

Food Protein-Induced Enterocolitis Syndrome



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KEYWORDS

- Non-IgE-mediated food allergy
- Food protein-induced enterocolitis syndrome (FPIES) • Cow's milk • Soy
- Oral food challenge • Failure to thrive

KEY POINTS

- Awareness of food protein-induced enterocolitis syndrome is low.
- Food protein-induced enterocolitis syndrome (FPIES) can present as a medical emergency with symptoms including delayed persistent emesis with or without bloody diarrhea that can lead to severe dehydration and hemodynamic instability with abnormal laboratory markers.
- The mainstay of management is trigger avoidance.
- The natural history of the disease is spontaneous resolution over time.
- More studies are needed to better drive evidence-based practices for FPIES in clinical practice.

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) was first formally recognized by Powell in the 1970s.¹ FPIES is a non-immunoglobulin E (IgE)-mediated food allergy characterized by repetitive vomiting and frequent diarrhea that may lead to dehydration, lethargy, and pallor in the acute form. The chronic form is characterized by failure to thrive, emesis, and diarrhea. An atypical form, in which there is concomitant presence of specific IgE to the triggering food, has also been described.² Limited prevalence data exist, but this disorder is thought to be relatively rare.³ The diagnosis is often missed likely because of the broad differential, delayed presentations, and limited awareness in the medical community.^{4,5} Furthermore, the diagnosis is based solely on clinical criteria because no confirmatory test exists.⁶ Implicated foods, onset

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of the disorder, and time to resolution vary by geographic area and regional dietary practices.^{2,3,7,8} Treatment consists of education and avoidance of the offending foods. Many questions remain regarding this syndrome, and further research is needed.

EPIDEMIOLOGY

Food allergy prevalence has overall been increasing over the last 10 to 20 years.⁹ FPIES, a non-IgE-mediated food allergy, has been reported as rare, although more than 1000 cases have been reported and cases reported per year have varied from 1 to 90.¹⁰ There are few studies reviewing the prevalence of FPIES, and the true prevalence is unknown. The single population-based birth cohort study to date is by Katz and colleagues³ in Israel, who prospectively studied 13,019 infants for development of FPIES related to cow's milk over 2 years. The study results showed a cumulative incidence for FPIES of 0.34% (44/13,019), with 8 of these patients subsequently developing IgE-mediated cow's milk allergy. In comparison, 0.5% (66/13,019) of the study population had IgE-mediated cow's milk protein allergy. All patients were diagnosed within the first 6 months of life in the study; however, the age of presentation can vary anywhere from 7 days of life to about 12 months of age.^{2,3,8} Multiple studies report a male predominance similar to IgE-mediated food allergy.^{3,8,11} There is an increased incidence of comorbid atopic disease in infants with FPIES, with about 30% of infants having atopic dermatitis, asthma, allergic rhinitis, or IgE-mediated food allergy.^{8,11,12} Family history of atopy is common (40%–80%) in infants with FPIES; however, there are no cases of parents of infants with FPIES having had childhood or adult-onset FPIES, suggesting a lack of familial association.^{10,12}

DIAGNOSIS

Symptoms

FPIES usually presents between 2 and 7 months of age as formulas and solid foods are introduced into the infant's diet. Milk and soy protein are the most common causes, although several studies also report reactions to other foods, including rice, oat, or other cereal grains, such as barley and wheat.^{3,11,13} Children may have multiple food triggers. Cow's milk and soy FPIES often present at an earlier age than solid food-induced FPIES to grains, which is likely due to earlier introduction of cow's milk and soy. There are geographic variations of food triggers and age of diagnosis, likely based on differences in dietary implementation practices, with solid food-induced FPIES being more common in Europe and Australia than in North America (Table 1).¹⁴ FPIES can present with both acute and chronic symptoms that are reflective of the non-IgE-mediated process and usually lack the typical expected IgE-mediated symptoms.

Acute symptoms

FPIES usually presents initially in infancy as severe emesis with or without diarrhea that may contain blood or mucous with exposure to the causative food (Table 2). The severe emesis is repetitive and may include up to 15 to 20 episodes of projectile repetitive vomiting within 1 to 4 hours of ingesting the suspected food.^{4,9,14} The timing of onset of symptoms is important for the diagnosis. Secondary to these symptoms, children may have pallor, lethargy, metabolic acidosis, and hypothermia.^{8,9,14} Laboratory abnormalities also include an increased neutrophil count, which peaks at 6 hours, and thrombocytosis ($>500 \times 10^9/L$).⁸ Often with this presentation, infants will undergo evaluation for sepsis, especially if marked laboratory abnormalities and hemodynamic

Table 1
Geographic variance of *typical* cow's milk/soy-induced versus solid-food induced food protein-induced enterocolitis syndrome

References and Year	Country	Number of Patients	Foods Assessed	Age at Onset of Diagnosis (CM/Soy)	Age at Onset of Diagnosis (Solid Food)
Sicherer et al, ² 1998	United States	n = 16	Cow's milk, soy, solid foods	Median = 6 wk Mean = 7.52 wk	Median = 22 wk Mean = 22 wk
Nowak-Wegrzyn et al, ⁷ 2003	United States	n = 14	Solid foods	—	Median = 22 wk Mean = 20.6 wk
Fogg et al, ¹⁶ 2006	United States	n = 19	Cow's milk, soy, solid foods	Median = 8 wk Mean = 8.1 wk	Median = 18 wk Mean = 22.5 wk
Ruffner et al, ¹⁹ 2013	United States	n = 462	Cow's milk, soy, solid foods	Mean = 28 wk	Mean = 48.4 wk
Caubet et al, ¹¹ 2014	United States	n = 160	Cow's milk, soy, solid foods	Mean = 20 wk	Mean = 28 wk
Mehr et al, ⁸ 2009	Australia	n = 35	Cow's milk, soy, solid foods	Median = 16 wk Mean = 19.6 wk	Median = 23.6 wk Mean = 24.4 wk
Hwang et al, ¹³ 2009	South Korea	n = 23	Cow's milk, soy	Mean = 5.14 wk	—
Katz et al, ³ 2011	Israel	n = 44	Cow's milk	Median = 4.3 wk Mean = 8.3 wk	—
Sopo et al, ²⁰ 2012	Italy	n = 66	Cow's milk vs other foods	Mean = 14 wk (CM only)	Mean = 42.4 wk

Table 2 Symptoms of food protein-induced enterocolitis syndrome	
Acute FPIES	Chronic FPIES
Vomiting in the 1- to 4-h period after ingestion of the suspected food	• Intermittent emesis
± Diarrhea within 24 h, usually 5–10 h, occasionally bloody	• Progressive diarrhea, ± blood
Decreased activity level/lethargy	• Lethargy/fatigue
Pallor	• Dehydration
Dehydration/hypovolemic shock with hypotension	• Poor growth/failure to thrive
Hypothermia	
Laboratory findings	Laboratory findings
• Increased neutrophil count of ≥ 1500 neutrophils above baseline	• Thrombocytosis
• Thrombocytosis	• Metabolic acidosis
• Metabolic acidosis	• Methemoglobinemia
• Methemoglobinemia	• Hypoalbuminemia
• Stool + for leukocytes, eosinophils, or increased carbohydrate content	

Adapted from NIAID-Sponsored Expert Panel, Boyce JA, Assa’ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126(6 Suppl):S1-S8; with permission.

instability are present.² Diarrhea may be delayed and may occur 5 to 10 hours after ingestion of trigger foods. There is often no report of abnormal longitudinal growth or failure to thrive.¹⁴

Chronic symptoms

Chronic FPIES can vary in its clinical presentation and is not as well defined as acute FPIES (see [Table 2](#)). Chronic FPIES usually presents in neonates (less than 4 months of age) who were fed with cow’s milk–based or soy–based formula from a young age.⁴ These patients usually develop a more progressive diarrhea with intermittent emesis over time.¹⁴ Poor weight gain and failure to thrive are common. However, patients can still present with ill appearance early in life, including lethargy, dehydration, metabolic acidosis, and methemoglobinemia.^{4,9,14} They can also have laboratory abnormalities such as anemia, hypoalbuminemia, and an elevated white blood count with left shift and eosinophilia.⁴ Despite their ill appearance, neonates or infants with chronic FPIES will improve once the offending food or foods are eliminated from the diet.

Diagnostic Criteria

International consensus guidelines outline that the diagnosis can often be made based on clinical history and noted improvement in symptoms once the suspected trigger or triggers have been removed from the diet, with an oral food challenge (OFC) as the gold standard for the confirmation of the diagnosis if there is uncertainty ([Table 3](#)). Given the relative rarity of the syndrome and lack of laboratory diagnostic tools for FPIES, it can be difficult to diagnose FPIES and can often be a diagnosis of exclusion. History taking should include a complete narrative of all possible reactions with a detailed record of symptoms, timing of symptoms in relation to food intake, a list of notably suspicious possible food triggers, and an indication of a pattern of reactions related to a specific food or foods.¹⁵ It is in very rare cases that invasive procedures

Table 3
Diagnostic criteria of food protein-induced enterocolitis syndrome

Reproducible Reactions to Suspected Foods Based on History or Oral Food Challenge	
Acute FPIES	Chronic FPIES
Major criteria: Vomiting in the 1- to 4-h period after ingestion of the suspected food without typical IgE-mediated skin or respiratory symptoms	• Intermittent but progressive vomiting and diarrhea ($\pm$ blood) • Poor weight gain/failure to thrive • Dehydration • Metabolic acidosis
Minor criteria:	• Resolution of symptoms within days after elimination of the offending food or foods and with recurrence of symptoms upon reintroduction • Requires confirmatory challenge
1. Episode(s) of repetitive vomiting after eating the same suspected food	
2. Repetitive vomiting episode 1 to 4 h after eating a different food	
3. Presentation of lethargy with any suspected reaction	
4. Presentation of pallor with any suspected reaction	
5. Presentation requiring an emergency room visit with any suspected reaction	
6. Presentation requiring fluid resuscitation with any suspected reaction	
7. Diarrhea presenting within 24 h of ingestion of suspected food (usually 5–10 h)	
8. Hypotension	
9. Hypothermia	
10. Increased neutrophil count of ≥ 1500 neutrophils above the baseline count	
The diagnosis of FPIES requires that a patient meets the major criterion and ≥ 3 minor criteria	

Adapted from NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126(6 Suppl):S1-58; with permission.

such gastrointestinal endoscopy is required.⁶ If performed, friable mucosa, rectal ulceration, and bleeding can be seen with biopsies showing villous atrophy, tissue edema, crypt abscesses, and increased inflammatory cells.⁴ There are no specific imaging studies for FPIES. It is important to continue to follow up with the patient at regular intervals and consider reintroduction or OFC to the causative food or foods to see if the allergy has resolved.⁶ Although skin prick testing and specific IgE testing are negative in this non-IgE-mediated food allergy, it may be helpful to obtain skin prick testing in infants and children with comorbid conditions, such as atopic dermatitis or other signs of atopy. Children with FPIES may have detectable levels of specific IgE to the triggering food at presentation or on follow-up assessment; in this case the patient is defined as having "atypical FPIES."¹⁵

Atopy patch testing has been evaluated for its ability to predict reactivity to a food in FPIES at baseline,¹⁶ with no value in predicting tolerance development in follow-up,^{16,17} but data are scarce and the test is not in clinical use. The International Consensus Guidelines recommend an OFC to confirm the diagnosis if the causative food is unclear, if the symptom time course is unusual, or if there is lack of symptom resolution with removal of the suspected food from the diet. For many years the Powell criteria were used to define a positive challenge (3 or more of the following): vomiting,

diarrhea, fecal blood (visible or occult), fecal leukocytes, fecal eosinophils, and a significant increase in the polymorphonuclear cell count greater than 3500 cells/mm³.¹⁸ The International Guidelines present revised diagnostic criteria to help interpret OFCs for patients with confirmed or possible FPIES (see [Table 3](#)). Major criterion for acute FPIES includes emesis within 1 to 4 hours after consumption of the food of concern without IgE-mediated respiratory or skin findings. Minor criteria include lethargy, pallor, diarrhea within 5 to 10 hours, low blood pressure, low body temperature, and an increase of ≥ 1500 neutrophils above the prechallenge count. If the major criterion and ≥ 2 of the minor criterion are met, the challenge is diagnostic of FPIES. Consideration must be given to therapies that may limit some of the signs and symptoms, like the use of ondansetron, and clinical judgment is needed in these circumstances. Outside of the research setting and in some centers, neutrophil counts may not be able to be performed promptly or the physician may choose not to pursue this.

For chronic FPIES, symptom resolution should occur within a few days of elimination of the food or foods of concern. If the suspected food is reintroduced to the diet, acute vomiting occurs within 1 to 4 hours after ingestion and diarrhea within 24 hours (more commonly between 5 and 10 hours, as above). The investigators point out the heterogeneity in presentation from milder forms, with intermittent emesis and/or diarrhea and typically poor weight gain, to severe forms, which also include metabolic acidosis, dehydration, and possibly bloody diarrhea.⁹

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of FPIES is broad, encompassing multiple gastrointestinal, metabolic, allergic, infectious, cardiovascular, and neurologic disorders.⁴ Fiocchi and colleagues⁵ explored the diagnosis most often offered in acute and chronic presentations of FPIES in the literature. In the acute form, in order of decreasing frequency, the diagnosis offered was sepsis, acute gastroenteritis with dehydration, necrotizing enterocolitis, pyloric stenosis, intussusception, allergic proctocolitis, anaphylaxis, volvulus, epilepsy, food poisoning, Munchausen syndrome, and neurologic causes of shock. In the chronic form, the diagnosis offered was eosinophilic esophagitis, eosinophilic enterocolitis, eosinophilic gastroenteritis, celiac disease, gastroesophageal reflux, food allergy, metabolic disorders, food intolerances, primary immunodeficiency, and alpha-1 antitrypsin deficiency.

FOOD TRIGGERS

The most common causal food internationally is cow's milk.^{8,11,19,20} Soy is the next most common causal food in the United States, but is not as common in other countries, where the most common foods vary relative to feeding practices and exposure. In Australia, rice was reported as the most common food trigger followed by soy and cow's milk.⁸ In the United States, the next most common foods after milk and soy are grains such as rice and oat, which are typically the first weaning foods, followed by eggs, meats/fish, vegetables, fruits, peanuts, and tree nuts.^{11,19} In Italy, fish was the second most common food reported.²⁰ FPIES to fish,²¹ shellfish,^{21,22} and mollusks has been described in adults.^{21,23}

Internationally, patients vary in the number of trigger foods. The retrospective study of 35 children with FPIES in Australia, 83% reacted to a single food and the remainder had reactions to 2 foods.⁸ In Italy, the retrospective study by Sopo and colleagues²⁰ found that 15% reacted to more than one food. In contrast, 2 studies in the United States showed a higher percentage of patients with FPIES reacting to more than

one food. Caubet and colleagues¹¹ found in a retrospective study of 160 subjects, that most patients (65%) reacted to one food, 26% reacted to 2 foods, and 9% had reactions to 3 or more foods. Diagnosis was based on OFC (30%) or typical symptoms following ingestions within the preceding 12 months (70%). In another retrospective US study of 462 patients, 70% of subjects reacted to 1 or 2 foods, and approximately 30% reacted to 3 or more individual foods as determined by reproducible history of prolonged vomiting that may or may not have been accompanied by diarrhea 2 to 6 hours after ingesting the implicated food.¹⁹

ACUTE MANAGEMENT

When a patient experiences an acute reaction, traditionally intravenous (IV) fluids (10–20 mL/kg boluses of normal saline) have been recommended. Oral rehydration can be considered for mild reactions.³ IV corticosteroid medications (methylprednisolone 1 mg/kg, up to 60–80 mg) have been recommended for more severe reactions. Chronic FPIES with dehydration and the most severe acute reactions may require vasopressors for hypotension not responsive to fluids, bicarbonate for acidemia, and methylene blue for methemoglobinemia. Recently, the use of ondansetron has been tried as well. Hollbrook and colleagues²⁴ report resolution of symptoms in an acute FPIES reaction during an OFC within 15 minutes of the administration of IV ondansetron in 5 children aged 3 to 12 years. They suggest the use of ondansetron for accidental ingestions and during OFCs. Subsequently, Miceli Sopo and colleagues²⁵ reported resolution of symptoms within 15 minutes with intramuscular (IM) ondansetron in 5 patients aged 12 months to 4 years. A retrospective, nonrandomized study of 66 children comparing the use of IV or IM ondansetron with traditional treatment showed a relative risk reduction of 0.2 favoring the ondansetron group, when comparing vomiting after the administration of therapy.²⁶ Of note, treatment was not successful in all cases, and they were unable to predict efficacy by timing of administration or patient factors. Leonard and Nowak-Wegrzyn²⁷ reports empiric use of oral ondansetron in at home reactions and cautions that medical evaluation should be sought as well.

DIETARY MANAGEMENT AND TREATMENT

Strict avoidance of the offending foods in all forms is the first line of treatment in managing FPIES. Some investigators have reported tolerance of the triggering food in baked goods in a few patients; however, this has not been found with all patients.²⁸ Furthermore, others have reported reacting to lower doses of the trigger food with subsequent exposures.^{29–31} In acute and chronic FPIES to cow's milk, a hypoallergenic formula is often used because U.S. studies have shown that 40% to 50% of these patients will react to soy as well.^{7,11,19} Studies from Israel,³ Australia,⁸ and Italy²⁰ have not found the same association between cow's milk and soy FPIES. In a population-based study designed to explore the prevalence and natural history of FPIES to cow's milk discussed earlier, no patient reacted to soy or other foods.³ The difference in reactivity may be a result of differences in genetics, feeding practices, exposure patterns, or patient selection/referral patterns.⁴ As such, one could consider soy as a cow's milk substitute if an OFC is performed (at home or in a supervised setting at the discretion of a physician) without an incident. An extensively hydrolyzed casein formula can be used as well.^{2,7} Approximately 20% of infants with cow's milk FPIES will not tolerate this and will need an amino acid formula.^{15,32,33}

It has been recognized that patients with cow's milk FPIES are also at greater risk of solid food FPIES. This number was higher with concomitant atopic dermatitis.³³

One-third of infants with cow's milk or soy FPIES developed FPIES to a solid food.³³ In more recent series, the rate of reaction to a solid food in milk and soy FPIES was about 25%.¹¹ In the study by Sicherer,³³ 32% of children with liquid FPIES also developed solid food FPIES. Interestingly, in another study, many of the patients with solid food FPIES were already found to be on an extensively hydrolyzed formula and reacted to a median of 4 (range 1–5) solid food proteins.⁷ However, although about one-third of children with cow's milk FPIES may react to solids, patients with solid food FPIES may not have as frequent reactions to liquids. A recent retrospective chart review of 39 patients diagnosed with FPIES found that most patients with oat FPIES tolerated cow's milk.³⁴ Ultimately, larger, multicenter studies will be needed to clarify the rate of multisensitization in FPIES using standard criteria.

The goal of dietary management is to avoid acute and chronic reactions, while using the least restrictive diet. For patients with early-onset FPIES, breastfeeding or an extensively hydrolyzed formula is recommended for this group in the first year of life.^{15,33} A small percentage of patients will require an amino acid formula.^{15,32,33} The consensus guidelines for FPIES suggest introducing complementary foods, when a child is developmentally ready at around 6 months of age. Consideration can be given to starting with lower-risk fruits and vegetables, followed by meats and cereals with each new food introduced over a period of 4 days.^{15,35} Tolerating one food from a group is thought to convey a favorable prognosis for the other foods in the group. To promote healthy dietary variety and unnecessary limitation, supervised challenges to one or mixed foods can be considered for patients that had severe cow's milk or soy FPIES. Accordingly, the International Guidelines¹⁵ for a 1-year-old with FPIES suggest considering a challenge to high-risk foods not already introduced, singly or together, depending on the level of concern for a reaction. Because children frequently have to avoid several food items or groups, consideration should be given to dietician involvement to make sure nutritional needs are met.³⁶

Breastfeeding is generally thought to be protective with respect to FPIES in that it is rare to see this entity in breastfed babies.^{7,12} A few cases of FPIES due to cow's milk or soy have been described while breastfeeding.^{29,30,37} In the very rare cases when patients experience a classic FPIES reaction when exposed to the allergic trigger protein in breast milk, maternal restriction is recommended. Although studies are lacking on the best approach, many practitioners would allow maternal consumption of the trigger food if this has been tolerated.^{4,29}

OFCs are used to confirm the diagnosis, assess for tolerance of foods within the same food group, and assess for resolution of FPIES.^{27,36} Timing of challenge has not been systematically examined, and physician discretion, the impact of food avoidance, as well as family preference should also play a role in the decision of when to proceed with a challenge.¹⁴ Sicherer³³ recommends considering a food challenge 12 to 18 months after the previous symptomatic ingestion in a facility with the ability to rapidly replace fluid loss. Significant dehydration due to recurrent emesis is seen in approximately half of reactive challenges,⁴ and hypotension is seen in about 15%.¹¹ For FPIES, consideration should be given to placing an IV line before the challenge given the risk for dehydration and hypotension especially if they have experienced previous severe reactions or might have difficult IV access.¹⁵ After careful discussion with the family regarding the risk of a reaction, need of IV access, distance from care, previous reaction severity, and the trigger food, some practitioners may elect to allow home introduction.¹⁵ Many protocols exist for performing OFCs for FPIES in the literature. Historically, 0.6 g of protein per kilogram of body weight was used to calculate dosing. Subsequently, it was recommended to use 0.15 to 0.3 g of protein per kilogram of body weight or less if the child has had a severe reaction

or reacted with ingestion of a small amount of the food protein.^{2,7,33} The doses are calculated based on the protein content of the food, and they recommend that the protein content of the challenge dose does not exceed 3 g protein or total food weight of 10 g. Three equal doses are administered over 30 to 45 minutes, and the patient is observed for 4 to 6 hours.^{2,7,33,38}

Overall, it is difficult to predict the severity of a reaction. In one study, rice FPIES was associated with more severe reactions than milk and soy.^{8,39} Nowak-Węgrzyn and colleagues⁷ compared patients with milk or soy FPIES with patients with solid food FPIES and found a trend toward more severe reactions in solid food FPIES; however, this was not statistically significant ($P = .2$).⁷ Most of the 462 patients in the study by Ruffner and colleagues¹⁹ had a relatively mild phenotype, and only 5% presented with pallor, hypotension, or cyanosis.¹⁹ In the study by Katz and colleagues,³ 44 patients were diagnosed with milk FPIES, and details of physician-supervised OFCs were provided for 24 symptomatic patients all of whom were successfully treated with oral rehydration, suggesting milder presentation.

NATURAL HISTORY

Time to resolution of FPIES varies according to the food, area of the world, the presence of IgE, atopic dermatitis, methodological/protocol differences, referral patterns, and type of center the data comes from.^{4,8,33} Time to resolution for cow's milk FPIES has ranged from 10 months in 90% of the patients in Korea to 3 years in 90% of patients in Israel, and to 5 years in 85% of patients in the United States {3, 13, 19, }. For soy, the earliest age resolution was similarly seen in Korea with resolution at 10 months of age in 90% of patients and the latest age of resolution in a US tertiary referral center at 6 to 7 years{13,11}. The early rate of resolution of cow's milk and soy FPIES in Korea may be explained by the earlier age at performance of food challenges. They were performing OFCs 6 months after their diagnosis and every 2 months after that, which is more frequent than practices reported elsewhere.¹³

Regarding solid food FPIES, resolution of rice FPIES occurred by 3 years in 80% in the study by Mehr⁸ from Australia but only in 40% in the study by Caubet and colleagues¹¹ from the United States. In the United States, resolution for vegetables and oat occurs by 3 years in two-thirds of patients.⁷ However, in a subsequent US report, resolution in grain FPIES was seen only by 5 years in two-thirds of the patients. In this report, an average age to tolerance with oat was 4 years and rice 4.7 years.¹⁹ Jarvinen and Nowak-Węgrzyn⁴ caution that for foods that were easy to avoid and not considered essential to the diet, challenges were often deferred perhaps making age of resolution appear later. Meat FPIES resolved in 50% of patients in 5 years, but no cases of fish FPIES resolved in that same time period in the U.S. study.

Those patients with concomitant IgE sensitization (ie, "atypical" FPIES) remained symptomatic to the trigger food until a later age.² Of patients with persistent milk FPIES at age 3 years, 46% had detectable IgE to milk, whereas those who experienced resolution did not.¹¹ Conversely, one-fourth of FPIES patients had a positive food-specific IgE, mostly milk or soy, and one-third of these patients progressed to immediate symptoms with milk. Onesimo and colleagues⁴⁰ described children with cow's milk FPIES and specific IgE to milk who developed IgE-mediated symptoms on subsequent exposure. As a result, it is prudent to check specific IgE before challenge, particularly to milk. If IgE is detectable, the challenge should be modified to follow suggested protocols for an IgE-mediated allergy and treatment of anaphylaxis should be available.

SUMMARY AND FUTURE CONSIDERATIONS

Dietary education and avoidance of the trigger foods are the first-line treatment. Assessment with respect to growth is prudent. Consultation with a dietician to further assess nutritional adequacy can be helpful if the child is avoiding multiple foods or common ingredients.^{36,41} Direction on emergency management should be provided to patients including a letter describing the syndrome and treatment to the emergency personnel.^{15,33} As addressed previously, fluid resuscitation, corticosteroid medications, and possibly ondansetron can be used in FPIES. Unless a patient has atypical FPIES with the presence of specific IgE, epinephrine and antihistamines typically do not have a role in FPIES management.

The diagnosis of FPIES is based on clinical criteria. In the future, validation of these clinical criteria is needed. Ideally, a diagnostic test would be developed to help with the diagnosis,^{15,42} and further studies addressing the pathophysiology of this syndrome are needed.⁴² The optimum frequency and protocols for OFCs need to be determined.^{15,42} More epidemiologic studies are needed to help with the prevalence, risk factors, natural history, and the impact of the disease.^{39,42} Further studies are also needed on how strict dietary avoidance needs to be such as whether baked foods need to be avoided and in which patients. Until then, a high clinical suspicion is needed not to miss the diagnosis of FPIES, and a thoughtful approach to OFCs and follow-up is needed to avoid unnecessary food avoidance.

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