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Food Protein-Induced Enterocolitis Syndrome: a Comprehensive Review

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Abstract

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy that has been well-characterized clinically, yet it is still poorly understood. Acute FPIES is characterized by vomiting 1–4 h and/or diarrhea within 24 h after ingestion of a culprit food. Chronic FPIES is the result of chronic exposure to an offending food that can result in chronic watery diarrhea, intermittent vomiting, and failure to thrive. FPIES typically presents in infancy and self-resolves by school age in most patients. Adult-onset FPIES is rare, but it has been reported. Cow's milk and soy are the most common triggering foods in infants in the US, and as solids are introduced in the diet, FPIES reactions to grains (rice, oat) increase in prevalence. Variability in common trigger foods exists depending on the geographical origin—for example, fish is a frequent trigger in Spanish and Italian patients. Heavy reliance on a detailed history is required for the diagnosis as physical exam findings, laboratory tests, and/or imaging studies are suggestive and not specific for FPIES. Oral food challenges remain the gold standard for confirming diagnosis, and the challenge protocol may be for an individual depending on risk of reaction, prior reaction severity, and positive-specific IgE status. The recent development of diagnostic criteria in 2017 will serve to increase recognition of the disorder and allow for early implementation of management strategies. Acute management during reactions includes IV hydration, anti-emetics, and IV corticosteroids. Reaction prevention strategies include strict food avoidance until the physician deems a food reintroduction challenge clinically appropriate. Future efforts in FPIES research should be aimed at elucidating the underlying disease mechanisms and possible treatment targets.

Keywords FPIES · Food protein-induced enterocolitis syndrome · Food allergy · Cow's milk · Soy · Oral food challenge

Abbreviations

CM	cow's milk
FPIES	food protein-induced enterocolitis syndrome
sIgE	specific IgE
OFC	oral food challenge

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a cellular, non-IgE-mediated, allergy to food that typically manifests as delayed gastrointestinal symptoms after the ingestion of a specific food culprit(s) [1]. In an acute form of FPIES, most patients present with repetitive vomiting and/or diarrhea, 1–4 h after exposure to a trigger food [2]. However, laboratory abnormalities and failure to thrive can also be present, especially in the chronic form. Diagnosis strongly relies on clinical symptoms, given labs and imaging tends to be non-specific. The lack of specific diagnostic testing, coupled with non-specific symptoms and low awareness among general clinicians, is likely associated with frequently missed and delayed diagnosis. There are also many aspects of FPIES that are still contested, including its pathogenesis, course in adulthood, and its management. Thus, better understanding of the nuances of this disease is clearly warranted.

In this review, we aim to provide a comprehensive and up-to-date summary of FPIES literature, including its phenotypes, mechanisms of pathology, clinical course and prognosis of disease, and management guidelines. We also incorporate global perspectives of how the disorder manifests in patients and is managed.

Historical Review

Powell initially described what has become known as FPIES, in the 1970s as a disorder of enterocolitis in infants who consumed cow's milk (CM) or soy-based formula [3]. The infants

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developed recurrent severe vomiting and/or diarrhea 1–4 h after ingestion of CM or soy-based formula and neutrophil leukocytosis with no other signs of infection. These symptoms were reproducible with the reintroduction of CM formula and improved with intravenous hydration and changing formula to a hypoallergenic hydrolyzed cow's milk formula.

Further investigations were performed by Powell to describe the range of symptomatology of the disorder, create diagnostic criteria, and standardize the challenge for diagnosis confirmation [4]. Sicherer et al., in 1998, later described an additional cohort of patients with protracted vomiting and/or diarrhea in the setting of ingesting CM or soy and symptom resolution with the removal of CM or soy within 24 h [5]. These initial landmark studies provided the catalyst catalyst to pursue further understanding of FPIES and ultimately better serve patients with this rare syndrome.

Definition and Manifestations

Acute FPIES

FPIES is classically described in its acute or chronic form, although other subtypes exist [6]. Acute FPIES is usually characterized by recurrent vomiting and/or diarrhea approximately 1–4 h after ingestion of a triggering food [7]. The vomiting is usually protracted and severe, often resulting in dehydration, lethargy, and/or pallor. Watery diarrhea can follow within 24 h, usually appearing within 5–10 h after the onset of symptoms (Table 1).

Measurable laboratory findings include neutrophilia, eosinophilia and thrombocytosis, metabolic acidosis, and methemoglobinemia. Hypotension and vital sign instability present frequently, mimicking sepsis/shock in these infants and resulting in an infectious work-up that is usually negative (Table 1) [8]. The child returns to baseline about 24 h after the inciting agent has been discontinued, and symptoms do not reappear unless the child is exposed to the trigger food(s) again. Growth and development is unaffected in these children [1].

Chronic FPIES

Chronic FPIES is usually reported in infants younger than 4 months of age and is the result of chronic exposure over several days to triggering foods—typically cow's milk or soy protein. These infants classically exhibit symptoms of intermittent vomiting and/or watery diarrhea as long as the offending food is administered. Chronic diarrheal symptoms tend to predominate in infants, as noted in published case series [6, 9]. Additionally, over time (days to weeks), they can also exhibit the clinical symptoms and lab findings resembling acute FPIES, such as lethargy, dehydration, and neutrophilia. Poor growth and hypoalbuminemia are hallmarks of chronic FPIES (Table 1) and can be used to distinguish its presentation from other non-IgE-mediated food allergic disorders, such as food protein-induced enteropathy or allergic proctocolitis [10]. Symptoms resolve in several days to weeks after eliminating the triggering food from the diet. Reintroducing the food after avoidance will produce an acute FPIES reaction and confirm chronic FPIES diagnosis [11].

Atypical FPIES

Up to 24% of patients with FPIES have atypical FPIES in which there is a detectable specific IgE to their FPIES-inducing food (Table 1) [8]. The sensitization can be present at diagnosis or develop over time. These patients present similarly to acute FPIES patients; however, IgE sensitization is associated with a more protracted course of FPIES and decreased likelihood of resolution. Caubet et al. noted that children with this atypical phenotype were more likely to continue to have CM-FPIES after 3 years of age than their counterparts with CM-FPIES who did not have IgE sensitivity [8].

Epidemiology and Risk Factors

The true prevalence of FPIES is unknown. Katz et al. conducted the first prospective population study attempting to characterize the incidence of FPIES in Israel by following over 10,000 infants over the course of 2 years [12]. The study revealed an incidence of 0.34% of infants with cow's milk-FPIES, as compared to 0.5% prevalence of patients with IgE-mediated cow's milk allergy. Mehr et al. recently published a population-based study in Australia, in which they accounted for new diagnoses of FPIES from 2012 to 2014 in infants younger than 24 months of age [13]. The incidence of FPIES was 15.4/100,000 cases per year, signaling that FPIES is not as rare as once believed [14]. Alternatively, the perceived increase in FPIES cases might be related to the increased awareness of the disorder.

Risk factors for FPIES include a slight male preference, atopy, and birth by Cesarean section [7, 8, 12]. In one study, FPIES was associated with the presence of atopic disease, such as asthma (25%), allergic rhinitis (38%), atopic dermatitis (57%), and IgE-sensitized food allergy to other foods (39%) [8]. A family history of atopic disease has been highly associated with the development of FPIES, with evidence of atopic disease found in > 70% of patient families [15]. A linear inheritance pattern of FPIES from parent to child has not been established. A general family history of FPIES is not commonly associated with developing FPIES and has been noted in up to 7% of siblings of FPIES patients in a recent population study from Australia [13].

Table 1 Clinical phenotypes of FPIES and laboratory findings

	Acute FPIES	Chronic FPIES	Classic	Atypical
Clinical symptoms	-Repetitive vomiting 1–4 h after food ingestion -Diarrhea within 24 h (5–10 h) -Pallor -Hypothermia -Dehydration and/or hypovolemia with shock -Lethargy -Normal growth	-Intermittent emesis -Progressive, watery diarrhea -Dehydration -Failure to thrive/poor growth -Pallor -Hypothermia -Dehydration and/or hypovolemia with shock -Lethargy	-Acute/chronic FPIES	-Develop IgE positivity -A subset may transition to IgE-mediated allergy to food -More prolonged FPIES course
Laboratory values	-Increased white count & neutrophilia in peripheral blood -Metabolic acidosis -Methemoglobinemia -Thrombocytosis -Stool leukocytes, eosinophils -Increased stool carbohydrate content -Stool occult or frank blood -CSF neutrophilia	-Increased white count & neutrophilia -Anemia -Thrombocytosis -Hypoalbuminemia -Metabolic acidosis -Methemoglobinemia -Stool-reducing substances	-Negative IgE to trigger food	-Positive IgE to trigger food, usually low level

Adapted from Ref. [1]

Natural History

FPIES classically presents in infants less than 9 months, with median age of 5.5 months; however, the age of presentation greatly varies. For example, CM-FPIES symptoms can initiate anywhere from a few days of life to 12 months of age but usually occur before 6 months of age with the first or second ingestion of CM [16]. Resolution of symptoms can occur just as suddenly as the onset of symptoms, with no preceding events. In Israel, Katz et al. demonstrated that by 1 year of age, 50% of children with CM-FPIES had resolution of symptoms and by 2 years of age 88.9% no longer reacted with exposure to triggers [12]. Ruffner et al., in the US, reported less promising observations with only 35% of children outgrowing their CM-induced FPIES by age 2 and the majority of patients did not outgrow FPIES until age 5 (85%) [6].

The onset of symptoms and resolution of solid food-FPIES tend to occur at an older age (median of 12.1 months) and may be explained by the later introduction of solid foods into their diets [6]. Caubet et al. reported resolution of solid food-FPIES to rice at median age 4.7 years and 4 years for oats [8]. Fish and egg were reportedly resolved after a median of 60 months [17]. However, age of introduction may not play a role since Ruffner et al. did not find any difference in the age of resolution between liquid- and solid-triggered patients in their study [6]. Overall, FPIES is a self-limiting syndrome in children and appears to have no long-term complications.

Adult-onset FPIES is rare but not unheard of, and it was first described by Fernandes et al. in 2012 in an adult triggered by scallop [18]. Adults have been described with FPIES most commonly to crustaceans (shrimp), mollusks, fish, and egg [19, 20]. Unlike children, the adult form is acquired after previous years of tolerating the food trigger without issue. There are no clear findings predicting when and if their clinical symptoms resolve, and symptoms are often persistent throughout life.

Trigger Foods

Approximately 65% patients with FPIES are reactive to a single food, whereas about 35% will react to two foods or greater. Multiple studies have indicated that the most common food triggers in infants are cow's milk (44–70%), soy (36–40%), or both, in approximately 44% of infants with FPIES, particularly in the US and South Korea [6, 51]. While cow's milk-FPIES is also the most common trigger in Israel, co-existing reactions to soy appeared to be uncommon in cohorts studied [12]. This might be explained by low utilization of soy infant formula in Israel. Nonetheless, liquid food-induced FPIES accounts for approximately 65% of cases overall and more frequently present in infants consuming cow's milk and/or soy infant formula. Breastfed infants appear to be protected against CM- and soy-FPIES [21, 22]. Less than 5% of exclusively breastfed infants develop FPIES, and those that do are suspected to have CM allergen exposure via transmission of breast milk. However, in Japan, FPIES-like symptoms during breastfeeding occur in up to 20% of young infants with FPIES diagnosis [23]. No reports of soy FPIES in exclusively breastfed infants have been documented.

Solid food-induced FPIES occurs in 35% of cases and with rice as the usual culprit in places like the US and Australia [15, 24]. Any solid food can trigger FPIES; however, the most prevalent and well-described foods include rice, oats, barley (and other grains), egg, vegetables (peas, sweet potato),

banana, poultry, fish and shellfish, nuts, and legumes in the US [6, 8]. Depending on the geographical location, the frequency of certain solid foods triggering FPIES can vary greatly. For example, fish was the most common solid food trigger in studies in Italy and Spain alone, likely owing to the early introduction of these foods in a Mediterranean diet [25, 26]. Italian studies have also noted goat's milk, albeit rare, as a cause of FPIES [17]. In an Australian cohort examined in 2017, the predominant solid food (and the overall food) cause of FPIES was rice [13].

There is an increased likelihood of multiple FPIES triggers in an individual with solid food allergy—greater than 40% of individuals with FPIES react to multiple grains [15]. Though usually lower risk, FPIES to fruits and vegetables was more likely in infants with FPIES to grains in a recent study [13]. In both solid- and liquid-FPIES, the threshold dose of food ingestion to elicit a reaction decreases with subsequent exposures. Observational studies have demonstrated this phenomenon with rice, chicken, cod, and wheat [16].

Pathophysiology

The exact mechanism whereby FPIES exerts pathology continues to be poorly understood. Consensus among experts is that FPIES is a non-IgE-mediated food allergy that predominately relies on cellular mechanisms to produce inflammation in the gut after exposure to a food. Endoscopy and colonoscopy studies confirm the colon (and ileum), as main sites of inflammation, which ultimately produces increased permeability of the intestines and fluid shifts into the gut lumen [1, 27]. The intersection between neurological and immune systems has also been implicated in the pathogenesis of FPIES as studies have demonstrated the improvement of repetitive vomiting and abdominal cramping with infusion of ondansetron [11, 28, 29].

On a cellular level, antigen-specific T cells were implicated in FPIES pathology via increased CD4 cellular proliferation on stimulation, increased TNF-alpha and increased Th2 (not Th1) cytokine response with cow's milk challenge [30–32]. However this line of thinking remains controversial. Caubet et al. did not see a difference in proliferation of T cells or Th2 cytokine production when children with CM-FPIES were challenged with casein [30]. Recent studies have implicated the innate immune system in FPIES, specifically demonstrating activation of monocytes, neutrophils, NK cells, and eosinophils after challenges with trigger foods to patient with FPIES [33].

As discussed, patients with atypical FPIES can have elevated specific IgE to their trigger foods, thereby suggesting a role of antibody sensitization in FPIES. These patients can have a more severe phenotype and disease with a protracted course [8]. Patients switching from IgE-mediated food allergy symptoms to non-IgE-mediated FPIES and vice versa have also been described in relation to CM [34]. A potential mechanistic relationship between non-IgE-mediated FPIES and specific IgE development has not yet been established and requires further investigation.

Diagnosis

The diagnosis of FPIES is difficult and greatly relies on a detailed history of clinical symptoms that align with diagnostic criteria of acute or chronic FPIES (Table 2). Delay of diagnosis is common, with some studies reporting a median delay of four to seven months [35]. Important aspects of the history for the clinician to obtain include the following: a detailed description of the reaction symptoms, food(s) ingested that are associated with symptoms, the timing of symptoms in relation to food intake, and reaction reproducibility with food [1]. FPIES is a diagnosis of exclusion, and several other entities on the differential must be considered and ruled out before making the diagnosis (Table 3). There are no diagnostic laboratory or imaging tests available to confirm the diagnosis—only labs that may be suggestive of the diagnosis [1]. Diagnostic criteria are further discussed in Table 3.

Oral Food Challenges

The oral food challenge (OFC) is the gold standard for diagnosis of FPIES and can be used if the diagnosis cannot be made with the history alone. An OFC is not required for diagnosis in infants, especially if symptoms are compelling for FPIES and prior reactions have been severe. OFCs are often indicated in suspected cases of chronic FPIES, when there is not a clear history and food elimination trial is attempted without a conclusion [1].

OFCs should be conducted under physician supervision and with access to intravenous (IV) hydration. Up to 50% of patients who have positive challenges are being treated with IV hydration; thus, immediate access is recommended [36]. The patients' clinical reaction history should heavily be considered prior to the challenge. The clinician should recognize that a lower dose of the food may need to be administered initially, and more observation time may be needed if the previous reactions were severe. These patients may also benefit from obtaining a peripheral IV line before the start of the challenge [1].

In 2009, an international work group report developed a protocol for OFCs to confirm the diagnosis of FPIES, which is now used as the standard FPIES challenge protocol in many centers in the US [37]. The protocol consists of administering 0.3 g (can range from 0.06 to 0.6 g) of the trigger food protein per kilogram of body weight as 1 dose or divided into 3 equal

Table 2 Acute and chronic FPIES diagnostic criteria

Acute FPIES	
Major criterion	Minor criteria
Vomiting 1–4 h after ingestion of culprit food, without IgE-mediated allergic skin or respiratory symptoms	1. Two or more episodes of repetitive vomiting after ingesting the same trigger food 2. Repetitive vomiting episode 1–4 h after ingestion a different food 3. Significant lethargy with a suspected reaction 4. Significant pallor with a suspected reaction 5. Necessary visit to the emergency room with a suspected reaction 6. Diarrhea within 24 h of onset of symptoms (typically 5–10 h) 7. Hypothermia 8. Hypotension
A positive diagnosis must meet the major criterion and ≥ 3 minor criteria. A positive FPIES OFC confirms the diagnosis, particularly if only one FPIES episode has occurred.	
Chronic FPIES	
Major criterion: resolution of the symptoms within days after elimination of the trigger food and occurrence of acute FPIES reaction when food is reintroduced (vomiting 1–4 h after ingestion and diarrhea within 24 h). Diagnosis only confirmed with positive OFC.	
Mild presentation: low or infrequent doses of the suspected food induce the following: • Intermittent vomiting and/or diarrhea, • Poor weight gain/failure to thrive, • No dehydration or metabolic acidosis	Severe presentation: regular ingestion of suspected food induces the following: • Intermittent, worsening vomiting and/or diarrhea (can be bloody) • Dehydration and metabolic acidosis

Adapted from Ref. [1]

doses over the course of 30 min. The total dose should be lower than 3 g of food protein or 10 g of the total food in the initial administration. The patient should be monitored for 4–6 h after this feeding. It is advisable to obtain a CBC at the start of the challenge and a post-challenge CBC (4–6 h after the start of the challenge) when within a research setting.

Various other protocols for FPIES challenges have also been published, with some recommending to administer an entire dose in a single serving and monitoring for 4–6 h [1]. Alternatively, if a very low dose (e.g., 0.06 g food protein per kilogram body weight) is administered initially with no reaction for 2–3 h, some recommend the patient then consume a full serving size (according to age) and then monitor the patient for an additional 4–6 h [1]. A very low dose is recommended in patients with history of severe reactions that were treated with intravenous fluids or resulted in hospitalization.

It is ultimately up to the discretion of the supervising physician to review the clinical history and decide how to administer the OFC to their patient, adjusting the guidelines where they see fit. For instance, patients with FPIES and specific IgE to their trigger food are at risk for immediate IgE-mediated reactions. A physician should modify the FPIES-OFC protocol to administer food in an incremental manner and combine this with a longer observation period typical for FPIES OFC [1].

Positive OFCs are determined by a set of criteria that evaluates symptoms, vital signs, and laboratory results if available (Table 4). Symptoms will include recurrent vomiting, lethargy, and pallor within 1–4 h after consumption of the food. Diarrhea can also develop later, about 8–10 h after the ingestion of food. Stool can be evaluated for occult blood, leukocytes, and red blood cells to help support the diagnosis of a positive challenge. Additionally, a post-challenge CBC can demonstrate increased neutrophils of greater than 1500 cells/mL, peaking 6 h after ingestion [1].

Skin Prick Testing and IgE Testing

Skin prick testing (SPT) is negative for the majority of patients with FPIES. Most patients with FPIES also have undetectable sIgE to their culprit foods, though there exists a small subpopulation with atypical FPIES who have detectable IgE to their trigger foods. Since FPIES cannot be ruled out with negative skin prick testing or undetectable sIgE levels, these tests are not routinely recommended [1]. Obtaining a food-specific sIgE level should be considered when following-up patients with FPIES, as up to 24% of patients develop sensitization to their FPIES trigger food(s), and this finding is associated with a more protracted phenotype (Table 1) [5, 8]. In general, there is a high co-morbidity of FPIES with food allergy and eczema; thus, sIgE can also be obtained to rule out IgE-mediated allergy to other foods. Patients with CM-FPIES are at higher risk of developing into IgE-mediated CM allergy; thus, obtaining CM-sIgE in these patients is also useful [1].

Atopy Patch Testing

Atopy patch testing (APT) was initially proposed as a means to identify patients with FPIES, secondary to the belief that

Table 3 Differential diagnosis of FPIES

Diagnosis	Similar features with FPIES	Differentiating features from FPIES
Infections		
Sepsis	Sudden lethargy, vomiting, hypotension, hypothermia, peripheral blood neutrophilia	Fever present, treatment with fluid resuscitation alone does not improve
Gastroenteritis	Vomiting, watery diarrhea	Fever present, slower course over days, no specific food trigger, family members maybe affected
Anatomical gastrointestinal obstruction		
Malrotation/volvulus	Vomiting in an infant, bloody stool (bowel ischemia), dehydration and shock, failure to thrive, distended loops of bowel on X-ray	Bilious vomiting, abdominal distension, sepsis from necrotic bowel, fluid resuscitation alone does not improve
Intussusception	Vomiting, bloody diarrhea, intermittent, lethargy, and pallor	Severe intermittent, crampy abdominal pain, not associated with food, abdominal mass on exam, detectable on ultrasound
Hirschsprung's disease	Vomiting, failure to thrive in infant/young child	Abdominal distention, constipation, delayed passage of meconium, bilious emesis
Pyloric stenosis	Recurrent projectile vomiting leading to dehydration	No diarrhea, diagnosis with ultrasound
Necrotizing enterocolitis	Lethargy, vomiting, bloody diarrhea, neutrophilia	Higher risk in premature and or low-birth weight infants and formula-fed infants. Requires parental nutrition, intravenous antibiotics, pneumatosis intestinalis on X-ray
Gastrointestinal disorders		
Celiac disease	Failure to thrive, chronic diarrhea, vomiting, anemia	Celiac serology positive and confirmed with biopsy, malabsorption
Gastroesophageal reflux	Intermittent vomiting	No diarrhea, no dehydration, vomiting usually minimal
Lactose intolerance	Diarrhea with ingestion of specific food (lactose)	Symptoms only with cow's milk/lactose, bloating, flatulence, low prevalence under 5–6 years of age
Cyclic vomiting	Repetitive recurrent vomiting, lethargy	Not associated with food, stereotypical vomiting typically early in the day, associated with prodrome (can be associated with headache, photophobia)
Allergic disorders		
Eosinophilic esophagitis	Triggered by specific food, vomiting, failure to thrive	Dysphagia/food impaction sensation, chronic
Food protein-induced allergic proctocolitis	Stool with blood or mucous, associated with cow's milk formula intake	No failure to thrive, no vomiting, resolution sooner (approx 1 year of age), patients not sick appearing
Food protein-induced enteropathy	Failure to thrive, intermittent vomiting or diarrhea with ingestion of specific food (i.e., cow's milk, egg, etc.)	Small bowel injury and malabsorption. No lethargy, pallor, or dehydration; no methemoglobinemia or acidemia. Confirm diagnosis with endoscopy and biopsy
Anaphylaxis	Vomiting, diarrhea with ingestion of specific food, reproducible	Immediate symptoms with ingestion of food (minutes to 1 h), positive SPT and sIgE, other systemic symptoms (i.e., urticaria, angioedema, etc.)
Metabolic disorders; inborn errors of metabolism, storage diseases	Failure to thrive, metabolic acidosis, lethargy	Failure to thrive, developmental delay, dysmorphic features, urine organic acids, plasma amino acids and hyper/hypoglycemia, hepatosplenomegaly
Congenital methemoglobinemia	Methemoglobinemia	Mostly asymptomatic, no vomiting or diarrhea, general fatigue
Primary im`munodeficiency	Chronic diarrhea (due to frequent or persistent GI infections)	Not specific to food, abnormality in lymphocyte counts, immunoglobulins, etc.
Immune enteropathy	Chronic diarrhea	Diarrhea frequently with blood or mucous, severe diarrhea with no food association, rare in infants and toddlers

Adapted from Ref. [1]

allergen-specific T cells mediated the clinical pathology of FPIES [38]. Studies evaluating APT demonstrate that it is not particularly useful for diagnosing FPIES to the most common triggers, CM, soy, oat, or rice. Sensitivity of APT in one study reached only 12%, and positive predictive values of 40% and negative predictive values of 55% were also noted [39]. These findings correlate well with other attempts to evaluate the strength of APT in diagnosis and confirm its inaccuracy in use [6, 40]. APT is not recommended in diagnosing FPIES reactions [1].

Table 4 Criteria for diagnosing a positive FPIES oral food challenge

Major criterion	• Vomiting 1–4 h after ingestion of culprit food, without IgE-mediated allergic skin or respiratory symptoms
Minor criteria	• Lethargy • Pallor • Diarrhea 5–10 h after food ingestion • Hypotension • Hypothermia • Increased neutrophil count > 1500 neutrophils above baseline

In order for the OFC to be diagnostic of FPIES, 1 major and ≥ 2 minor criterion must be met. Exceptions include the following: use of ondansetron may preclude the development of minor criteria, such as pallor, lethargy, repetitive vomiting, and obtaining a neutrophil account may not be possible within the necessary time frame. In these two scenarios, a challenge may be considered positive on the major criterion alone

Adapted from Ref. [1]

Other Testing

Patients with acute FPIES reactions often develop abnormalities in general hematological and metabolic lab tests. This includes an increased white blood cell count and thrombocytosis. Peripheral neutrophil counts become elevated at the onset of an acute reaction, peak at 6 h after the ingestion, and return to baseline in about 18–24 h [4]. Neutrophilia in cerebral spinal fluid has also been demonstrated in acute FPIES. When diarrhea is present, the stool is often positive for red blood cells, mucus, increased carbohydrates, and leukocytes.

Chronic FPIES patients can present with hypoalbuminemia, anemia, eosinophilia, and leukocytosis with a left shift [10, 41]. Their stool, similar to acute FPIES, demonstrates occult blood and neutrophils but also contains eosinophils, reducing substances, and Charcot-Leyden crystals. Acute and chronic FPIES patients notably both develop metabolic acidosis and methemoglobinemia that can also be detected in the serum [42, 43].

Hwang et al. attempted a more invasive approach to describe findings of local disease, specifically gut inflammation in patients with positive FPIES OFC [44]. In this study, gastric aspirates were obtained and examined for leukocyte count per high-powered field (hpf). Patients with > 10 leukocytes/hpf in their aspirate were much more likely to have a positive FPIES challenge and, thus, diagnosis. None of the negative challenge patients developed more than 10 leukocytes/hpf. While the aforementioned tests examining widespread and localized inflammation and metabolic function are suggestive of an FPIES diagnosis, none are diagnostic and therefore not routinely recommended for diagnosis.

Imaging

Radiologic studies are non-specific in FPIES patients. X-Rays and barium studies of the small bowel have included air fluid levels, thickened plicae circulares in the small bowel, and a ribbon-like ileum. Evidence of narrowing and spasm of the large bowel with thumb printing has also been detected [27]. Endoscopies can be normal, although many patients at least exhibit rectal ulceration and some degree of friability of the gut mucosa [45]. However, since these radiographic studies do not help distinguish FPIES from other acute gastrointestinal processes, imaging studies are not recommended as a part of the diagnostic work-up [1].

Management

Acute Reaction

The first steps to management of an FPIES reaction are discontinuing ingestion of the culprit food. An acute FPIES reaction can be expected to resolve in 4–12 h after the onset, while chronic FPIES resolves about 3–10 days after discontinuing the trigger food and starting a hypoallergenic formula. In severe cases of chronic FPIES, temporary bowel rest and parenteral nutrition may be required.

Dehydration that progresses into hemodynamic instability and shock are the most imminent concerns in a patient with a severe acute or chronic FPIES reaction. Supportive care is often needed and includes rapid intravenous boluses (10–20 ml/kg of normal saline), dextrose maintenance fluids, and even bowel rest in chronic FPIES [46]. Oral rehydration, with breastmilk or clear fluids, can be attempted at home with mild to moderate reactions [1, 12].

Intravenous corticosteroids, such as methylprednisolone (1 mg/kg for a maximum of 60–80 mg), have also been recommended as a one-time dose to decrease inflammation at the onset of severe symptoms [1]. Severe reactions may require ICU-level care, which can provide supplemental oxygen and positive pressure or mechanical ventilation. Significant or prolonged dehydration, for example, in chronic FPIES, may not respond to initial intravenous boluses and may require the use of vasopressors. Subsequent metabolic acidemia or methemoglobinemia resulting from hypovolemia may require bicarbonate supplementation or methylene blue, respectively [1].

Ondansetron has also been studied for its effectiveness in reducing vomiting in acute FPIES reactions. Early administration of intravenous or intramuscular ondansetron, within 15 min of a

reaction, has been demonstrated to halt symptoms of vomiting in small case studies of young children undergoing FPIES OFCs [28, 29]. A larger, retrospective case-controlled study comparing ondansetron administration to standard treatment demonstrated a 0.2 relative risk reduction in vomiting [47]. In this study, almost 20% of patients did not improve with IV ondansetron, but overall, those who did improve were less likely to require hospital admission. In authors' experience [unpublished], ondansetron should not be relied upon in patients with history of severe reactions. There are no double-blinded randomized trials evaluating the use of ondansetron, in FPIES reactions; thus, further evaluation of its efficacy is needed. However, for now, in infants over 6 months of age, an IM or IV dose of 0.15 mg/kg may be attempted to mitigate the severity of an FPIES reaction with a max dose of 16 mg [1]. Oral ondansetron has also been suggested for home use with accidental reactions, with the caution that these patients continue to seek medical attention [48].

Self-preparedness and quick action are extremely important for families dealing with FPIES, in the event of exposure to a food trigger. Clinicians should provide families with an emergency action plan as well as a letter explaining the diagnosis and management options to emergency room physicians who may be less familiar with FPIES. The clinician can recommend patients to have epinephrine available in case an IgE-mediated food allergy coexists or if the patient has atypical FPIES. However, neither epinephrine nor antihistamines are useful in classic FPIES reactions [11].

Avoidance of Trigger Foods

The first-line approach in the long-term treatment of acute and chronic FPIES is the strict avoidance of triggering liquid and solid foods. As discussed previously, CM is the most common culprit in infants; thus, infants who are formula-fed should receive an extensively hydrolyzed casein formula for their first year of life. This is preferred to a soy formula as an empiric alternative, given the US studies demonstrate 30–65% of patients have coexisting acute CM and soy FPIES. Conversely, international studies have demonstrated a much lower prevalence of simultaneous FPIES to CM and soy [7, 12, 17]. Therefore, soy formula can be used as an alternative to CM if an FPIES OFC to soy is performed with no reaction. Similarly, CM can be an alternative for children with FPIES to soy, provided there is no incident with physician-observed intake. Elemental formula is ultimately required in up to 20% of cases, if hydrolyzed casein formula and soy formula are not tolerated. Alternate mammalian milks (specifically, sheep and goat) are not recommended due to their homology and, thus, high cross-reactivity with CM [49]. Donkey and camel's milk are options that may be tolerated in children with CM-FPIES and can be used if available.

While there are strict recommendations of avoidance of trigger foods in FPIES, there are some exceptions to this rule that are less understood. For example, it is unclear if there are thresholds of tolerance for FPIES trigger foods and ways to predict which patients may tolerate more of the food. By convention, patients do not have to avoid foods with "precautionary allergen labeling" unless there has been a history of severe reactions to minute amounts. Additionally, there is no compelling data to support if baked forms of trigger foods (e.g., baked milk and/or baked egg) should be challenged for tolerance in FPIES reactions as they are in children with IgE-mediated food reactions. One small study with seven patients demonstrated that baked milk or egg products may be tolerated in a small subset of children with FPIES to these foods [50]. In a population-based study from Australia, four out of five patients with FPIES to egg reacted to baked egg, whereas twelve children with CM-FPIES and exposure to baked milk tolerated baked milk [13]. Both studies were observational, and neither has long-term data available. Thus, for now, the FPIES guidelines recommend avoidance of baked products unless the child is already tolerating baked forms and does not display evidence of symptoms or poor growth. Baked food introduction can be discussed between the parent and clinician on a case-by-case basis and should only occur under physician supervision [1].

Infants who are exclusively breastfed can continue breastfeeding without maternal avoidance of the food culprit. Maternal avoidance is only recommended if there has been a history of FPIES symptoms with breastfeeding, after maternal ingestion of the trigger food. This is uncommon but has been documented in cases in Japan and Australia [13]. The food should also be eliminated from the maternal diet if the infant presents with failure to thrive. If the symptoms do not resolve despite maternal elimination from the diet, switching to a hydrolyzed or elemental formula would be the next steps in management [1].

Food Introduction

Ultimately, the goal of avoidance diets is preventing FPIES reactions in the least restrictive dietary settings possible. Clinicians must emphasize the introduction of new safe foods to diversify nutrition sources in growing infants while being cognizant of risk of reacting in patients with multi-food sensitization. Patients with CM or soy-FPIES are more likely to also have FPIES reactions to solid foods, particularly oat and rice. Thus, we take the approach of introducing developmentally appropriate lower-risk foods and do not delay solid food introduction past 6 months of age. Introduction of solids can begin with lowest-risk foods and progress, for example, beginning with fruits and vegetables, followed by meats, and then grains [1]. If the child tolerates a food from one food group, there is an increased likelihood that they will tolerate all foods from that group [36]. Those with more severe reactions to FPIES may consider the introduction of new foods in the office setting.

The reintroduction of foods that have caused FPIES reactions should be performed with physician-supervised OFCs. The data are lacking on the appropriate time with which to re-challenge these patients to evaluate for resolution of FPIES. Conventionally, in the US and Europe, an OFC to test for resolution is performed about 12–18 months after the last reaction in children with FPIES. However, Korean infants diagnosed with CM or soy-FPIES at a median of 36 days demonstrated tolerance to CM and soy respectively at 6 months of age (27 and 75%), 8 months of age (42 and 91%), and 10 months of age (66 and 92%) [51]. This suggests that earlier attempts at reintroduction of food allergens can be performed. Larger cohorts would need to be studied to confirm this. Once the OFC is passed, the patient can begin gradual home introduction of one new food at a time over 4 days and observed for any sign of reactions [52, 53].

While these recommendations are targeted towards young children, there is no compelling data on food introduction and the ideal timing to test for resolution of FPIES in older children and adults. Adults and older children more frequently suffer from seafood-induced FPIES, particularly in studies in Italy and Spain. Experts recommend periodically re-challenging adults to determine if their FPIES has resolved [54].

Utilizing the expertise of allied health professionals may be necessary to optimize management in children with FPIES. Dietician consultation is recommended to optimize the nutrient intake in the setting of food restriction, whether one or multiple foods are avoided [1]. Also, the introduction of a variety of foods during infancy is essential for an infant's development of feeding skills. When introduction is inhibited, infants can develop oral aversions to textures and flavors and have an overall poor relationship with foods. Thus, even if the diet is significantly restricted, guidelines recommend varying the preparations of the foods tolerated (i.e., pureed vs. baked vs. raw fruits) to diversify early experiences with food. If this cannot be accomplished at home, feeding therapy may be necessary to assist patients with feeding difficulties after the prolonged avoidance of multiple foods [1, 52, 55].

Conclusion

This review of literature demonstrates that the field has made important progress in understanding FPIES in multiple areas, culminating in publication of the first international consensus guidelines on the diagnosis and management of FPIES in 2017 [1]. The phenotype of FPIES has been well-characterized, with ingestion of food triggers resulting in protracted vomiting and/or diarrhea in the acute form and prolonged diarrhea with intermittent emesis in the chronic form. There has been noteworthy advancement in characterizing likely food triggers (CM, soy, rice, and oat) and patients at risk for multiple food triggers. Additionally, multiple studies support that this is a self-limited disease in infants and young children, often resolving by the time they enter school. The recent publishing of evidence-based international consensus guidelines significantly contributes to recognizing FPIES patients and standardizing and optimizing FPIES treatment.

Although FPIES is one of the best-studied non-IgE-mediated food allergies in the literature, many aspects of this disorder remain under debate. Some of which includes the following: explaining its underlying mechanism, characterizing its true population prevalence and risk factors, and optimizing management with food introduction, such as examining the tolerance of baked allergen products. Future studies should prioritize clinical management, such as developing diagnostic testing/biomarkers, and developing protocols for re-introducing foods into the diet. Finding effective ways to educate general practitioners about FPIES and establishing multidisciplinary teams to care for these patients will also support early diagnosis and optimization of care.

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Compliance with Ethical Standards

Conflicts of Interest ANW and AA report that they have no conflict of interest.

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