



Food protein-induced enterocolitis syndrome epidemiology, diagnosis, and treatment

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Purpose of review

In the last years, the interest of the scientific community toward food protein-induced enterocolitis syndrome (FPIES) has grown exponentially. We review here the peculiar characteristics of this syndrome.

Recent findings

The recent publication of the First International Consensus Guidelines allowed a positive interaction between different research groups with the aim of improving the diagnosis and management of patients affected by FPIES.

Summary

Several fixed points have been placed on the diagnosis and management, but further studies are needed to clarify the many shadows that still surround different aspects of the syndrome, especially regarding the pathophysiology.

Keywords

diagnostic criteria, epidemiology, food allergen, food protein-induced enterocolitis syndrome, management of acute reaction, oral food challenge

INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated immune reaction in the gastrointestinal system to one or more specific foods, commonly characterized by profuse, repetitive emesis, lethargy, and pallor accompanied or followed by watery/bloody diarrhea. Peculiarly, the onset of gastrointestinal symptoms develops 1–4 h after ingestion of the specific food allergen. In severe cases, hypothermia, acidemia, and hypotension/hypovolemic shock may ensue, showing several similarities to a septic state. The first descriptions of FPIES clinical features emerged in the 1960s and 1970s [1–3] describing case series of milk and soy-‘intolerant’ infants. These reports underlined the weird delayed onset of gastrointestinal symptoms compared with the ingestion of the offending food. The first medical report of enterocolitis reaction to solid food characterized by a similar timeline as that observed in the case of milk ingestion dates back to 1963 [4]. Twenty years later, McDonald *et al.* [5] described a severe reaction characterized by delayed onset of vomiting in three patients upon first ingestion of hen’s egg. During the early 1990s, Borchers [6] and Vandenplas [7] described a case report of infants who showed a severe reaction after

ingesting respectively rice and chicken. The authors defined the clinical presentation as ‘anaphylactoid reaction.’ In the second report, the colonoscopy performed after the onset of gastrointestinal symptoms showed a red, fragile, and hemorrhagic mucosa, with a biopsy evidence of a severe inflammation and an increased number of eosinophils [7]. In the late 1990s, the identification of specific clinical features allowed the designation as a ‘syndrome’ and the introduction of the term FPIES [8]. Over the years, reports regarding patients with FPIES reactions increased exponentially, allowing the recent publication of studies that included a greater number of FPIES patients. In 2014, Caubet *et al.* [9] published their 10-year experience regarding oral food challenge tests performed in 160 patients with acute FPIES reaction. The authors reported as the most common incriminated foods cow’s milk and

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Curr Opin Allergy Clin Immunol 2020, 20:316–322

DOI:10.1097/ACI.0000000000000643

KEY POINTS

- FPIES is a non-IgE cell-mediated gastrointestinal food hypersensitivity that typically appears in the first year of life with a delayed onset of profuse, repetitive emesis, lethargy, and pallor accompanied or followed by watery/bloody diarrhea.
- FPIES seems to be not as rare as initially believed; indeed, it seems to be increasingly recognized in clinical practice.
- Acute FPIES is a clinical diagnosis. Laboratory testing may help to support the diagnosis without a specificity.
- The management of acute FPIES reactions is based on rehydration. Oral rehydration at home is recommended in mild reactions, whereas intravenous fluid replacement is mandatory in severe forms characterized by protracted emesis, lethargy, pallor, diarrhea up to hypotension, and metabolic acidosis. Intramuscular or intravenous administration of ondansetron could represent a valid support to stop vomiting and limit fluid losses.

soy (44 and 41%, respectively), followed by rice (22.5%) and oat (16%). The largest cohort of patients with FPIES available to date included 462 cases seen at a single medical center [10]. Milk and soy-triggered FPIES were common (67 and 41%, respectively), and 43.5% of patients who had a milk trigger reacted to soy. In order of relevance, the other offending foods were rice (19%), oat (16%), and egg (11%). However, it is necessary to point out that there is a significant geographical variation in FPIES food trigger. Although rice and egg were the solid foods most frequently involved in Australian FPIES children [11], fish represents the most common solid food trigger in Spanish pediatric population [12]. It is useful to underline that these clinical observations are not immutable. Recently, Blackman *et al.* [13] noticed that rice (53%) was the most common individual food trigger, surpassing cow's milk and soybean, previously reported as the most prevalent FPIES triggers in the United States. Banana (24%) and avocado (16%) rates were also much higher than in other studied populations, likely a reflection of different dietary and weaning habits.

Not until 2017, the first international evidence-based guidelines to improve the diagnosis and management of FPIES patients was published [14[■]]. The document provided useful information regarding prevalence in different geographical areas, pathophysiology, diagnostic markers, and possible management of FPIES patients. Although almost 60 years have passed since the first report, yet many questions referred to FPIES remained unanswered.

EPIDEMIOLOGY

Data on prevalence of FPIES is lacking. All the current large studies on FPIES are from industrialized countries; therefore, data regarding the clinical presentation and the natural history from the other ethnicities and cultures are not available. One prospective birth cohort study from Israel reported the cumulative incidence of cow's milk (CM) FPIES over two years to be 0.34% in infants born at a single hospital [15]. A more recent population-wide study in Australia reported the estimated incidence of FPIES to be 15.4/100 000/year in infants less than two years old [11]. As awareness of FPIES increases, it is probable that future studies will report higher incidence rates. In the Spanish PREVALENCE of food allergies in LEganés pediatric population (PREVALE) study [16], the total incidence of FPIES was estimated to be 0.7%, which is considerably higher than the figure exposed by Mehr *et al.* [11]. This difference may reflect geographical variations or an underestimation because of methodological limitations regarding the prevalence of FPIES. With regard to cow's milk FPIES, the incidence was 0.35%, which was in line with the figure presented in the prospective study carried out by Katz and Goldberg [15]. A majority of case series have noted a slight male predominance, ranging from 50 to 60% [1–3,9,10,15]. In reaching a presumptive diagnosis of FPIES, clinicians should bear in mind that gastrointestinal symptoms were identified as the most frequent symptoms that suggest neonatal cow's milk allergy [17].

No data are available about the time-trends of FPIES in repeated birth cohorts. In a retrospective study, its recognition was found increased from 0.17 to 0.42% of children followed in a primary care birth cohort between 2001 and 2018 [18]. However, some indirect evidence indicates that the trend is increasing. In the EuroPrevall study, aimed at food allergy prevalence in 10 European countries including the United Kingdom, none of 12 000 infants born in 2005–2007 – including 1500 UK infants – presented with FPIES [18,19]. The EAT study, in a similar UK cohort of 1303 UK infants born in 2009–2011, found three confirmed cases of FPIES with a prevalence of 0.23% [20].

FPIES usually presents when formula and/or solid foods are introduced, between 2 and 7 months. Infants on formula typically present earlier than six months of age with CM and soy FPIES, compared with infants with solid food FPIES who present at a median age of 5–7 months [14[■]]. Depending on the population, between 65 and 80% of patients have FPIES to a single food, most often CM, whereas 5–10% have reacted to more than three foods [14[■]]. In a large US case series, 5% of patients reacted to as many as six foods [10]. In the Australian birth cohort, infants with multiple

versus single food group FPIES were younger at first presentation (mean 4.6 versus 5.8 months, $P=0.001$) and were more likely to have FPIES to fruits, vegetables, or both (66 versus 21%, $P<0.0001$) [14[■]]. In addition, infants exclusively breast-fed for more than four months appeared to have lower rates of multiple food group FPIES (23 versus 36%, $P=0.06$). Atopic conditions are commonly seen in FPIES patients in some populations. Between 11 and 57% of patients had eczema in US and Australian populations, whereas only 0–9% did in Korean, Israeli, and Italian populations [14[■]]. Also, in US and Australian populations, food sensitization to foods other than FPIES triggers was seen in 16–39% of FPIES patients. In a recent birth cohort study, atopic comorbidity was higher in patients with FPIES compared with healthy children (atopic dermatitis, 20.6 versus 11.7%; IgE-food allergy, 23.8 versus 4.0%; asthma, 26.6 versus 18.4%; allergic rhinitis, 28.0 versus 16.7%; $P<0.001$ χ^2) [21[■]]. In the large Israeli birth cohort, cow's milk FPIES was associated with birth by Caesarean section and Jewish religion [15]. It was not associated with gestational age, maternal age, number of siblings, maternal dairy consumption, or age of introduction of cow's milk.

The majority of large-scale studies have been retrospective case series, which have provided insights into the male predominance, occurrence mainly in infancy, atopic comorbidity, and common food allergen triggers.

Thus, FPIES seems to be not as rare as initially believed. Nevertheless, further prospective studies involving population-based cohorts are necessary to provide additional and useful epidemiological information.

DIAGNOSIS

Until now, the FPIES diagnosis is based on a clinical history consistent with typical signs and symptoms, and resolution of symptoms with avoidance of the

suspected food trigger. FPIES can present in two particular phenotypes: acute and chronic.

Acute food protein-induced enterocolitis syndrome

The international guidelines proposed accurate diagnostic criteria [14[■]]. The diagnosis of acute FPIES requires that a patient meets the major criterion and at least three minor criteria. The major criterion is vomiting 1–4 h after ingestion of a food with absence of IgE-mediated skin or respiratory symptoms. The minor criteria include: a second or more episode of repetitive vomiting after ingestion of the same suspect food, repetitive vomiting episodes 1–4 h after eating a different food, extreme lethargy, marked pallor, need for an emergency department visit, need for intravenous fluids, diarrhea within 24 h (usually 5–10 h after food ingestion), hypotension, and hypothermia (Table 1).

FPIES symptoms should be reproducible if there is reexposure to the food trigger. Oral food challenges (OFCs) may be needed if the diagnosis is not clear. It is recommended that if only a single episode occurs to consider an OFC as acute gastroenteritis is common in infants. Acute FPIES reactions will typically resolve over a matter of hours, compared with the usual several daytime courses of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.

Chronic food protein-induced enterocolitis syndrome

In contrast to acute FPIES, in which symptoms are more easily correlated with the culprit food, chronic FPIES occurs when the trigger food is not quickly removed from the diet. The lack of a clear temporal relationship between the exposure to incriminated

Table 1. Acute FPIES: diagnostic criteria [14[■]]

Major criterion	Minor criteria
Vomiting in the 1–4-h period after ingestion of the suspect food Absence of classic IgE-mediated allergic skin or respiratory symptoms	1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1–4 h after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency room visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 h (usually 5–10 h) 8. Hypotension 9. Hypothermia

FPIES, Food protein-induced enterocolitis syndrome.

The diagnosis of FPIES requires that a patient meets the major criterion and at least three minor criteria.

Table 2. Chronic FPIES: clinical presentation [14[■]]

Severe presentation: When the offending food is ingested in on a regular basis (e.g., infant formula). Intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis

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

The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days following elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1–4 h, diarrhea in 24 h (usually 5–10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains putative

FPIES, Food protein-induced enterocolitis syndrome.

food allergen and symptom onset may influence a diagnostic delay. The consensus guidelines do not have suggested specific criteria [14[■]]. The diagnosis should be considered if there is intermittent but progressive vomiting and diarrhea (with or without blood) in an infant, particularly in infants on regular cow's milk or soy formula (Table 2). There is often poor weight gain and possibly failure to thrive, particularly in very young infants. If severe, symptoms can lead to dehydration and metabolic acidosis. Symptoms typically resolve within days of avoidance and reintroduction results in an acute FPIES reaction. Without an OFC or an acute reaction, the diagnosis of FPIES is putative.

Oral food challenge

The OFC represents the 'gold standard' in confirming the diagnosis, but it is not indicated if the patient had experienced at least two episodes in the past six months [9]. If only a single episode has occurred an OFC is able to confirm the diagnosis allowing a differential diagnosis with other gastrointestinal disorders (infectious gastroenteritis, sepsis, necrotizing enterocolitis, metabolic disorders, gastroesophageal reflux disease, and gastrointestinal obstruction). OFCs are also useful to assess whether FPIES has been outgrown. There is no standard protocol for an FPIES OFC. Considering that 45–95% of FPIES OFC reactions have been treated with

intravenous fluids, steroids, or both [14[■]], placement of peripheral intravenous access is suggested particularly in patients with a history of severe reactions, emergency department treatment, or hospitalization. Owing to the potential for a severe reaction, home reintroduction of the suspected trigger food is not recommended for suspected FPIES triggers. Criteria for determining a positive FPIES challenge are reported in Table 3.

Laboratory findings

A diagnostic laboratory test is not available for FPIES currently, reflecting the absence of a comprehensive pathophysiology. Laboratory findings can help support a diagnosis or rule out other conditions.

In acute FPIES, an increased blood neutrophil count more than 1500 cells/ml above baseline may be seen that peaks about 6 h after food ingestion. In one case series, thrombocytosis was present in 65% of reactions [22]. If severe, methemoglobinemia and metabolic acidosis may be present in both acute and chronic FPIES. Recently, some reports emphasized the increase of C-reactive protein (CRP) after the OFC or during an acute FPIES reaction, and a correlation between CRP levels and the degree of reaction severity was observed [23,24,25[■]]. Increased levels of blood lactate dehydrogenase (LDH) and serum glutamic oxaloacetic transaminase (SGOT) in resting conditions were observed in FPIES patients,

Table 3. Diagnostic criteria for the interpretation of OFCs in patients with suspected FPIES [14[■]]

Major criterion	Minor criteria
Vomiting in the 1–4 h period after ingestion of the suspect food Absence of classic IgE-mediated allergic skin or respiratory symptoms	1. Lethargy 2. Pallor 3. Diarrhea in 5–10 h after food ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of at least 1500 neutrophils above the baseline count

FPIES, Food protein-induced enterocolitis syndrome; OFCs, oral food challenges.

The OFC will be considered diagnostic of FPIES if the major criterion is met with at least two minor criteria.

suggesting the presence of some preexisting intestinal cellular damage. Diarrhea with blood, leukocytes, or increased carbohydrates in stool may be detected during reactions. In one study, gastric aspirates collected pre and postchallenge showed an increase of 10 leukocytes/high-powered field about 3 h after food ingestion of a positive challenge, which was not seen in patients who did not react [26]. Some of these tests may not be practical in a clinical setting but can be observed during supervised OFCs or in a research setting.

In chronic FPIES, anemia from chronic blood loss in the stool and hypoalbuminemia may be seen. Peripheral neutrophilia and eosinophilia have also been noted. Diarrhea or blood, neutrophils, eosinophils, Charcot Leyden crystals, or reducing substances in stool may be detected. Stool cultures should be negative for organisms and parasites. It is not recommended that stool tests be used to diagnose FPIES as the findings are nonspecific [14[■]].

Food-specific IgE testing has not been found to be helpful because of the inability to identify serum IgE to the culprit food allergen in the majority of

FPIES patients [8,11,15,27]. In addition, negative-specific IgE testing does not exclude acute FPIES.

TREATMENT

According to the recent international guidelines [14[■]], the clinical management involves different approaches depending on the severity of FPIES reaction (Table 4). The priority in management is rehydration in all types of reactions and restoration of hemodynamic stability in case of hypovolemic shock. Starting from 6 months of life, intramuscular ondansetron administration (0.15 mg/kg/dose with a maximum recommended dose of 16 mg) can be considered in all conditions representing a valid support to contain the fluid losses.

When the patients experienced maximum two episodes of emesis in the absence of lethargy or pallor an oral rehydration at home should be attempted, using breastfeeding or clear fluids.

If the acute reaction is characterized by more than three episodes of emesis, mild lethargy, and pallor, the patient has to be transported to the

Table 4. Management of acute FPIES reactions

Type of reaction	Symptoms	Management
Mild	1–2 episodes of emesis without lethargy or pallor	1. Attempt oral rehydration (e.g., breastfeeding or clear fluids) 2. Starting from 6 months of life, intramuscular ondansetron administration (0.15 mg/kg/dose, maximum 16 mg/dose) can be considered 3. Monitor for resolution about 4–6 h after the onset of gastrointestinal symptoms
Moderate	>3 episodes of emesis, mild lethargy and pallor	1. Starting from 6 months of life, intramuscular ondansetron administration (0.15 mg/kg/dose, maximum 16 mg/dose) can be considered 2. Peripheral intravenous line placement is always recommended 3. If oral hydration is not adequate, an isotonic fluid resuscitation (e.g., 10–20 ml/kg boluses of isotonic saline) is required 4. Monitor vital signs 5. Transfer the patient to the intensive care unit for managing extreme lethargy, respiratory distress, persistent or severe hypotension even to a hypovolemic shock condition 6. Monitor for resolution at least 4–6 h after the onset of gastrointestinal symptoms 7. Discharge to home if the patient is able to tolerate clear liquids
Severe	>3 episodes of emesis, severe lethargy, hypotonia, ashen or cyanotic appearance	1. An emergency transportation is required 2. Detection of vital signs and place a peripheral intravenous line 3. A rapid restoration of stable hemodynamics through aggressive isotonic fluid resuscitation (e.g., 10–20 ml/kg boluses of isotonic saline), repeated as needed to correct the hypotension 4. Starting from 6 months of life, intravenous ondansetron administration (0.15 mg/kg/dose, maximum 16 mg/dose) is recommended 5. Consider the intravenous administration of methylprednisolone 1 mg/kg (maximum 60–80 mg/dose) 6. Monitor and correct acid–base and electrolyte abnormalities 7. Correct methemoglobinemia if present 8. Monitor vital signs 9. Discharge to home after 4–6 h from the onset of reaction when the patient's condition is back to baseline tolerating oral clear fluids 10. Transfer the patient to intensive care unit for managing extreme lethargy, respiratory distress, persistent or severe hypotension even to a hypovolemic shock condition

FPIES, Food protein-induced enterocolitis syndrome.

Table amended by Nowak-Węgrzyn *et al.* [14[■]].

emergency room for the appropriate management. The priority in the moderate FPIES reactions is to perform continuous hemodynamic monitoring as a tool to help maintain patient fluid balance. If the fluid loss is not excessive, an oral rehydration may be attempted. Peripheral intravenous line placement is always recommended. In case of poor clinical control coming from oral hydration, an isotonic fluid resuscitation (e.g., 10–20 ml/kg boluses of isotonic saline) is required.

More than three episodes of emesis, severe lethargy, hypotonia, ashen, or cyanotic appearance characterize a severe FPIES reaction. The detection of vital signs and the placement of peripheral intravenous line represent the first steps of an appropriate clinical management. The severe reactions require a rapid restoration of stable hemodynamics through aggressive isotonic fluid resuscitation (e.g., 10–20 ml/kg boluses of isotonic saline), repeated as needed to correct the hypotension. To reduce a presumed cell-mediated inflammation, a single dose of intravenous methylprednisolone (at 1 mg/kg, with a maximum of 60–80 mg) could be administered [28]. Additional precautions must be put in place including supplemental oxygen, mechanical ventilation or noninvasive positive pressure ventilation for respiratory insufficiency, vasopressors for hypotension, bicarbonate for acidemia, and methylene blue for methemoglobinemia. Epinephrine (Adrenaline) autoinjectors are not routinely prescribed to FPIES patients, because the hypotension occurred during a severe reaction is theoretically nothing but the result of fluid loss from the gastrointestinal symptoms (prolonged vomiting and diarrhea). For this reason, epinephrine without intravenous hydration may not be effective. There is no evidence that the administration of antihistamines may play a role in this type of reactions.

CONCLUSION

FPIES is a non-IgE-mediated food allergy with a delayed onset of repetitive protracted vomiting, lethargy, diarrhea and in severe cases hypotension and shock. Although the overall incidence is not yet known, it appears to be increasingly recognized in clinical practice. The most common offending foods are milk, soy, and grains (rice, oat). FPIES phenotype depends on age of onset, trigger foods, and nationality. Diagnosis of FPIES is clinical and OFCs may be used if the diagnosis is unclear. Criteria for diagnosing acute FPIES, which occur when the food is ingested intermittently, are proposed in the First International Consensus Guidelines. Until now, a diagnostic laboratory test is not available, but in this regard, the interest of the scientific community

grows every day more. Studies on FPIES pathogenesis are fervid and could provide new biomarkers [29]. Treatment is focused on exclusion of culprit food and management of gastrointestinal symptoms. Diagnosis and management would benefit significantly from the greater understanding of the pathophysiological mechanisms that are currently still unclear.

Acknowledgements

None.

Financial support and sponsorship

No funding was secured for this study.

Conflicts of interest

There are no conflicts of interest.

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