during a possible period of developmental susceptibility during infancy.⁶ Because of the high rate of FPIES to multiple grains in infants, Caubet and colleagues⁶ recommend delaying other grains until 1 year of age. With data from larger cohorts showing low rates of solid food FPIES, some investigators do not recommend precautionary avoidance. Fewer than 25% of CM FPIES subjects reacted to other foods besides soy in the cohort of Ruffner and colleagues,⁵ leading the investigators to suggest that other foods can be introduced. Sopo and colleagues³ recommend OFCs for the initial introduction of CM, grains, legumes, and poultry only in infants with solid food FPIES; otherwise, no restrictions on solid foods in CM or soy FPIES were recommended. In general, dietary advice should take into consideration sufficient nutritional intake to maintain and ensure growth and development.³⁹

Natural Course

The reported rates of FPIES resolution for different foods are listed in [Table 6](#). The differences across populations are likely explained by having more subjects with positive IgE testing, the increased prevalence of other atopic diseases at major

Table 6
Rates of FPIES resolution by cohort population

Cow's Milk	Soy	Grains	Meat/Fish
South Korea ¹⁰ : >60% by 10 mo	South Korea ¹⁰ : >90% by 10 mo	Australia ⁴ : 80% rice by 3 y	USA ⁶ : 50% meat by 5 y USA ⁶ : 0% fish by 5 y
Italy ³ : 63% by 24 mo	Israel ⁴ : 83% by 3 y	USA ⁶ : 66% grain by 5 y	
Israel ² : 94% by 3 y	USA ⁶ : 20% by 3 y		
USA ⁶ : 20% by 3 y			

referral centers, and differences in methodologies.⁶ Resolution of solid food FPIES appears later in some cohorts, while other cohorts show no difference in resolution between CM/soy and solid food.^{5,11} Sopo and colleagues³ reported CM tolerance at a mean age of 24 months (± 8 months) compared with solid food tolerance at a mean age of 53 months (± 17 months). Alternatively, Caubet and colleagues⁶ reported tolerance at a median age of 4.7 years for rice, 4 years for oats, 6.7 years for soy, and 5.1 years for CM (without detectable CM-sIgE level). No subjects with detectable CM-sIgE level became tolerant during the study. Ruffner and colleagues⁵ reported an overall FPIES resolution of 85% by age 5 years, and in 2 subjects, FPIES persisted into adolescence. Adult FPIES seems to persist for many years. In the cohort of Tan and Smith,⁷ no resolution was observed in patients who all continued to avoid their trigger foods, but many had accidental ingestions and reactions at intervals of up to 30 years.

SUMMARY

FPIES continues to be an underrecognized condition of food allergy. Repetitive vomiting after causative food ingestion remains the predominant feature. The addition of larger cohort descriptions has improved our understanding of varied presentations of FPIES, particularly with respect to food triggers. Milk, soy, rice, and oats are the most common FPIES triggers in United States cohorts, while fish and egg have been identified as common triggers in other cohorts. FPIES is most often diagnosed in infants and resolves by school age; however it may present at any age and persist into adolescence or adulthood. Further study into the prevalence, pathophysiology, and natural course of FPIES is still needed.

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