Food protein–induced enterocolitis syndrome

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ABSTRACT

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that primarily affects the gastrointestinal tract. The underlying pathophysiology of FPIES has yet to be fully elucidated; however, FPIES is believed to be secondary to intestinal inflammation after exposure to a food antigen, which thereby leads to increased permeability and fluid shifting into the intestinal lumen. FPIES is categorized into acute and chronic forms. Acute FPIES is characterized by repetitive vomiting that occurs 1–4 hours after food ingestion. Severe vomiting may progress to dehydration, lethargy, and pallor, which potentially leads to hypovolemic shock. In some patients, diarrhea may present within 24-hours of food ingestion. Patients are clinically well between acute episodes. Chronic FPIES presents with intermittent vomiting and/or diarrhea, followed by failure to thrive. FPIES characteristically presents in infancy, with resolution of the disease typically occurring by school age. However, analysis of recent data indicates that FPIES may persist into adulthood. In addition, late- or adult-onset FPIES has also been reported. The diagnosis of FPIES is based on clinical history; however, oral food challenge currently remains the criterion standard for diagnosis. Management of FPIES requires strict avoidance of food triggers, and treatment requires rapid fluid rehydration. Currently, there are no reliable biomarkers to diagnose FPIES; however, investigations to better understand the role of the innate immune system have been promising. Future studies are needed to better understand the true prevalence and pathophysiology of FPIES.

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Food protein-induced enterocolitis syndrome (FPIES) is a non–immunoglobulin E (IgE) mediated food allergy that presents with delayed onset of gastrointestinal symptoms in infants and young children, and, less commonly, in adults. The lack of disease-specific diagnostic tests and reliable biomarkers makes the diagnosis challenging. In addition, symptoms associated with FPIES can be observed in other conditions, which thus makes the diagnosis even more challenging. The first FPIES guideline[1] was published in 2017 and has provided clinicians a comprehensive overview on the diagnosis and management of FPIES. This review summarizes the clinical presentation, epidemiology, diagnosis, triggers, pathophysiology, management, and prognosis of FPIES.

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CLINICAL PRESENTATION

FPIES typically presents in infants and young children. However, disease onset has also been reported to occur later in life. In the 2017 guidelines, defining features for clinical FPIES phenotypes were proposed and include the following categories: age of onset, severity of symptoms, timing and duration of symptoms, and the presence of food-specific IgE.[1] The age of presentation includes "early" (<9 months old) and "late" (>9 months old) FPIES (https://www.cdc.gov/nchs/icd/icd10cm.htm). The severity of disease is divided into "mild-to-moderate" (repetitive vomiting with or without diarrhea, pallor, mild lethargy) and "severe" (repetitive projectile vomiting with or without diarrhea, pallor, lethargy, dehydration, hypotension, shock, methemoglobinemia, metabolic acidosis). The timing and duration of symptoms are categorized into "acute" or "chronic." "Acute" symptoms are defined as vomiting within 1–4 hours of intermittent food exposure, followed by lethargy and pallor. Watery and/or bloody diarrhea could present within 5–10 hours. Symptoms resolve within 24 hours of food elimination.

In between "acute" episodes, patients are well and have normal growth. In contrast, "chronic" symptoms present with intermittent vomiting, chronic diarrhea, and failure to thrive after daily ingestion of the food trigger (*e.g.*, cow's milk or soy formula) and is commonly seen in young infants < 4–6 months of

Table 1 **Diagnostic criteria for patients presenting with possible FPIES: Acute FPIES**

	Major Criterion[1]	Minor Criteria (≥3)
Diagnosis Criteria*:	Vomiting 1–4 hr after ingestion of food	≥2 Episodes of vomiting after eating the same food
	(absence of IgE-mediated allergic skin or respiratory symptoms)	Repetitive vomiting 1–4 hr after eating a different food
		Lethargy
1 Major AND		Pallor
≥3 Minor criteria		Emergency department visit
		Need for intravenous fluid support
		Diarrhea in 24 hr (usually 5–10 hr)
		Hypotension
		Hypothermia

FPIES = Food protein–induced enterocolitis syndrome; IgE = immunoglobulin E.
**Adapted with permission from Ref. 1.*

age. Symptoms resolve within 3–10 days after elimination of the food trigger. However, after a period of elimination, the reintroduction of food can lead to "acute" symptoms. Finally, FPIES is subcategorized by the absence (classical FPIES) or presence (atypical FPIES) of food specific IgE. Twenty-five percent of patients with atypical FPIES can develop classic IgE–mediated food allergy to their FPIES food trigger after a period of avoidance.[2] In addition, patients with comorbid IgE sensitization are likely to have a slower resolution of FPIES. FPIES from exclusive breast-feeding is rare. However, a few cases of acute and chronic FPIES in exclusively breast-fed infants have been reported when the offending food was in the mother's diet.[3,4]

EPIDEMIOLOGY

Since the implementation of the *International Classification of Diseases, Tenth Revision* code for FPIES in 2015, the region-specific incidence and estimated prevalence rates have been reported throughout the world. The incidence of infant FPIES in Israel and Spain was estimated to be between 0.34% and 0.7%,[5,6] whereas, in Australia, the cumulative incidence of infant FPIES was ~0.015%.[7] More recently, a U.S. population–based survey reported the estimated prevalence of FPIES to be 0.51% in children and 0.22% in adults.[8]

DIAGNOSIS

The diagnosis of FPIES relies on a clinical history with characteristic symptoms from the common food triggers. The diagnosis can be difficult to make because symptoms mimic other disease states. Currently, there are no diagnostic tests to confirm whether a patient has FPIES; however, oral food challenge (OFC) is considered when the diagnosis is in question.[1] The 2017 FPIES guidelines[1] provides diagnostic criteria to help standardize the diagnosis of a patient who presents with possible acute or chronic FPIES (Tables 1 and 2). To diagnose acute FPIES, patients would require one major and three or more minor criteria. The major criterion includes vomiting 1–4 hours after ingestion of the suspected food and absence of IgE-mediated skin and respiratory symptoms. The minor criteria include the following: two or more episodes of repetitive vomiting after eating the suspected food, repetitive vomiting 1–4 hours after eating a different food, extreme lethargy, pallor, need for emergency department visit after a reaction, requirement of intravenous fluids, diarrhea within 24 hours, hypotension, or hypothermia.

The diagnosis of chronic FPIES is based on the presentation with symptoms over several days or weeks. In a "severe presentation" of chronic FPIES, regular ingestion of the food is followed by intermittent but progressive vomiting and diarrhea, which may lead to dehydration and metabolic acidosis. In a "milder presentation" of chronic FPIES, patients consume lower doses of the food and experience symptoms of intermittent vomiting and/or diarrhea and failure to thrive but do not develop dehydration or metabolic acidosis.[1] Regardless of the presentation type, patients with chronic FPIES must show resolution of the symptoms within days or weeks of removing the food trigger but will experience acute FPIES reactions after reintroduction of the food.

In cases of suspected FPIES, clinicians should consider ruling out other diagnoses. For example, infectious gastroenteritis, sepsis, anatomic gastrointestinal obstruction, necrotizing enterocolitis, or anaphylaxis should be ruled out when acute FPIES is suspected.

Table 2 **Diagnostic criteria for patients presenting with possible FPIES: Chronic FPIES**

Milder	Intermittent vomiting and/or diarrhea occurs with regular ingestion of the food trigger; the patient presents with poor weight gain and/or failure to thrive, without dehydration or metabolic acidosis
Severe	Intermittent vomiting and diarrhea (with or without blood) occurs with regular ingestion of the food; the patient may also present with poor weight gain and/or failure to thrive; the patient may develop dehydration and metabolic acidosis
Important Criterion	The resolution of symptoms can occur within days to weeks of discontinuing the food trigger(s); reintroduction of the food trigger(s) will lead to acute symptoms (vomiting in 1–4 hr, diarrhea within 24 hr); the diagnosis of chronic FPIES is confirmed by food challenge

FPIES = Food protein–induced enterocolitis syndrome.
**Adapted with permission from Ref. 1.*

In addition, eosinophilic gastrointestinal disorders, gastrointestinal reflux disease, early onset inflammatory bowel disease, inborn errors of metabolism, lactose intolerance, immune enteropathies or primary immunodeficiency and/or dysregulation, Hirschsprung disease, or alpha-1-antitrypsin deficiency should be ruled out when chronic FPIES is suspected.[1]

TRIGGERS

Food triggers can vary by age and phenotype of the disease. For an acute FPIES reaction in infants and young children, the common triggers have been reported to include rice, oats, cow's milk, or soy.[1] In addition, egg, fruits, vegetables, poultry, and seafood have also been reported as triggers. Theoretically, any food can be a trigger for FPIES, and this is likely reflective of dietary preferences and cultural practices.[9–11] Geographic differences in triggers have been observed. For example, rice is a common trigger for solid-food FPIES, but this is not seen in Italy.[12] In Italy and Spain, fish is a common FPIES trigger but is less common in other parts of the world.[12,13] As for chronic FPIES, the most common triggers include cow's milk and soy.[1] In addition, common FPIES triggers in older children and adults include fish and shellfish.[14–16] Approximately 60% of infants with FPIES react to a single food, 33% react to two to three foods, and ~10% react to multiple foods.[9]

PATHOPHYSIOLOGY

FPIES is a non–IgE-mediated food allergy. The pathophysiology of FPIES has not been fully elucidated. However, FPIES is believed to be secondary to intestinal inflammation after food antigen exposure and T-cell activation, which thereby leads to increased permeability of the gut and fluid shifting into the intestinal lumen.[1] Neutrophilia has also been observed after cases of patients with acute FPIES, which makes up one of the minor diagnostic criteria for a positive FPIES OFC.[1] The mechanism that underlies FPIES has been suggested to be T-cell mediated, with a T-helper type 2 biased proinflammatory cytokine profile, including increased tumor necrosis factor α, interleukin (IL) 5, IL-9, and IL-13 after an acute reaction.[17,18]

A study by Goswami *et al.*[19] demonstrated that patients with resolved FPIES, as confirmed by supervised OFC, had significantly reduced $CD154^+/CD4^+$ T-cell activation after antigen-specific stimulation compared with patients with active FPIES. Although reduced, the $CD4^+$ T-cell numbers were within a normal range for patients with resolved FPIES and those with active FPIES.[19] When comparing allergen-specific $CD154^+/CD4^+$ T cells in patients with active FPIES with healthy controls, no differences were observed.[19] Unlike patients who had outgrown their FPIES, patients with active FPIES and who had reacted on their food challenge exhibited significant systemic activation of innate immune cells, including monocytes, neutrophils, natural killer cells, and eosinophils, which was not observed in the subjects who had outgrown FPIES.[19]

A recent study by Mehr *et al.*[20] examined blood before and immediately after a food challenge reaction or at the end of a nonreactive challenge from subjects with FPIES. When using transcriptional immune profiling of blood, the investigators used gene co-expression network analysis and identified genes associated with innate immune activation in patients with FPIES and who had a positive reaction on food challenge.[20] Their findings supported that FPIES reactions are a result of innate immune activation.[20] In addition, studies are needed to further investigate the role of the innate immune mechanisms observed during an FPIES reaction.

TREATMENT OF REACTIONS

The management of an FPIES reaction includes early recognition and treatment based on presenting symptoms. FPIES reactions can be categorized as mild, moderate, or severe (Table 3). Mild symptoms include one or two episodes of vomiting and no lethargy. Moderate symptoms are defined by more than three episodes of vomiting and mild lethargy, whereas severe symptoms include more than three episodes of vomiting, with severe lethargy, hypotonia, and change in color.[1] First-line treatment for an

Table 3 **Management of acute FPIES episode at a medical facility**

	Mild	Moderate	Severe
Symptoms	1–2 Episodes of vomiting and no lethargy	≥3 Episodes of vomiting and mild lethargy	≥3 Episodes of vomiting and severe lethargy, hypotonia, ashen, or cyanotic
Management	1. Attempt oral hydration (*e.g.*, breast-feeding or clear fluids)	1. ≥6 mo: give ondansetron intramuscular (0.15 mg/kg/dose; maximum, 16 mg/dose)	1. Place a peripheral intravenous line and give normal saline solution bolus (20 mL/kg), repeat as necessary
	2. ≥6 mo: consider ondansetron intramuscular (0.15 mg/kg/dose; maximum 16 mg/dose)	2. Consider a peripheral intravenous line for a normal saline solution bolus (20 mL/kg), repeat as necessary	2. ≥6 mo: give intravenous or intramuscular ondansetron (0.15 mg/kg/dose; maximum, 16 mg/dose)
	3. Monitor for resolution; 4–6 hr from onset of symptoms	3. For persistent or severe hypotension, shock, extreme lethargy or respiratory distress, transfer to the emergency department or intensive care unit	3. Consider giving intravenous methylprednisone (1 mg/kg/dose; maximum 60–80 mg/dose)
		4. Monitor vitals	4. Monitor and correct acid base and electrolyte abnormalities
		5. Monitor for resolution at least 4–6 hr from the onset of symptoms	5. Correct methemoglobinemia if present
		6. Discharge home if stable and tolerating clear liquids	6. Monitor vitals
			7. Discharge home, 4–6 hr from onset of symptoms, once at baseline and when tolerating clear liquids
			8. Transfer to emergency department or intensive care unit for persistent or severe hypotension, shock, severe lethargy, respiratory distress

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acute reaction includes oral or intravenous fluid rehydration. Oral hydration is attempted in patients with mild symptoms, whereas boluses of intravenous normal saline solution are administered in patients with moderate-to-severe FPIES.[1]

In addition, ondansetron (0.15 mg/kg; maximum 16 mg/dose) can be given in patients > 6 months of age and with moderate-to-severe reactions. Ondansetron should not be given in infants < 6 months due to the lack of safety data. Caution should be taken when using ondansetron in patients with heart arrhythmias, given the risk of QT prolongation. Vital signs should be closely monitored during the treatment period. The administration of intravenous methylprednisone (1 mg/kg; maximum, 80 mg) may be considered in patients with severe symptoms. There is insufficient evidence to recommend its routine use for an FPIES reaction.[1] The patient should be observed at least 4–6 hours from the onset of reaction and when tolerating oral fluids before discharge. In cases of severe hypotension, shock, extreme lethargy, or respiratory distress, the patient should be transferred to the emergency department or

intensive care unit. The use of epinephrine is not helpful in the management for an FPIES reaction.[1]

Long-Term Management

Once the diagnosis of FPIES has been made, strict elimination of the food trigger is recommended. To alleviate anxieties associated with new food introductions as well as avoiding the risk of nutritional deficiencies from dietary restrictions, a dietetic consultation is highly recommended. Monitoring growth regularly in infants and children with FPIES is recommended as part of the long-term FPIES management. Guidelines for dietary weaning in patients with FPIES are available and have been outlined in the 2017 International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome.[1] The guidelines promote the introduction of low-risk foods and recommend delaying introduction of high-risk foods that are likely to trigger an FPIES reaction. High-risk foods include cow's milk, soy, rice, oats, eggs, sweet potato, poultry, and seafood. When selecting weaning foods in infants with FPIES, it is important to assure parents that a majority of children will only have one food trigger and that the disease has a good prognosis.

Furthermore, maternal dietary elimination of offending triggers would not be recommended while breastfeeding an infant who is thriving and who remains asymptomatic. To assess for a new food reaction, it is suggested that one new food be introduced every 4 days as a single ingredient.[1] Supervised food introductions may be considered by the clinician in cases of high-risk food introductions or family concerns and/or anxieties. A written action plan should be provided and reviewed with family members so that appropriate action and prompt treatment can be given for any future reactions. Important information to consider in the action plan includes the following: the patient's food trigger(s), a brief explanation of signs and symptoms, and actions to take to manage and/or treat symptoms. Patients with FPIES should be evaluated at regular intervals to monitor growth and diet history, and to consider the ideal time of the OFC to assess disease resolution.

DISEASE PROGNOSIS AND RESOLUTION

The natural history of FPIES varies, depending on the food. The development of a tolerance to cow's milk and soy occurs earlier than to grains or other foods. Overall, FPIES has been shown to resolve by school age for the majority of patients.[1,9,21,22] Reintroduction of the food triggers should be considered in a medically supervised setting in which access to rapid fluid resuscitation is available and prolonged observation can be provided. Reintroductions should occur no sooner than 12 months from the patient's last reaction.[1] OFCs to cow's milk, egg, and rice may be considered by 18 to 24 months of age if the reaction was >12 months earlier. An OFC to seafood, however, can be delayed until the patient is ≥5 years.[1] Clinicians should be aware of the possibility of IgE sensitization to the food allergen; therefore, food-specific skin and/or serum specific IgE testing should be performed before OFC.

All OFCs should be conducted in a medical facility with proper emergency medical supplies and medications available. Intravenous access may be secured before starting OFC. Doses for emergency medications should be calculated before starting a challenge and include the following: (a) normal saline solution 0.9% isotonic (20 mL/kg bolus), (b) ondansetron in patients >6 months old (0.15 mg/kg/dose IV/IM; maximum dose, 16 mg), and (c) glucocorticoids (1 mg/kg intravenous; maximum dose, 80 mg). Before challenge, a baseline complete blood cell count with differential can be obtained to assess neutrophil counts. Patients with acute reactions demonstrate neutrophilia 4–6 hours after the onset of the reaction. The food protein administered for the challenge is calculated and given as 0.06–0.6 grams of food protein per kg of body weight (typically 0.3 grams of food protein per kg of body weight) as a single dose (low-risk challenge) or in three divided doses, with 15-minute intervals between each dose with observation for 4–6 hours after the last dose.

Lower starting doses, increasing observation times between doses, or both should be considered in individuals with a history of severe reactions. The initial challenge dose should not exceed 3 g of protein or 10 g of total food (100 mL of liquid). The diagnostic criteria for a positive OFC result in a patient who presents with a possible history of FPIES is outlined in Table 4. Patients with evidence of IgE sensitization on skin and/or serum testing should undergo an IgE-mediated challenge protocol, followed by a >2-hour observation period after the last dose. If a patient was given a lower starting dose (0.06 g protein/kg of body weight) and tolerates the dose after a 2–3-hour observation, then it is recommended that an age-appropriate serving of the food be administered, with observation for an additional 2–4 hours. Once the challenge is complete and the patient is discharged, it is advised that the food be slowly reintroduced at home.[1]

CONCLUSION

FPIES is a rare non–IgE-mediated food allergy reported to affect infants, children, and adults. Currently, there are no diagnostic biomarkers associated with FPIES. The diagnosis is based on a clinical history. The criterion standard to diagnosing FPIES is through OFC; however, this is not always necessary if the patient's history is consistent with an FPIES reaction and all other diagnoses have been ruled out. It is important to recognize the signs and symptoms of an

Table 4 **Diagnostic criteria for interpretation of OFCs in patients presenting with history of possible or confirmed FPIES**

	Major Criterion (1)	Minor Criteria (≥2)
FPIES OFC	Vomiting 1–4 hr after ingestion of food (absence of classic IgE-mediated allergic skin or respiratory symptoms)	Lethargy Pallor Diarrhea in 24h (usually 5–10h) Hypotension
Diagnosis for positive OFC*: 1 Major and ≥2 Minor criteria		Hypothermia Increased neutrophil count of ≥1500 neutrophils above the baseline count

OFC = Oral food challenge; FPIES = food protein–induced enterocolitis syndrome; IgE = immunoglobulin E.
**Adapted with permission from Ref. 1.*

FPIES reaction to quickly initiate treatment. Finally, strict avoidance of the food trigger is essential with OFCs performed in a supervised medical setting no sooner than 12 months after the patient's last reaction.

CLINICAL PEARLS

- FPIES is a non-IgE, cell-mediated food allergy that typically presents in young children.
- Acute FPIES classically presents with repetitive vomiting within 1–4 hours after ingestion of the food allergen.
- The most common triggers for acute FPIES include grains, cow's milk, and soy; the common triggers for chronic FPIES include cow's milk, and soy.
- Sixty-percent of infants with FPIES react to a single food, ~30% react to two to three foods, and 10% may react to more than three foods.
- OFC for FPIES diagnosis, depending on the food, should be considered no sooner than 12 months after the last reaction.

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