Curr Pediatr Rep (2014) 2:135–143
DOI 10.1007/s40124-014-0043-y

ALLERGY (WG SHREFFLER, SECTION EDITOR)

Non-IgE-Mediated Food Allergy: FPIES

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Published online: 19 March 2014

Abstract Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food hypersensitivity with usual onset in infancy. The most common FPIES triggers are cow milk, soy and rice; in addition, oats, vegetables, egg, poultry and seafood have been reported. In the acute form, when food is ingested on an intermittent basis or following a period of avoidance, FPIES presents with profuse vomiting within 1–3 h after ingestion, occasionally accompanied by diarrhea and dehydration. In the chronic form, when food is ingested on a regular basis, FPIES presents with intermittent vomiting, diarrhea, weight loss and failure to thrive. FPIES is diagnosed based on history and typical symptoms, which improve with food avoidance, and exclusion of other etiologies. Oral food challenge remains the gold standard for FPIES diagnosis. Most CM or soy FPIESs resolve within the first 3–5 years; solid food FPIES or FPIES associated with positive food-specific IgE may have a more protracted course. The prevalence of FPIES is unknown.

Keywords Food allergy · Allergic colitis · Allergic enterocolitis · Milk allergy · Food protein-induced enterocolitis syndrome (FPIES) · Non-IgE mediated food allergy

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Introduction

Non-IgE and mixed pathophysiology gastrointestinal food allergic disorders are estimated to account for 40 % of cow's milk allergy in infants and young children [1]. They encompass food protein-induced enterocolitis syndrome (FPIES), allergic proctocolitis, enteropathy and eosinophilic gastrointestinal disorders. Most are self-limiting and resolve by 3–5 years of age. FPIES is an underrecognized and frequently misdiagnosed non-IgE-mediated food hypersensitivity, manifesting as a severe, repetitive vomiting within 1–3 h following food ingestion, lethargy, pallor and/or diarrhea, usually within 5–10 h following food ingestion. Classic allergic symptoms of the skin, such as urticaria, pruritus or angioedema, and of the respiratory tract, such as cough, wheezing or shortness of breath, are absent [2•]. In the US, the most common food triggers are cow milk (CM), soybean and rice [3]. Symptoms induced by milk or soy typically begin in the first month of life in association with failure to thrive and may progress to acidemia and shock. FPIES to cereal grains, vegetables and meats usually starts after these solid foods have been introduced into the infant's diet, whereas FPIES to fish or shellfish may have onset in older children or adults. Despite the potential severity of acute reactions, FPIES can be considered self-limiting as avoidance of the incriminating allergen(s) leads to resolution of symptoms.

Defining FPIES

Allergic reactions to foods affecting the gastrointestinal tract have been known since ancient times. Hippocrates noted that cow's milk caused gastrointestinal symptoms as

well as urticaria, and that some infants fed cow's milk developed prolonged diarrhea, vomiting and failure to thrive that resolved only after removal of cow's milk from their diet. Rubin reported intestinal bleeding due to cow's milk allergy in newborns [4]. Gryboski and Powell described infants presenting in the first 6 weeks of life with recurrent vomiting, bloody diarrhea and abdominal distension while being fed with cow's milk-based formula [5, 6]. They appeared dehydrated and severely ill. Sepsis evaluations were negative, but they improved with intravenous fluids or hydrolyzed casein-based formula, but not with soy-based formula. Reintroduction of cow's milk-based formula resulted in recurrence of severe emesis, diarrhea and elevation of the peripheral blood neutrophil count. Powell characterized major features of the disorder and established criteria for the diagnosis of cow's milk-induced enterocolitis and a standard challenge protocol [7]. Reports of large series of infants with food protein-induced enterocolitis by Sicherer et al. [8] (16 patients) and Burks et al. [9] (43 patients) further characterized clinical features and modified food challenge protocols. More recent reports have identified various solid foods as triggers for FPIES, including oat, wheat, vegetables and shellfish in adults [3, 10–18].

Prevalence of FPIES

The prevalence of FPIES in the US is not known; generally, FPIES is considered to be an uncommon food allergy. However, in a large Israeli population-based birth cohort FPIES incidence was 0.34 % (44/13,019); by comparison, the incidence of IgE-mediated CM allergy in this population was 0.5 % [19••]. The Israeli study suggested that FPIES may be more common than previously appreciated. It is likely that mild phenotypes of CM and soy FPIES are not being diagnosed as FPIES and are managed empirically with formula changes in the first year of life with resolution of symptoms.

Risk factors for development of FPIES include cesarean delivery, male gender and FPIES to another food [19••]. FPIES is associated with atopy, with 30 % of FPIES patients having a personal history of atopic disease, 40–80 % reporting family history of atopic disease and 20 % family history of food allergy [3, 8]. Our own unpublished data suggest that early introduction of CM may be a risk factor for FPIES. In addition, although egg is not a common cause of FPIES, when it was introduced at 5.5 months as a control allergen, it caused FPIES symptoms in 30 % of the infants with milk or soy FPIES [20].

Wheat is also not a common trigger; however, wheat FPIES prevalence is likely to be modified by the common practice of delaying wheat introduction in infants with rice or oat FPIES past 12 months of age. These observations and the optimal timing of the food introductions need to be validated by prospective studies in larger populations.

Breastfeeding appears to have a protective role against FPIES as infants exclusively breast-fed without formula supplementation are asymptomatic until direct feeding with the offending food. CM-FPIES to the mother's milk in exclusively breastfed infants is rare, with only four case reports to date [3, 21, 22].

FPIES Manifestations

FPIES manifestations depend on the frequency and the dose of food ingested. FPIES may present in either acute or chronic form. It is important to point out that there are no classic allergic symptoms from the skin (such as itching, hives, swelling) or respiratory tract (wheezing, cough, sneezing) in either form of FPIES (Table 1). Chronic FPIES occurs with frequent ingestion of the trigger food and typically presents in a formula-fed infant in the first weeks of life, with symptoms of intermittent emesis, watery or mucous diarrhea, poor weight gain and dehydration [5–7]. These symptoms are non-specific and have a very broad differential diagnosis including infection, metabolic disorders, structural defects and inflammatory gastrointestinal disorders, among others. Acute FPIES occurs with intermittent ingestion of the trigger food, with symptoms' onset 1–3 h after ingestion, typically with somewhat more severe presentation than chronic FPIES. In addition to profuse emesis (which may be projectile and occur up to 10–20 times) and dehydration, infants may develop lethargy, pallor, hypotension, hypothermia and methemoglobinemia [5, 6, 23–25]. Typically, avoidance of the culprit food for several days results in the resolution of symptoms; upon subsequent food ingestions FPIES symptoms usually re-occur within 1–3 h. In children with ongoing gastrointestinal symptoms that persist despite extensive dietary eliminations or while the child is exclusively fed with an amino acid-based formula, further evaluation is necessary to confirm the diagnosis of FPIES and to avoid misdiagnosing other conditions (e.g., metabolic disorders, eosinophilic gastroenteropathies or gastrointestinal inflammatory diseases) as chronic FPIES.

Food Triggers and Age of Onset

In the US, the most common triggers are CM and soy formulas and rice in young infants [3, 5–7, 26]. In Israel, Australia and Italy, soy FPIES is rare [19••, 24, 25]. In infants fed with the infant formula, CM and soy FPIES usually starts within the first few months of life. When the

Table 1 Manifestations of chronic and acute FPIES

	Chronic FPIES	Acute FPIES
Food ingestion	Food ingested on a regular basis, initially described in young infants being fed with milk or soy-based formulas; food ingestion following a period of avoidance results in the symptoms of acute FPIES	Food ingested on an intermittent basis, or following a longer period of avoidance
Onset of symptoms	Intermittent vomiting without clear temporal association with food ingestion, chronic diarrhea that may contain blood or mucous; may lead to weight loss or failure to thrive	Typical onset of vomiting in 1–3 h following food ingestion, accompanied by pallor, lethargy; may be followed by diarrhea in 5–8 h in some patients
Symptoms and signs	Intermittent vomiting	Repetitive, vomiting (95–100 %)
	Diarrhea	Lethargy (75–85 %)
	Lethargy	Pallor
	Pallor	Dehydration
	Weight loss	Diarrhea (25–40 %)
	Failure to thrive	
	Severe	*Severe*
	Bilious vomiting	Repetitive, projectile vomiting,
	Bloody diarrhea	up to 10–20 times
	Abdominal distention	Bilious vomiting
	Dehydration	Bloody diarrhea
	Limpness	Abdominal distention
	Dusky appearance	Limpness
		Dusky appearance
		Hypotension (15–20 %)
		Temperature <36 °C
Laboratory findings	Anemia	Neutrophilia >3,500 cells/ml
	Hypoalbuminemia	peaking at about 6 h
	Leukocytosis with left shift	Thrombocytosis >500 × 10^9/l
	Eosinophilia	Elevated gastric juice leukocytes >10/hpf at 3 h (research setting)
	Metabolic acidosis	Metabolic acidosis
	Methemoglobinemia	Methemoglobinemia
	Stool reducing substances	Fecal leukocytes and eosinophils

direct introduction of milk or soy is delayed, e.g., because of breastfeeding, initial reactions may begin after the first year of age. Solid food FPIES includes grains (rice, oats, barley, corn), meat and poultry (beef, chicken, turkey), egg white, vegetables (white potato, sweet potato, squash), fruit (tomato) and legumes (peanut, green pea, lentil, string bean) [27]. It usually occurs within several days after the solid foods are introduced. It is not uncommon for the parents to report that the solid food was initially tolerated fine for several sequential feedings; however, when feedings were interrupted for several days or weeks, subsequent ingestion resulted in acute FPIES reaction. FPIES to seafood (fish, crustaceans, molluscs) may occur in older children and adults [28].

Diagnosis

The NIAID Food Allergy Guidelines recommend using the medical history and oral food challenge (OFC) to establish a diagnosis of FPIES [1]. When the history indicates that infants or children have had experienced hypotensive episodes or multiple reactions to the same food, a diagnosis may be based on a convincing history and absence of symptoms when the causative food is eliminated from the diet. The original diagnostic criteria as proposed by Powell included: (1) exposure to the incriminating food elicits repetitive vomiting and/or diarrhea within 4 h, without any other cause for the symptoms; (2) symptoms are limited to the gastrointestinal tract; (3) avoidance of the offending protein from the diet results in resolution of symptoms; (4) a standardized OFC or isolated re-exposure elicits the typical symptoms [7]. An International Working Group on Consensus Guidelines for FPIES has been formed under the auspices of the AAAAI Adverse Reactions to Food Committee and the International Association of Food Protein-induced Enterocolitis in 2013. The Expert Panel is working on evidence-based guidelines for the diagnosis and management of FPIES to improve the care provided for patients with FPIES.

There are no pathognomomic laboratory or radiographic findings specific to FPIES. An elevated white blood count with left shift (peaking at 6 h after food ingestion and after the onset of the first symptoms) and methemoglobinemia following food ingestion support diagnosis of FPIES.

Food-specific IgE and/or skin prick testing may be performed to provide complete evaluation for food sensitization, particularly when considering a food challenge. Though the majority of patients with FPIES have undetectable serum IgE at the time of diagnosis, 18–30 % of FPIES patients may develop IgE mediated food sensitivity to the same food at some point during their course, with some developing immediate type symptoms of classic IgE-mediated food allergy [8, 24, 29].

Gastric juice leukocytosis at 3 h after a food challenge and atopy patch testing with fresh foods (APT) have been investigated in FPIES patients [30–33]. However, the results are equivocal, and therefore their diagnostic utility remains unclear and they are not recommended for routine evaluation of FPIES [1, 26].

Delays in Diagnosis/Misdiagnosis in FPIES

Infants with FPIES often present with multiple reactions and undergo extensive evaluations before the diagnosis of FPIES is considered [3, 24, 25]. Diagnostic tests include sepsis workup, abdominal imaging, electrocardiograms and electroencephalograms. In one case presenting with severe abdominal distension, an exploratory laparoscopy was performed [34]. Delays in diagnosis of infants with FPIES may be due to the non-specific nature of the symptoms FPIES patients are experiencing, lack of classic allergic skin and respiratory reactions, broad differential diagnosis (anaphylaxis and allergic gastrointestinal disorders, infections, metabolic disease, gastrointestinal obstruction, inflammatory bowel disease, neurologic disorders), relative lack of knowledge among physicians and, in the case of FPIES to solid foods, the perception that grains and vegetables are hypoallergenic as they rarely cause IgE-mediated food allergy [35, 36].

Oral Food Challenge in FPIES

The physician-supervised OFC remains the gold standard for an initial diagnosis of FPIES as well as for monitoring the resolution of FPIES [1]. The OFC is usually done in an open manner under physician supervision in a facility appropriately equipped for managing dehydration and allergic reactions (Table 2) [37]. In our practice, a peripheral intravenous line is placed before the challenge to secure immediate access for rapid intravenous fluid rehydration. The baseline complete blood count with differential is obtained immediately before the challenge [2•]. The challenge food amount is based on the food protein content (maximum 3 g of protein or 10 g of food or 100 ml of liquid food) and administered in three equal portions over 30 min, followed by a minimum 4 h of observation prior to discharge (Table 2). Patients who tolerated the challenge without any symptoms are usually discharged 4 h after eating the last portion of the challenge food; a post-challenge blood sample is obtained for a complete blood count with differential at 4 h. Patients who reacted to the challenge are usually discharged when 6 h have passed since ingestion of the food and their symptoms have resolved. A post-challenge blood sample is obtained for a complete blood count with differential at 6 h post challenge to calculate the increase in peripheral blood neutrophils, which is one of the major criteria for challenge positivity, as proposed by Powell (Table 2) [7]. In recent experience, diarrhea is seen in 20–40 % of the patients [24, 25, 38]. In addition, the magnitude of the neutrophil count increase during the challenge seems to be less than 3,500/cu mm. These observations suggest that criteria for challenge positivity should be updated and revised based on observations from a large number of food challenges. The initial criteria were established based on the outcomes of 14 challenges in 9 infants with median age of 36 days who had just recently removed the offending food from their diet and who were clearly at the peak of their disease [6, 7]. In our clinical practice, we do not perform challenges in infants. The challenge is usually delayed by 12–18 months from the most recent FPIES-like reaction; therefore, the magnitude of the inflammatory response could be lower. Cooperative efforts

Table 2 Oral food challenge in FPIES

Basic requirements	Physician supervision Secure peripheral intravenous access Immediate availability of fluid resuscitation
Baseline laboratory tests	Peripheral neutrophil count (CBC with differential)
Challenge administration	Food amount is calculated as 0.06–0.6 g[a]/kg body weight in three equal doses, generally not to exceed total 3 g protein or 10 g of total food (100 ml of liquid)
	Food is divided in 3 equal portions and fed over 30 min if food-specific IgE is negative
	Modification of the challenge and more incremental dosing is used for patients with positive food-specific IgE
Treatment of the reaction	Fluid resuscitation: 20 ml/kg intravenous boluses of normal saline
	Steroids: methylprednisolone 1 mg/kg intravenous, max 60–80 mg
	A majority (>50 %) of positive challenges require treatment with intravenous fluids and steroids
	The role of intravenous ondansetron in the management of acute FPIES reactions is being currently evaluated
	Epinephrine and antihistamines are not effective in FPIES for managing vomiting but epinephrine and vasopressors may be indicated for hypotension
Post-challenge laboratory tests	Peripheral neutrophil count [CBC with differential]: at 6 h if the patient reacted or at discharge if the patients tolerated the challenge
	If stool sample available: test for occult blood and stool smear for leukocytes
Post-challenge observation	About 6 h after the resolution of symptoms or 4 h after feeding in case of no symptoms

[a] Lower initial challenge doses are used for patients with history of severe reactions. Four hours after an asymptomatic feeding with a low initial dose (0.06 g protein/kg body weight), a full challenge dose can be administered (0.6 g protein/kg body weight), followed by 4–6 hour observation prior to discharge

among the centers providing the challenges for patients with FPIES are needed to standardize the challenge criteria.

Management

Management of acute and chronic FPIES consists of dietary food elimination, supportive therapies for acute and chronic FPIES on presentation, and providing an emergency treatment plan for episodes due to accidental exposures [2•]. Children are re-evaluated periodically and oral food challenges are repeated every 12–18 months to evaluate for resolution (Fig. 1). This is an empiric approach and shorter intervals between the food challenges may be appropriate for individual patients.

Infants with suspected FPIES to cow or soy milk protein should strictly avoid all forms of the inciting food, including baked and processed foods. They may either exclusively breastfeed or start a casein hydrosylate-based formula. Ten to 20 % may require an amino acid-based formula [3, 39]. Infants with chronic FPIES usually return to their usual state of health within 3–10 days of switching to a hypoallergenic formula; infants with acute FPIES reactions generally recover rapidly with rehydration alone [6, 7].

For the rare cases of FPIES in breastfed infants, breastfeeding mothers should eliminate the suspected trigger food(s) from her diet. For infants with FPIES to one solid food, in our practice we recommended delaying introduction of grain, legumes, poultry, as well as cow and soy milk until the first year because of the high rate of FPIES to multiple foods [2•, 40].

On presentation, the first line in management of FPIES is vigorous intravenous hydration, usually a 10–20 ml/kg bolus of normal saline, repeated as needed. The second line includes a single dose of intravenous methylprednisolone (dosed at 1 mg/kg, with a maximum of 60–80 mg) in order to decrease presumed cell-mediated inflammation [37]. A recent small case series highlighted the effectiveness of intravenous ondansetron for stopping emesis during FPIES OFC [41•]. In severe reactions, patients may need other supportive therapies including supplemental oxygen, vasopressors, bicarbonate and methylene blue for methemoglobinemia. Epinephrine and antihistamines do not appear to stop emesis in acute FPIES [28].

Emergency treatment plans outlining clinical features and management of acute reactions should be provided to patients with FPIES (a template can be accessed on the

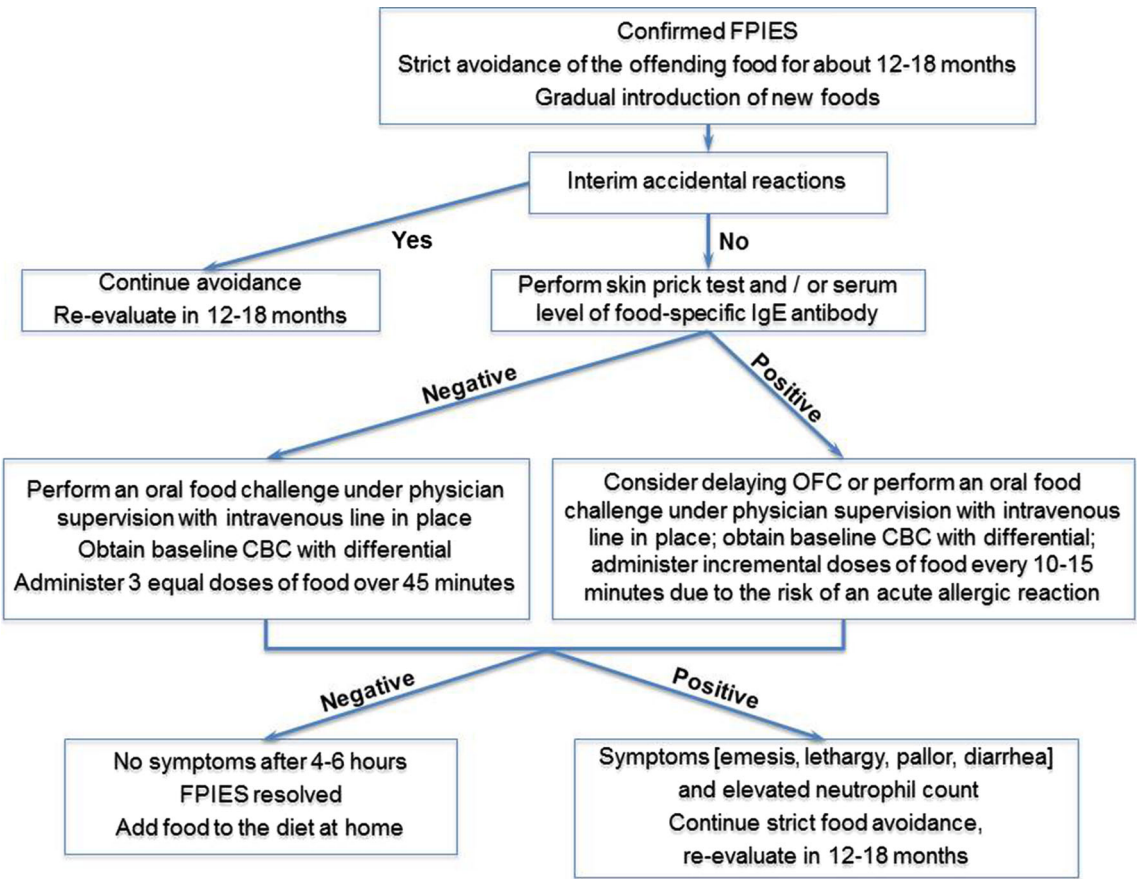

Fig. 1 An empiric management algorithm for FPIES in children

International Association for Food Protein Enterocolitis website, http://iaffpe.org/docs/Emergency_Plan.pdf). Mild reactions may be managed with careful oral rehydration at home. Infants with more severe reactions require resuscitation in the emergency department or inpatient unit (see "Acute episode" above).

Natural History of FPIES

Age of resolution of FPIES varies widely depending on the type of food, the country and the population studied. For CM-FPIES, resolution rates by age 3 years range from about 50 % in a US referral population to 90 % in an Israeli population-based birth cohort [3, 19••]. For soy FPIES, resolution rates range from 25 % by age 3 years in a US referral population [5] to 90 % by age 10 months in a Korean cohort [3, 19••, 38]. For solid food FPIES, a retrospective study in Italy reported a resolution rate of 48 % by 29 months of age [25]. In US referral populations, resolution rates range from 40 % for rice, 66 % for oats and 67 % for vegetables by 3 years of age [3]. These differences could be explained by the more severe FPIES phenotype reported from the referral allergy clinic in the US compared to the milder phenotypes among the children with FPIES from a general population.

Taking into account the average age of resolution, in our practice we usually recommend OFC to trigger foods every 12–18 months after the first year of life along with testing to evaluate for the development of food-specific IgE [2•, 8] (Fig. 1). Though the majority of FPIES patients have negative food-specific serum IgEs and skin prick tests at diagnosis, those with positive IgE tests tend to have a more protracted course and are at risk for developing IgE-mediated food allergy [8].

Pathophysiology of FPIES

T Lymphocyte-mediated Immune Response

The mechanisms underlying FPIES remain poorly characterized. FPIES is often considered to be a T cell-mediated disorder; however, few studies have investigated T cells in FPIES. There is some evidence of T cell proliferation upon stimulation with food antigens; however, the stimulation index is not consistently different from control, non-allergic subjects [42–47]. T-cell activation by food allergens may mediate local intestinal inflammation through the release of proinflammatory cytokines, e.g., TNF-α and IFN-γ, causing increased intestinal permeability and fluid shift that is thought to underlie the pallor, poor perfusion, hypothermia and methemoglobinemia [48]. Local inflammation may be mediated by activated peripheral mononuclear cells, increased TNF-α and decreased expression of TGF-β receptors in the intestinal mucosa [44, 49–51]. However, baseline antigen absorption is normal in FPIES [52]. Acute FPIES reactions seem to be associated with a Th2 skewing of the T cell cytokine profile, in keeping with the classical IgE-mediated allergic reactions to foods. An increase in IL-4 and decrease in IFN-γ expression in peripheral blood T cells has been shown after a positive oral challenge. After tolerance had been acquired, IFN-γ and IL-10 increased significantly [48].

Neutrophils, Platelets and Eosinophils

Powell reported leukocytosis with a left shift as a common finding for patients presenting with acute FPIES and included it as one of the diagnostic criteria. In the Powell study, peripheral blood neutrophil counts were elevated in all positive challenges, peaking at 6 h with a mean increase of 9,900 cells/μl [6, 7]. These results were confirmed by subsequent studies [8, 9]. Neutrophils have also been found in stool mucous of FPIES patients and in the gastric juice aspirate. This increase in peripheral neutrophils is likely due to the acute inflammatory reaction of the gastrointestinal tract leading to secretion of different cytokines (TNF-α) and chemokines.

Thrombocytosis was recorded in 63 % of episodes in a report from Australia [24]. One possible explanation for this acute thrombocytosis is a response to epinephrine induced by stress, which can shift platelets from the spleen into the circulation. The potential active contribution of neutrophils and platelets in FPIES pathophysiology requires further investigation.

Eosinophils reside in the GI tract, except in the esophageal squamous mucosa. Eosinophil accumulation in the GI tract is commonly found in many GI disorders, including eosinophilic gastroenteropathies, food-induced proctocolitis as well as classic IgE-mediated food allergy, inflammatory bowel diseases and gastroesophageal reflux [53]. Eosinophil inflammation has been found in intestinal biopsies from infants with FPIES [50]. In FPIES with chronic diarrhea, eosinophils and Charcot-Leyden crystals were detected with Hansel's stain in stool samples. Blood eosinophilia may be present in conjunction with or independent of eosinophil accumulation in the GI tract. These findings, however, are not specific for FPIES.

Humoral Immune Responses

Humoral responses are poorly characterized in FPIES. Since FPIES is a GI-food allergy disorder and considering the importance of IgA in mucosal immunity, impairment in IgA production or secretion might play a role in FPIES pathophysiology. This is supported by the epidemiological observations that FPIES occurs predominantly in cow's milk-formula-fed infants, and it is extremely rare in

exclusively breastfed infants [22]. It is not clear how exclusive breastfeeding prevents FPIES, but it has been hypothesized that breast milk IgA, either alone or as a complex with secreted antigens, may play a protective role [54]. However, there are only a few, small studies in which the potential role of IgA in FPIES has been examined [20, 42]. In a study by McDonald et al. [20], children with FPIES to cow's milk had comparable levels of serum milk-specific IgA levels to children with FPIES to other foods. Similar results were observed in the infants with FPIES to egg and soy. These studies also reported near absence of serum allergen-specific IgG4 in FPIES. IgG4 antibodies fix complement poorly and have a protective role in competing with other antibody subclasses that activate complement. The relative lack of IgG4 in FPIES patients may be involved in the pathogenesis of this disorder. However, these are findings from the peripheral blood and not from the GI tract. Jejunal biopsies reveal increased numbers of IgM- and IgA-containing plasma cells [50, 55], but it is unclear how this increase affects antibody secretion in the GI tract.

Systemic food protein-specific IgE antibody responses are usually absent in FPIES [3, 8]. However, if skin tests are positive to the trigger food, case series suggest that these patients have a decreased probability of developing tolerance to the implicated food. The relationship between IgE and non-IgE mechanisms in FPIES requires further investigation. The gastrointestinal inflammation caused by FPIES could enhance penetrability of food proteins and their presentation to the immune system with subsequent generation of food-specific IgE antibodies. Conversely, local intestinal mucosal IgE antibodies could facilitate antigen uptake and intestinal inflammation.

Neuroendocrine Pathways

A recent case series of children with FPIES successfully treated with intravenous ondansetron during the supervised OFC raised questions about the role of serotonin signaling in FPIES [41•]. Ondansetron is a serotonin 5-HT_3 receptor antagonist used mainly to treat nausea and vomiting, often following chemotherapy but also in viral gastroenteritis. It reduces activity of the vagus nerve both peripherally and centrally. The effectiveness of ondansetron suggests the potential role of an impaired neuroendocrinologic pathomechanism in FPIES reactions and warrants further study.

Conclusions

FPIES represents a more severe spectrum of the non-IgE-mediated gastrointestinal food allergic disorders, with potential for hypothermia, methemoglobinemia, acidemia, hypotension and shock. Because of the delayed onset of symptoms and absence of classic allergic cutaneous and respiratory manifestations, the FPIES diagnosis is frequently delayed or missed. A low index of suspicion for the cereal grains, vegetables and fruit that have a low potential for inducing IgE-mediated reactions but are common triggers of FPIES also likely contributes to misdiagnosis. Management relies on food avoidance and symptomatic treatment of dehydration. The pathophysiology of FPIES remains obscure, and there are no biomarkers for diagnosis. While most patients with FPIES to cow's milk and soy resolve within the first 3–5 years of life, those with FPIES to solid food or with detectable systemic food-specific IgE tend to have a more protracted course. Studies documenting FPIES prevalence, natural history and pathophysiology are necessary to improve patient care and to develop evidence-based approaches to diagnosis and treatment.

Disclosure A. Nowak-Wegrzyn received research funding from NIAD, FARE, Nutricia and Nestle, and honoraria from Thermofisher Scientific and Nestle, served as board member for Merck and Stallergenes, and received royalties from UpToDate. George Konstantinou reports no conflict of interest.

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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