

Manifestations, Diagnosis, and Management of Food Protein-Induced Enterocolitis Syndrome

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Abstract

Food protein-induced enterocolitis syndrome (FPIES) is an under-recognized non-immunoglobulin E (IgE)-mediated gastrointestinal food allergy affecting primarily infants and toddlers. An abnormal response to food antigen resulting in local inflammation is thought to lead to increased intestinal permeability and fluid shift. The primary features of acute FPIES are repetitive, projectile vomiting, lethargy, pallor, diarrhea, and dehydration. Chronic FPIES is typically seen in young infants with continued exposure to cow's milk or soy-based formula. Biomarkers are lacking and patients may undergo extensive workups for their symptoms, which often leads to a delay in diagnosis and puts infants at risk for feeding difficulties, nutritional deficiencies, and failure to thrive. This review will provide a guide in how to recognize the clinical features of and manage FPIES.

CME EDUCATIONAL OBJECTIVES

1. Recognize manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome (FPIES) in an outpatient setting.
2. Assess nutritional needs and provide anticipatory guidance for dietary management.
3. Recognize the indications of when to refer for assessment of resolution of FPIES using physician-supervised food challenges.

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Food protein-induced enterocolitis syndrome (FPIES) is an under-recognized non-immunoglobulin E (IgE)-mediated gastrointestinal food allergy affecting primarily infants and toddlers. An abnormal response to food antigen resulting in local inflammation is thought to lead to increased intestinal permeability and fluid shift. The primary features of acute FPIES are now recognized and include repetitive projectile vomiting, lethargy, pallor, dehydration, and diarrhea. Chronic FPIES features include intermittent emesis, diarrhea, and poor weight gain or weight loss typically in young infants fed with cow's milk (CM) or soy-based formula (see Table).

Biomarkers are lacking and patients may undergo extensive workups for their symptoms, which often leads to a delay in diagnosis and puts infants at risk for feeding difficulties, nutritional deficiencies, and failure to thrive. This review will provide a guide in how to recognize the clinical features of and manage FPIES.

EPIDEMIOLOGY OF FPIES

Prevalence data for FPIES are limited. One population-based birth cohort in Israel reported a 0.34% prevalence of CM FPIES in the first year of life, compared with 0.5% CM allergy in the same population.¹ This is closer to the rate of IgE-mediated allergy than previously expected. Two retrospective cohorts suggest that the incidence of FPIES is increasing, although an increase of awareness cannot be ruled out.^{2,3} Additional population studies on the prevalence of FPIES are needed.

The mean age of FPIES' initial presentation was 5.5 and 5.7 months in two retrospective cohorts.^{2,3}

CM or soy FPIES may present in the first few weeks of life with the introduction of formula. This may be delayed in breast-fed infants if formula supplementation is introduced later. Solid food FPIES generally appears when solids

TABLE. Clinical Presentation of Acute and Chronic FPIES	
Acute FPIES Food ingested intermittently	Chronic FPIES Food ingested on a daily basis (eg, cow's milk or soy infant formula)
Vomiting (onset 1 to 3 hours)	Intermittent vomiting
Lethargy	Diarrhea
Pallor	Lethargy
Dehydration	Weight loss
Diarrhea (onset 5 to 8 hours)	Failure to thrive
Bloody diarrhea	Bloody diarrhea
Abdominal distention	Abdominal distention
Hypotension	Dehydration
Hypothermia	

FPIES = food protein-induced enterocolitis syndrome.

are first introduced beginning at 4 to 6 months of age. For example, in a tertiary care center cohort, the median age of CM and soy FPIES diagnosis was 1 month (range, 2 days to 12 months), and the median age of solid food FPIES diagnosis was 5.5 months (range, 3 to 7 months).⁴ FPIES may develop upon first exposure to the causative food, but is often reported to occur after several exposures.¹ While classic FPIES presents in infancy, cases of FPIES in older children and adults have been reported.⁵

There appears to be a slight male predilection (52% to 61%) in FPIES.¹⁻⁴ Family history of atopy (20% to 80%) and personal history of atopy (about 30%) is associated with FPIES.^{2,3,6} There is one case report of fraternal twins with soy FPIES and another case report of identical twins with symptoms consistent with CM FPIES; otherwise a family history of FPIES is not common.^{4,7}

CLINICAL PRESENTATION

Acute FPIES

FPIES is most clearly diagnosed when patients present acutely, when the food is ingested on an intermittent basis, or when the food is reintroduced following a period of avoidance. The differ-

ential diagnosis of FPIES can be found in the Sidebar. Symptoms of a typical acute FPIES reaction include delayed, repetitive vomiting (2 to 4 hours after ingestion), lethargy, pallor, diarrhea in a subset (about 5 hours after ingestion), and dehydration after ingestion of the offending food.⁸

Projectile, repetitive vomiting defines acute FPIES and is present in virtually all reported cases in the literature.^{1-4,9,10} These patients often present to the emergency department and may initially be diagnosed with an acute gastrointestinal illness (AGE). Key absent factors from the history will be a viral prodrome, fever and sick contacts, and the patient will usually return to baseline more quickly than expected with AGE. Parents may mention that a particular food was introduced for the first time or one of the first few times hours prior to development of symptoms.

More severe forms of acute FPIES that present with severe and protracted vomiting, severe lethargy or unresponsiveness, dehydration requiring intravenous fluid resuscitation, hypotension, and abdominal distention may lead to a workup for sepsis or gastrointestinal obstruction. In the most extreme cases,

exploratory laparotomy has been performed to rule out ileus.¹¹

In one cohort, 24% of FPIES episodes ($n = 66$) presented with hypothermia ($< 36^{\circ}\text{C}$).² Lymphocytosis with a left shift is frequently observed in acute FPIES and may lead to a presumed infectious diagnosis. Neutrophilia (> 3500 cell/mL) typically peaks at 6 hours after ingestion, as determined by oral food challenges.¹² Other laboratory findings may include thrombocytosis ($> 500 \times 10^9/\text{L}$) and metabolic acidosis.^{2,13} In one study, methemoglobinemia requiring methylene blue and bicarbonate treatment was reported in one-third of severe FPIES reactions with acidemia.¹⁴ Stools studies may reveal occult or frank blood, leukocytes, eosinophils, and/or increased carbohydrate content.

Unfortunately, it may be only after repeated reactions that a pattern is identified and a possible food allergy implicated. Three studies found that a range of one to five reactions occurred before FPIES was diagnosed, while one recent retrospective study reported a range of one to 10 reactions occurred prior to diagnosis.²⁻⁴ Sopo et al³ reported a mean delay in diagnosis of about 8.5 months. Awareness of FPIES in emergency medicine is increasing and a recent article recommended including a diet history in evaluation of children presenting to the emergency department with gastrointestinal symptoms and hypotension.¹⁵

Chronic FPIES

Symptoms of chronic FPIES include intermittent vomiting, chronic watery diarrhea with blood or mucous, weight loss, feeding difficulties, and failure to thrive. Chronic FPIES tends to be a diagnosis of exclusion or is diagnosed in retrospect when symptoms are relieved after avoidance of the offending food and return acutely when the food is reintroduced. Laboratory findings may include anemia, hypoproteinemia, elevated white blood cell count with a left

shift, and eosinophilia. Stools studies may reveal occult or frank blood, leukocytes, and stool reducing substances. Abdominal films may reveal distended bowel loops, intramural gas, and air-fluid levels.^{16,17} These findings may lead to a presumed diagnosis of abdominal obstruction or even necrotizing enterocolitis in young infants.

Acute versus Chronic

Patients presenting with acute FPIES are normal in between exposures. Once a reaction has resolved, typically within hours, the patient returns to baseline. It is in cases of continued exposure (eg, CM or soy formula) that chronic FPIES may develop. Symptoms of chronic FPIES usually improves within 3 to 10 days of removing the offending food. Chronic issues such as feeding difficulties or food refusal may develop in patients who have experienced chronic FPIES or multiple episodes of acute FPIES.

COMMON FOOD TRIGGERS

The three most common foods that cause FPIES are CM, soy, and rice. Other common foods include grains (oat, barley, wheat), orange vegetables (sweet potato, squash, carrot), egg white, legumes (peanut, green pea, string bean, lentil), chicken/turkey, fish, and banana.^{2-4,10,15,18} There are also case reports of FPIES to corn, lamb, rabbit meat, tomato, goat's milk, fruit protein, and white potato.^{2,19-22} FPIES in older children and adults have been reported with symptoms of abdominal pain, nausea, intense cramping, vomiting and diarrhea, typically to shellfish or mollusks such as scallops.^{5,23,24}

CM and Soy FPIES

It is common for patients to experience FPIES symptoms to more than one food; the proportion of which depends on the population studied. Three tertiary care centers reported 30% to 60% of patients with CM or soy FPIES reacted to

SIDEBAR.

Differential Diagnosis of FPIES

- Food-specific allergic disorders
 - Food protein-induced enteropathy
 - Food protein-induced proctocolitis
 - Eosinophilic esophagitis/gastroenteritis
 - Anaphylaxis
- Infectious
 - Gastrointestinal infection
 - Sepsis
- Gastrointestinal
 - Necrotizing enterocolitis
 - Intussusception
 - Volvulus
 - Pyloric stenosis
 - Hirschsprung's disease
 - Inflammatory bowel disease
 - Severe gastroesophageal reflux disease
 - Anal fissure
- Other
 - Food poisoning
 - Metabolic disorder
 - Hemolytic uremic syndrome

FPIES = food protein-induced enterocolitis syndrome.

both, while none of the 44 infants identified in the birth cohort with CM FPIES were reported to have concomitant soy FPIES.^{1,4,10,25}

This may highlight the potential difference between a more severe phenotype that is more likely to be referred to a tertiary center versus a milder phenotype more likely observed in a large, unselected population. Two retrospective studies using a tertiary center cohort and a multicenter cohort with a 60% self-referral population, reported no concomitant CM and soy FPIES in 19 and 47 infants, respectively.^{2,3} It appears that most infants were not offered a soy alternative in the Mehr et al cohort, while this was not addressed in the Sopo et al cohort.³ However, in a prospective study of challenge proven-FPIES in infants at a mean age 5.1 ± 1.7 months, 50% reacted to

both CM and soy, highlighting the high potential for coexistent reaction to both foods in young infants.²⁶

Solid Food FPIES

Regarding solid food FPIES, one review noted that as many as one in three infants with CM or soy FPIES develops solid food FPIES.²⁷ About 50% of infants with rice, oat, or barley FPIES in a US cohort experienced symptoms with other grains, whereas only one of 14 infants with rice FPIES in an Australian cohort experienced oat FPIES.^{2,4} This may represent differences in food introduction practices.

It is noted in several cohorts that it is not uncommon for infants with solid food FPIES to react to multiple foods. For example, in a US cohort, 80% of infants with solid food FPIES reacted to more than one food and 65% were previously diagnosed with CM or soy FPIES; in the retrospective Australian cohort, 17% (6 of 35) of infants with solid food FPIES reacted to more than one food; and in the retrospective Italian cohort 15% (10 of 66) of infants with solid food FPIES reacted more than one food.^{2,4} Data seem to indicate that infants with solid food FPIES present with more severe symptoms, are more likely to require fluid resuscitation and have a longer delay in diagnosis.^{4,28} This may be related to the perception of certain foods (eg, rice, oat or vegetables) as hypoallergenic foods.

DIAGNOSTIC TESTING

Skin testing and food-specific serum IgE levels are typically negative at diagnosis in FPIES (> 90%). However, up to 25% of children initially had or later developed detectable food-specific IgE levels or positive skin prick tests; they tended to have a more protracted course.^{1,4,9} These patients may also be at risk for acute immediate-type allergic reactions, including urticaria, angioedema, and/or upper and lower airway

symptoms. For this reason, IgE testing is recommended at diagnosis and/or prior to re-introduction of foods.

Attempts have been made to identify diagnostic tools that may help in diagnosis of FPIES. Atopy patch testing predicted 28 of 33 positive oral food challenges in one FPIES study.¹⁰ However, these findings have not been confirmed by another group.^{29,30} One study in infants with chronic gastrointestinal symptoms identified hypoalbuminemia and poor weight gain (< 10 g/day) as independent predictors of CM FPIES.¹³

The same group performed gastric juice analysis in one study of infants with suspected CM FPIES via orogastric feeding tube prior to and 3 hours after an oral food challenge. Elevated gastric leukocyte counts of greater than 10 per high-power field 3 hours after challenge correlated with 15 of 16 positive challenges, and was not elevated in eight negative control challenges.³¹ Gastric juice analysis may not be a practical laboratory test in every setting, and these results need additional validation.

At present, FPIES is a clinical diagnosis. Proposed clinical criteria include: 1) age at initial diagnosis younger than 9 months; 2) repeated exposure to causative food elicits gastrointestinal symptoms without alternate cause; 3) an absence of symptoms consistent with IgE-mediated reaction; 4) removal of causative food results in resolution of symptoms; and 5) re-exposure or oral food challenge elicits typical symptoms within 4 hours.^{9,32}

MANAGEMENT

Treatment of Acute Reactions

Treatment of acute FPIES reactions is primarily supportive. Oral rehydration can be attempted if the reaction is mild; intravenous fluids if dehydration is moderate to severe. Vasopressors should be used for hypotension if severe or unresponsive to fluids. Intravenous steroids (eg methylprednisolone 1 mg/kg, max

60 mg to 80 mg) are suggested in moderate to severe reactions, although there are no studies looking at the effectiveness of corticosteroids in the recovery from an FPIES reaction. Bicarbonate may be used to correct for acidemia, and methylene blue is used to treat methemoglobinemia.

Food Avoidance

The mainstay of management of FPIES is avoidance of the offending food. Breast-feeding is considered protective; however, there are two case reports of an acute FPIES reaction in breastfeeding infants after maternal ingestion of the offending food.^{33,34} Generally, it is not recommended that causative foods be removed from the maternal diet unless an FPIES reaction occurs. In formula-fed infants with CM FPIES, a casein hydrolysate formula is recommended as a substitution, instead of a soy formula, since many infants with CM FPIES may also react to soy. Up to 20% of FPIES cases may require elemental formula.^{35,36}

Due to the risk of multiple food FPIES, avoiding foods in the same category or that often occur together may be warranted. For example, if a patient with CM FPIES is not already tolerating soy, consider delaying soy introduction. If a patient with rice FPIES is not already tolerating other grains, consider delaying oat and wheat introduction. It is important, however, to begin introducing solids at the appropriate developmental age to avoid feeding difficulties or nutritional issues. In infants with multiple food FPIES, a hypoallergenic semi-solid food, for example Neocate Nutra, may be an initial alternative to pureed foods so that feeding development may continue while the patient is being evaluated. Children diagnosed with FPIES who display feeding difficulties and food refusal may require referral to occupational therapy for feeding therapy with safe foods.

PROGNOSIS

Most cases of FPIES diagnosed in infancy resolve by school age. However, in one cohort, two patients continued to demonstrate reactivity upon challenge; one to CM and soy at age 11.5 years, and the other to CM at age 15 years, which he outgrew at age 21 years, but also to soy at age 21 years.⁴

The age of resolution appears to depend on the population studied and the food implicated. CM-FPIES was reported to resolve in 60% by age 3 years in a US cohort, 90% by age 3 years in an Israeli cohort, and 64% by age 10 months in a Korean cohort.^{1,4,37} Soy FPIES was reported to resolve 27% in a US cohort and 83% in an Australian cohort by age 3 years.^{2,4} Rice FPIES was reported to resolve in 40% of a US cohort and 80% in an Australian cohort by age 3 years.^{2,4} These differences may represent variation in referral populations, how closely patients are followed and challenged, or the existence of different phenotypes.

Reintroduction of Foods

Follow-up is recommended to determine the appropriate time to reintroduce foods. Causative foods should be reintroduced under physician supervision. It is recommended that at least 12 to 18 months pass since the last reaction before an oral food challenge is undertaken. Children with a history of severe FPIES reaction should have intravenous access in place and fluid resuscitation available for the challenge. At one tertiary care center, 75% of infants appeared acutely ill and 15% developed hypotension requiring hospitalization.^{6,9}

Conversely, several studies have reported successful oral rehydration with mild reactions.^{1,3}

Those patients with positive skin testing or detectable food-specific IgE levels must also have medications and equipment available to respond to an acute allergic reaction or anaphylaxis. Antihistamine and injectable epinephrine should

also be available for food challenges in patients with detectable food-specific IgE levels or positive skin testing.

CONCLUSION

FPIES is a clinical disorder consisting of gastrointestinal symptoms and a systemic inflammatory response to food antigen that is under-recognized, often leading to a delay in diagnosis. It is important for primary care providers and emergency room physicians to keep FPIES in the differential when infants present with recurrent episodes of vomiting and diarrhea or failure to thrive. More research is needed on the prevalence and pathophysiology of FPIES. Differences in severity and age at resolution between cohorts in different populations in different countries may indicate the existence of different phenotypes of FPIES. It is recommended that patients with FPIES be closely followed and that food is reintroduced under physician supervision. ■

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