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FOOD ALLERGY (T GREEN, SECTION EDITOR)

Food Protein-Induced Enterocolitis Syndrome (FPIES): Review of Recent Guidelines

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Abstract

Purpose of Review To increase understanding of food protein-induced enterocolitis syndrome (FPIES), a non-immunoglobulin E (IgE)-mediated reaction to food, by reviewing a growing body of literature, including recently published international consensus guidelines.

Recent Findings FPIES primarily affects infants and young children and is characterized by the delayed onset of gastrointestinal symptoms, predominantly repetitive vomiting, in response to a trigger food. Symptoms are often severe and can lead to shock. Diagnosis can be challenging due to a wide differential diagnoses and lack of disease biomarkers. FPIES is a clinical diagnosis, with allergy testing playing a very limited role, if any. Medically supervised oral food challenges are used to monitor resolution of disease, which generally occurs in early childhood.

Summary FPIES is an important condition presenting to clinicians in a variety of settings. Recent international consensus guidelines and a growing body of literature can better equip practitioners to care for these often-challenging patients.

Keywords FPIES · Food protein-induced enterocolitis syndrome · Food allergy · Non-IgE-mediated food allergy

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is an increasingly recognized non-immunoglobulin E (IgE)-mediated reaction to food. Reactions are characterized by the delayed onset of gastrointestinal symptoms, predominantly repetitive vomiting, which is often severe and should be considered a medical emergency. FPIES most commonly presents in infants and young children [1]; few cases of FPIES have been described in adults [2•]. FPIES can be a diagnostic challenge due to the wide differential diagnosis and the lack of disease biomarkers. In 2017, the first international evidence-based guidelines for FPIES were released. The guidelines focus on the diagnosis and management of FPIES and assist clinicians in the care of patients with this condition [3••].

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Clinical Presentation

Acute FPIES, the most common form of the disease, presents between 2 to 7 months of age with repetitive vomiting occurring 1–4 h after ingestion of a trigger food. Vomiting is often severe and can lead to dehydration, lethargy, and pallor. Diarrhea can develop 5–10 h after food ingestion and can be watery or bloody. Symptoms can progress to hypovolemic shock, hypothermia, methemoglobinemia, and acidemia, resulting in a sepsis-like picture. Symptoms generally resolve within 24 h of removal of trigger food [3••].

Chronic FPIES has a more insidious onset and is generally seen in formula-fed infants less than 4 to 6 months of age. Chronic ingestion of cow's milk-based or soy-based formula leads to chronic vomiting, diarrhea, and failure to thrive. Patients improve within days after removal of the inciting food [3••]. Of note, patients develop symptoms of acute FPIES upon re-exposure to the culprit food.

Inciting Foods

The most common triggers of both acute and chronic FPIES are cow's milk and soy, typically via infant formulas. Solid foods trigger acute FPIES in older infants and young children, likely due to the typical practice of later introduction of solid foods. The most common causes of solid-food FPIES are grains such as rice and oat, legumes, and poultry. Reactions to other solid foods including eggs, vegetables, fruits, and seafood have been described [2•, 3••]. Fish and shellfish are the most commonly described triggers of FPIES in older children and adults. Patients with FPIES may have reactions to more than one food. Approximately one-third of infants with cow's milk or soy FPIES will react to a solid food [4, 5].

Although large-scale epidemiological data is limited, there are noted geographical differences seen in foods inciting FPIES. In the USA, cow's milk, soy, rice, and oat are the most common triggers of FPIES [2•]. However, soy-induced FPIES is not a common occurrence in Australia, Israel, or Italy [1, 6, 7]. Fish is a common FPIES trigger in both Italy and Spain [7, 8]. These differences may be due to variations in dietary practices, as fish is often introduced early in infant diets in Spain and Italy. However, genetic factors likely also play a role as rice, also a common early solid food in Spain and Italy, is not a common FPIES trigger in those countries, in contrast to the USA [8].

Pathophysiology

The pathophysiology of FPIES remains unclear, although both cell-mediated and humoral immune responses have been investigated [9]. Intestinal inflammation leading to increased intestinal permeability is the most commonly proposed mechanism of disease [10, 11]. Although considered a non-IgE-mediated disease, Th2 responses much like those seen in IgE-mediated allergies occur, showing an antigen-specific T cell-mediated modification of intestinal permeability characteristic of FPIES [11–13]. Humoral responses are less clear, but studies show a near lack of IgG4 in FPIES. IgG4 activates complement poorly and may compete with other antibody classes that more effectively fix complement. The absence of IgG4 in FPIES may be pathogenic due to the loss of this protective competitive role [14]. The more recent observation that ondansetron, a serotonin 5-HT_3 receptor antagonist, has been associated with clinical improvement may indicate that neuroimmune mechanisms also play a role [15, 16•].

FPIES and Atopic Disease

The absence of IgE-mediated symptoms, including cutaneous and respiratory symptoms, as well as the delayed onset of symptoms relative to IgE-mediated disease differentiates FPIES from IgE-mediated food allergy. Although not an IgE-mediated disease, children with FPIES do often have comorbid atopic disease, including atopic dermatitis, allergic rhinitis, and IgE-mediated food allergy [3••, 8].

Diagnosis

Diagnosis of FPIES is challenging for several reasons. An overall lack of familiarity with the illness, in conjunction with symptoms that often mimic other diseases such as viral gastroenteritis, anaphylaxis, or sepsis, frequently leads to delayed diagnoses or misdiagnoses. The false belief of low allergic potential of trigger foods such as grains and vegetables may contribute to the under recognition of FPIES [10]. The lack of diagnostic testing and biomarkers also contributes to the diagnostic challenge [8]. In a recent study by Greenhawt and colleagues, one-third of surveyed allergists reported "suboptimal familiarity with FPIES" [17]. The study also showed large variation in management practices, including incorrect utilization of epinephrine for FPIES, oral food challenges, and identification of proper alternative nutrition sources. It was found that allergists reported less full knowledge of FPIES with increasing years in practice, correlating with duration of time post training [17].

FPIES is a clinical diagnosis. Oral food challenge is considered the gold standard for diagnosis but is generally not recommended for diagnosis when the clinical history is typical of FPIES, and symptoms resolve with avoidance of the suspect food [10]. Lab studies have poor utility for diagnosis, although classic laboratory findings are seen during acute reactions. These include hypoalbuminemia, anemia, leukocytosis with left shift, and eosinophilia. Radiographic findings are non-specific, and thus, radiographic studies are of little value [3••].

The utility of allergy testing is limited. IgE testing tends to have low utility in the majority of cases, as FPIES is a non-IgE-mediated disease. Most patients with FPIES have a negative skin prick test (SPT) and negative food-specific IgE to suspected trigger foods. However, though not diagnostic, IgE testing can provide limited prognostic information in a small subset of cases. Detectable specific IgE to inciting foods has been associated with prolonged persistence of the disease, particularly for cow's milk; atypical FPIES is the term used to describe cases in which specific IgE is detectable. Patients with FPIES to a specific food may also develop an IgE-mediated allergy to the trigger food [2•, 6, 7]. While the cause of this phenomenon is not clear, it is theorized that prolonged avoidance of the trigger food, such as cow's milk protein, may increase the risk of developing IgE-mediated allergic disease [1]. Atopy patch testing has been studied and found to have poor utility in the diagnosis or prediction of resolution in FPIES [18].

Given the diagnostic challenges in evaluating patients with possible FPIES, proposed diagnostic criteria for acute FPIES

have been established and published in recent international consensus guidelines [3••]. The major criterion is vomiting in the 1-4 h period after food ingestion in the absence of other IgE-mediated allergic symptoms. Minor criteria include a second episode of repetitive vomiting after ingestion of the same suspect food, repetitive vomiting 1-4 h after a different food, extreme lethargy or marked pallor with any suspected reaction, need for an emergency department visit or intravenous fluids after a suspected reaction, diarrhea in a 24-h period, hypotension, and/or hypothermia. The one major criterion in addition to three minor criteria must be met for a diagnosis of acute FPIES. Diagnostic criteria for chronic FPIES are less well-defined; however, it is noted that symptoms abate after elimination of the inciting food(s) and can recur in the form of an acute FPIES reaction with reintroduction [3••].

Differential Diagnosis

As mentioned before, symptoms of FPIES can be seen in other diseases, as seen in Table 1, making recognition of FPIES difficult and misdiagnoses common. Conditions that commonly mimic acute FPIES include sepsis and other infectious etiologies, such as gastroenteritis. Other conditions on the differential diagnosis include intussusception, volvulus, pyloric stenosis, and, when presenting in neonates, necrotizing enterocolitis. In the emergency room setting, abdominal imaging, such as radiography, ultrasound, and barium enemas, may be used for the work up of these other conditions [6]. In cases of chronic FPIES, extensive medical workup is often performed with a differential including eosinophilic esophagitis, inborn errors of metabolism, gastroesophageal reflux, and inflammatory bowel disease [10, 19].

Treatment and Management

Management of FPIES reactions is based on severity of symptoms and is generally supportive, focusing on fluid replacement. Acute FPIES reactions should be treated as a medical emergency due to the risk of progression to hypovolemic shock. Severe reactions are treated with aggressive fluid resuscitation. Oral rehydration can be utilized if symptoms are mild. Ondansetron is an emerging and newly studied adjunctive treatment in halting emesis during oral food challenges, and thus may have an increasing role in acute FPIES reactions [15, 16•, 20]. Sopo et al. published a report of five patients undergoing oral food challenges in whom intramuscular ondansetron was used with resolution of acute FPIES symptoms within 15 min of administration. The use of ondansetron for acute FPIES reactions is an area in need of further study [15, 16•].

Table 1 Differential diagnoses of FPIES

Differential of acute FPIES	Differential of chronic FPIES
Sepsis	Eosinophilic esophagitis
Gastroenteritis/acute dehydration	Celiac disease
Necrotizing Enterocolitis	Inborn errors of metabolism
Pyloric Stenosis	Primary immunodeficiency diseases
Allergic proctocolitis	Inflammatory bowel disease
Anaphylaxis	Gastroesophageal reflux disease
IgE-mediated food allergy	Lactose intolerance
Intussusception	α1-Antitrypsin deficiency
Food poisoning	Food aversion
Volvulus	Hirschsprung disease

The elimination of trigger food(s) from the diet is the mainstay of treatment in FPIES. In cases of FPIES in breast-fed infants, maternal dietary restriction is not necessary in the vast majority of cases [5]. The threshold dose of a trigger food necessary to cause a reaction is higher for FPIES than in IgE-mediated food allergies, and the amount of food protein transferred into breast milk is typically not sufficient to cause a reaction [10]. However, in the uncommon case in which an infant is failing to thrive or has an observed reaction to a protein via breastmilk, it is recommended that the mother removes the suspected trigger food from her diet [3••].

Introduction of Foods

Introduction of new foods in patients with FPIES can be challenging for several reasons. Families are often fearful to try new foods due to past experiences with food trials. Additionally, oral aversion has been observed in a subset of patients with FPIES [21•]. The clinician should provide an approach to introduction of foods and may consider medically supervised introduction in certain cases.

One approach is to delay introduction of high-risk foods, such as grains, legumes, and poultry, in the first year of life in children with an established diagnosis of FPIES [10]. Other sources note empiric avoidance of all allergenic foods is not recommended [8]. In the case of cow's milk and soy, it should be noted that 20–40% of patients react to both, making it prudent for providers to be cautious in introducing cow's milk or soy to a patient with previously diagnosed FPIES caused by either one. Breastmilk or extensively hydrolyzed casein-based formulas are recommended in these cases [3••, 8]. Some infants with cow's milk and/or soy FPIES will require an elemental formula.

Introduction of solid foods in patients with FPIES should not be delayed past the standard 6 months of life [5]. The time between 4 to 7 months of age is known as the complementary feeding period and is a crucial time period in which infants learn to tolerate a variety of tastes and textures and develop oral motor skills. Delays in introduction of solid or "lumpy" foods past 10 months of age has been shown to correlate with

increased incidence of feeding difficulties, food refusal, and "picky" eating habits in toddlerhood and early childhood [22]. Evaluation by speech therapy should be considered if feeding difficulties occur as a result of reactions or delayed introduction of certain foods.

Solids should be introduced cautiously, starting with yellow fruits and vegetables. If tolerated, other fruits and vegetables, followed by red meats and low-risk cereals, may be tried. No previously tolerated foods should be eliminated or avoided in the diet [3••, 5]. Tolerance of a food from one food group also suggests tolerance to other foods from the same group, which can help liberalize the diet. For example, if a child tolerates turkey, other poultry may be introduced [5]. Physicians may choose to introduce high-risk foods under medical supervision in patients with cow's milk or soy-induced FPIES due to the increased risk of concurrent solid-food FPIES in these patients. Supervised introduction may also be considered in other cases due to medical complexity or family concern to help alleviate the fear of trying new foods and allow for the essential variation in diet and expansion of nutrient sources [3••].

Nutrition

Although no cases of poor growth in children with FPIES after having eliminated the trigger foods have been reported, it is believed that delayed introduction of solid foods or food avoidance or elimination can increase the risk of poor growth and nutritional deficiencies. Thus, growth should be monitored regularly in patients with FPIES, as in all patients with food allergy [23]. Clinicians should consider referral to a dietitian for detailed evaluation of nutritional status. In addition to an assessment done at the time of weaning and introduction of solid foods at around 6 months of age, a nutrition assessment should also be done at the transition from breastmilk/formula to a substitute beverage, and annually throughout childhood. More frequent assessments should be done if the patient exhibits poor growth, feeding difficulties, nutritional deficiencies, or has a history of exposure to trigger foods that should have been avoided. Common nutritional deficits in patients with FPIES include vitamin D, zinc, and iron due to avoidance of cow's milk and grains. Dieticians can help ensure proper substitutions for foods eliminated from the diet and educate on avoidance, including how to prepare allergen-free food recipes and how to properly read food labels. Avoidance of foods with precautionary labels (i.e., "may contain traces…") is not necessary in patients with FPIES [21•].

Prognosis and Resolution of Disease

Prognosis is generally good, with most children outgrowing FPIES in early childhood. Children with detectable food-specific IgE may have a more protracted course [10]. Studies have shown that IgE sensitization in patients with cow's milk-induced FPIES is correlated with protracted disease [3••]. Resolution of disease may be population-dependent. While one study in the USA found only 20% resolution of cow's milk FPIES by 3 years of age, Korean studies showed 60% resolution by 10 months and Israeli studies showed 90% resolution by 30 months [2•, 7, 24]. This variation can be explained by differences in methodology of these studies versus an increased number of high-risk patients (those with concomitant atopic disease) in the studies done in the USA [2•].

Resolution of disease should be assessed by a medically supervised oral food challenge at least 12 months after the most recent reaction. Some sources recommend waiting up to 18 months after the last reaction prior to attempting a food challenge [8]. Timing of an oral food challenge can also vary by individual preference and the importance of the food in the diet from a nutritional and social perspective. Patients should be followed at regular intervals to monitor for resolution of disease. Oral food challenges should occur under close medical supervision in a setting equipped to treat reactions and provide intravenous fluid resuscitation. If a history of FPIES reaction is particularly severe, securing peripheral intravenous access prior to the food challenge may be warranted. Food challenge protocols have been published [25••]. Three equal doses of the trigger food in doses of 0.15 to 0.3 g of protein per kilogram of body weight, but not more than 3 g of protein or 10 g of whole food, should be introduced over 45 min. If the patient has a history of severe FPIES reaction or IgE sensitization to the trigger food, the food challenge may be performed with smaller doses. The patient should be observed for 4 h or more due to the delayed onset of symptoms [3••, 25••]. Home oral food challenges are discouraged due to the possibility of severe reactions [3••].

Conclusions

FPIES is an increasingly recognized entity, and the need for complete studies to improve quality care has been identified. Recent international consensus guidelines and a growing body of literature on FPIES better equip practitioners to care for these often-challenging patients and have laid the groundwork for further advancement of best practices.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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