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REVIEW

Perspectives on Non-IgE-Mediated Gastrointestinal Food Allergy in Pediatrics: A Review of Current Evidence and Guidelines

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Abstract: Food allergy is an immune-mediated disease that can result in considerable morbidity and even mortality, with a significant negative impact on patients' quality of life. It is characterized by allergic symptoms that can occur shortly after a relevant food allergen ingestion, or can be delayed or chronic, which make it more difficult for diagnosis. The symptoms of this disease can range from mild to severe, and rarely can cause anaphylaxis, a life-threatening allergic reaction. The prevalence of non-immunoglobulin E (IgE)-mediated food allergy is poorly established outside of cow's milk allergy, with an adjusted incidence ranging between 0.13% and 0.72%. Several disorders are classified as non-immunoglobulin E (IgE)-mediated food allergies that predominantly affect the gastrointestinal tract including food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced allergic enteropathy (FPE), and food protein-induced dysmotility disorders (GORD and constipation). Eosinophilic esophagitis (EoE) is listed in this group, even though it considered by some authorities to be mixed reaction with both IgE and cell-mediated immune response to be involved in the reaction. The most common types of non-IgE-mediated food allergy are food protein-induced enterocolitis syndrome (FPIES) and food protein-induced allergic proctocolitis (FPIAP). These disorders typically present in infancy and are often triggered by cow's milk protein. Patients with FPIES present with profuse emesis and dehydration, while FPIAP patients present with hematochezia in otherwise healthy infants. Since there are no specific confirmatory non-invasive diagnostic laboratory tests, the diagnosis is usually made clinically when typical symptoms improve upon the removal of the culprit food. Food reintroduction should be attempted, when possible, with documentation of symptoms of relapse to confirm the diagnosis. The management includes dietary avoidance, supportive treatment in the case of accidental exposure, and nutritional counseling. This review focuses on the clinical manifestations, epidemiology, management, and recent guidelines of the most common non-IgE-mediated food hypersensitivity disorders (FPIES, FPIAP, and FPE).

Keywords: food allergy, allergic proctocolitis, protein-induced enterocolitis, food elimination

Introduction

Food allergy (FA) is characterized by an immune reaction to a particular food that can be triggered repeatedly. It can be categorized by pathophysiology into immunoglobulin E-mediated, non-IgE- mediated, or mixed IgE disorders (Figure 1). IgE-mediated reactions are the majority when it comes to food allergies; however, newborns and young children can suffer from non-IgE-mediated gastrointestinal food allergies. Presentation is often in infants with non-specific symptoms and signs, and because of lack of non-invasive reliable tests, diagnosis and treatment can be challenging.[1,2]

Non-IgE-mediated gastrointestinal food allergic disorders (non-IgE-GI-FA) are thought to be cell-mediated since they typically manifest many hours after eating the offending food and are accompanied by negative skin prick tests and absence of serum-specific IgE against the offending food.[1,3] These diseases are thought to be mediated by T helper cells and other activated lymphocyte populations, including cytotoxic CD8 T cells, unlike the classical pathogenesis of IgE-mediated food

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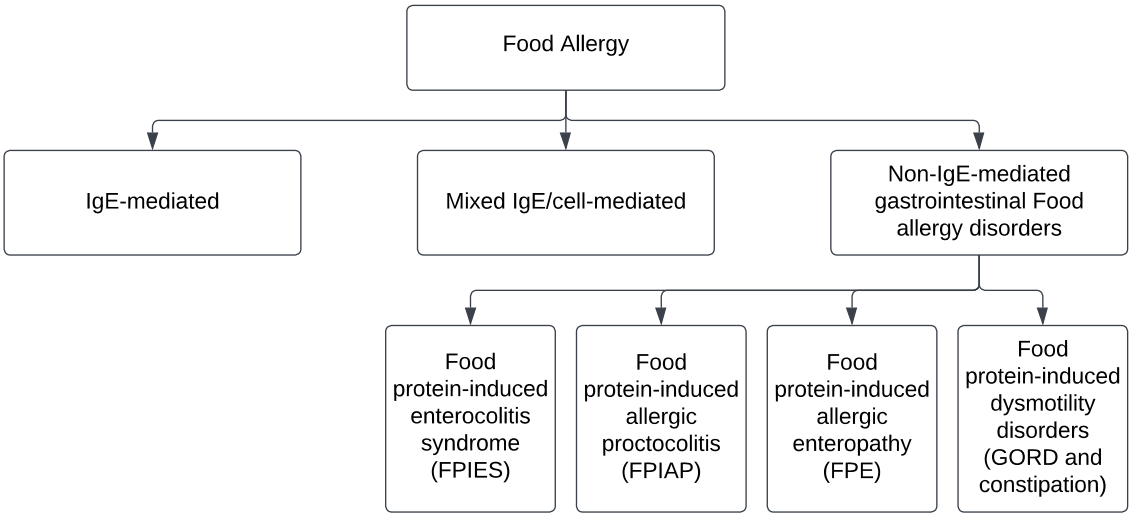

Figure 1 Classification of non-IgE-mediated food hypersensitivity.

allergy.[4–6] Non-IgE-mediated gastrointestinal food allergic disorders include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), and food protein-induced enteropathy (FPE).[4,7]

The diagnosis of non-IgE-mediated food allergy is typically based on the history of reproducible symptoms and signs following exposure to the offending food, due to the lack of specific biomarkers and non-invasive diagnostic tests. The mainstay of treatment is food avoidance and symptomatic treatment depending on the associated symptoms including vomiting and diarrhea that could lead to dehydration, lethargy, and hypotension.[3,8] In addition to the disease symptoms, parents of children with non-IgE FA disease often report lower quality of life and more challenges with feeding compared to those of children with IgE-mediated food allergy.[9,10]

Epidemiology

The prevalence and epidemiological features of non-IgE-mediated food allergies have not been well studied. However, available prevalence data suggest that these conditions are less common than IgE-mediated food allergies.[11]

There has been a recent interest in non-IgE-GI-FA knowledge and awareness around the world with FPIAP being the most frequent. A recent prospective study of 903 healthy infants found that, FPIAP incidence was 17% over 3 years, with the diagnosis being made by pediatrician caring for the infant; however, the diagnosis was not confirmed by re-introducing suspected food shortly after symptom resolution, as recommended.[12] During the first 2 months of life, infants who were fed a combination of breast milk and cow's milk-based formula or only breast milk had a lower risk of developing FPIAP compared to infants who were fed only formula, 61% and 53%, respectively.[12]

The cumulative incidence of FPIES in infants is predicted to be between 0.015% and 0.7%, although the population prevalence in infants in the United States is 0.51%.[13] The incidence of FPIES was reported to be 0.015% in Australian newborns, with rice being the most common food trigger.[14] However, a higher incidence 0.34% over a follow-up period of 2 years and 0.7% with an at least 18 months' follow-up has been reported.[15,16] According to a review of the epidemiology of FPIES, at the time of diagnosis, eczema and a family history of atopy are common, and with a slight male predominance.[17] FPIES is commonly diagnosed in infants. However, new-onset adult FPIES has been reported.[18] Nowak-Wegrzyn et al reported the first estimated prevalence of adult FPIES in the USA which was 0.22%.[19] Furthermore, González-Delgado et al reported the clinical characteristics of adult patients with FPIES where abdominal pain was the most common manifestation followed by diarrhea.[20]

FPE is relatively uncommon, affecting approximately a fifth of celiac patients, and it appears to be decreasing over time.[21] Over the past few decades, FPE incidence has generally decreased after its peak in Finland, in the 1960s, and instances brought on by cow's milk gradually disappeared after that.[21]

Food allergy has been reported to be higher in children with Down syndrome than seen in children without mental retardation.[22] Moreover, non-IgE-mediated gastrointestinal food allergy have been reported in children diagnosed with Down syndrome which is characterized by a severe long-lasting course.[23–25]

Clinical Manifestations and Diagnosis

FPIAP, FPIES, FPE

Diagnosing the cause of a child's gastrointestinal symptoms can be challenging due to the wide variety of symptoms and overlapping of the clinical features.[1] In addition, due to the lack of widely available, noninvasive confirmatory tests for most of non-IgE-mediated food hypersensitivity syndromes, accurate diagnosis of these disorders can be challenging.[2]

The diagnosis of non-IgE-GI-FA is based on the recognition of the symptoms pattern; therefore, it is necessary to pay attention to the history of gastrointestinal (GI) symptoms that vary with respect to their temporal relationship to food ingestion, severity, and natural history in order to differentiate between various causes. GI symptoms are usually subacute or chronic symptoms and delayed after exposure to foods with age of onset at 2–8 weeks of age and as early as first week.[26,27] Non-IgE-mediated food allergies typically manifest in the digestive tract, but can also manifest in other organ systems like the skin including contact dermatitis to foods and dermatitis herpetiformis and lungs including pulmonary hemosiderosis.[2,28] Symptoms could range from intermittent but progressive emesis that could lead to dehydration, diarrhea with or without blood, to failure to thrive (FTT) and nutritional deficiencies in severe cases.[2,27,28]

FPIAP represents the milder end of the spectrum; it is one of the most frequent causes of colitis in infants under 1 year of age and has a benign, transitory course.[4,29] It is characterized by intermittent moderate bloody stools that present as streaks of blood mixed with mucus in generally healthy infants with no effect on the growth and resolves by age 12 months in most of the cases.[4,27,30] The immune response occurs in most of the times in breastfed infants due to reaction to cow's milk allergy, soy, egg or wheat in maternal diet. Infant formulas containing cow's milk or soy can cause similar reaction.[31–33] Symptoms usually improve within few days after removal of the offending protein from maternal diet. However, complete resolution may be achieved after 2 weeks.[31] Although FPIAP has been thought to be a disease of infancy, it has been reported among older children; Ravelli et al in their case series, they described 16 patients aged 2–14 years who presented with a rectal bleeding that resolved with cow's milk protein elimination.[34] Furthermore, histologic findings of their endoscopic biopsies were consistent with FPIAP.[34] Odze et al reported that having 60 eosinophils/10 high-power fields in the lamina propria is enough to make the diagnosis in the vast majority of cases, even though the histopathological findings are not pathognomonic of the disease.[26]

FPIES is a severe form of non-IgE-mediated disorder that typically affects young infants and manifests as chronic emesis, diarrhea and failure to thrive with recurrent vomiting and dehydration upon re-exposure to the offending food.[4,27] Chronic FPIES develops if the food antigen is regularly taken, and it has been reported in infants with cow's milk and soya-based formula.[28] On the other hand, FPIES can has an acute manifestation as copious, repeated, projectile vomiting that begins 1–4 hours after eating the food and may accompany watery diarrhea that develops 5–8 hours later and may cause pallor, lethargy, dehydration, and/or hypovolemic shock.[28,35] The acute presentation of FPIES can mimic gastroenteritis, intussusception, sepsis, metabolic crisis, or even necrotizing enterocolitis.[36] The delayed diagnosis of FPIES due, perhaps, to little-to-lack of knowledge of pediatricians as shown in a survey done by Schultz and Westcott-Chavez[37] may lead to unnecessary medical investigations and frequent prescriptions of antibiotics compared to allergy-free infants.[38] Natural history of FPIES varies greatly depending on the study population, causal foods, and associated atopic disorders; nonetheless, the majority of children will outgrow FPIES by the age of 3 or 4.[39] Food triggers vary depending on the geographical origin, for example, the most frequent food triggers for infants in the US are cow's milk and soy, and as infants are introduced to solid foods, reactions to grains (rice, oat) become increasingly common.[35] However, in a recently published report from the east Mediterranean region, hen's egg (36.6%) was the most prevalent culprit food followed by fish (26.9%) and then cow's milk (21.5%).[40] An oral food challenge is the gold standard for diagnosis in cases of chronic FPIES and for which there is no clear history and no clear temporal link between symptoms and specific food intake.[41] However, it is not necessary for diagnosis in infants with typical characteristic signs and symptoms that improvement after elimination of the suspected trigger food. Although FPIES has been thought of as a disease that affects children, recent studies suggest that FPIES might

develop in older individuals.[11] Tan and Smith have reported 31 cases of acute onset of vomiting, diarrhea, and abdominal pain triggered by a specific food in patients older than 18 years.[42] Symptoms appeared 1–2 hours after food ingestion, lasted 1–3 hours and experienced on a median of two occasions with the suspected food.[42]

Patients with FPE or cow's milk-sensitive enteropathy usually depend on age of exposure to antigen. They usually complain of chronic diarrhea and malabsorption with steatorrhea, weight loss and failure to thrive that emerge soon after infants are exposed to cow's milk in the diet and improve when cow's milk is discontinued from the diet.[2,11,21,28,43] A close resemblance can be seen between these signs and those of celiac disease and post-enteritis syndrome.[2,43,44] A major difference between FPIAP patients and FPIES patients with acute symptoms, who usually do not need a biopsy, histologic confirmation of FPE necessitates a biopsy.[28] Eliminating the offending food causes symptoms to subside within 1–4 weeks, while the patchy villous atrophy continues months after there is apparent clinical improvement.[21]

Apart from the GI symptoms, non-IgE-mediated gastrointestinal food allergy is at risk of vitamin D insufficiency and deficiency.[45] In addition, it has been reported that it causes psychological distress not only to the child but also the parent QOL and family functioning was also observed to be worse in those families who had a child on an elimination diet for non-IgE-mediated allergies (Table 1).[46]

Table 1 Non-IgE-Mediated Allergic Disorders, Symptoms, and Differential Diagnoses (Taken from the European Academy for Allergy and Clinical Immunology Position Paper on the Management of Non-IgE-Mediated Allergies in Breastfed Infants)

Non-IgE-Mediated Food Allergy	Cardinal Symptoms	Additional Symptoms	Differential Diagnoses
Food protein-induced enterocolitis syndrome (FPIES)[3]	Acute FPIES: Vomiting 1–4 hours after ingestion Chronic FPIES: Intermittent but progressive vomiting and diarrhea	Acute FPIES: Pallor, lethargy, hypovolemia, hypotension, diarrhea Chronic FPIES: Faltering growth	Gastro-esophageal reflux disease, sepsis, inborn errors of metabolism, pyloric stenosis, malrotation, intussusception, gastroenteritis with vomiting
Food protein-induced allergic proctocolitis (FPIAP)	Blood in stool	Occasional loose stools, mucous in the stools, painful flatus, anal excoriation	Gastrointestinal infections, fissures Infantile polyp, necrotizing enterocolitis, Meckel's diverticulum, intussusception, infantile inflammatory bowel disease (rare)
Eosinophilic esophagitis (EoE)	Intermittent vomiting, abdominal discomfort, feeding difficulties	Faltering growth	Gastro-esophageal reflux of infancy, infantile inflammatory bowel disease
Food protein-induced constipation	Straining with soft stools	Fecal impaction, bloating, abdominal pain	Normal straining associated with infancy, idiopathic constipation, Hirschsprung's disease
Food protein-induced gastro-esophageal reflux disease	Intermittent painful vomiting/regurgitation	Faltering growth, feeding difficulties, back-arching with pain	Gastro-esophageal reflux of infancy, acute gastroenteritis, food poisoning
Food protein-induced enteropathy (FPE)	Failure to thrive, diarrhea	Mucus and, bloating, abdominal pain, faltering growth, hypoalbunemia	Sepsis, congenital disaccharide malabsorption, metabolic disorders, chronic kidney disease, neglect, secondary lactose intolerance, chronic FPIES, autoimmune enteropathies, epithelial dysplasia syndromes, cystic fibrosis, immunodeficiencies and/or chronic infection, coeliac disease

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Investigations and Biomarkers (Table 2)

Laboratory Findings

Laboratory tests can be helpful in supporting the diagnosis of non-IgE-GI-FA. In FPIES, blood testing may reveal anemia, thrombocytosis, high white blood cell count with left shift and hypoalbuminemia.[41] Patients with severe disease might develop metabolic acidosis and high levels of methemoglobin protein.[47] A promising diagnostic marker called thymus and activation-regulated chemokine (TARC) has been recently used.[48,49] It is a Th2 chemokine that is produced by fibroblasts, endothelial cells, and keratinocytes.[49,50] Although TARC is used to assess patients with atopic dermatitis, patients with symptoms of FPIES found to have an elevated level.[49,50] Makita et al have performed a longitudinal evaluation of TARC levels on FPIES patients which revealed a high level at 6 hours following the ingestion, and even higher level after 24 hours of the ingestion.[50] Therefore, they recommended TARC measurement after 24 hours for diagnosing FPIES.[50] In FPE, patients often develop iron deficiency anemia and hypoproteinemia,[51] which present in less than 15% of the patients with FPIAP.[32,52] Peripheral eosinophilia is a prominent feature in FPE and FPIAP and can be found in patients with FPIES.[52,53]

Table 2 Key Investigation Findings of FPIAP, FPIES, and FPE

	FPIES	FPIAP	FPE
Blood tests findings			
Low hemoglobin level	Moderate	Mild, infrequent	Moderate
Low albumin level	Acute	Mild, infrequent	Moderate
Malabsorption	Absent	Absent	Present
Leukocytosis with neutrophils	Prominent	Absent	Absent
Allergy evaluation			
Food skin prick test	May be positive in up to 30%	Negative	Negative
Serum food-allergen IgE	May be positive in up to 30%	Negative	Negative
Total IgE	Normal or high	Normal or high	Normal
Peripheral blood eosinophilia	Absent	Occasional	Absent
Biopsy findings			
Villous injury	Patchy, variable	Absent	Variable, increased crypt length
Colitis	Prominent	Focal	Absent
Mucosal erosions	Occasional	Occasional, linear	Absent
Lymphoid nodular hyperplasia	Absent	Common	Absent
Eosinophils	Prominent	Prominent	Few
OFC			
	Vomiting, lethargy, pallor in 1–6 h; diarrhea in 5–8 h	Rectal bleeding in 6–72 h	Vomiting and/or diarrhea in 40–72 h

Note: Adapted from Connors L, O'Keefe A, Rosenfield L, Kim H. Non-IgE-mediated food hypersensitivity. Allergy Asthma Clin Immunol. 2018;14(Suppl 2):56. doi:10.1186/s13223-018-0285-2. Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).[2]

Stool Studies

Stool studies results including eosinophils, neutrophils, reducing substances, and Charcot–Leyden crystals can be nonspecific in patients with FPIES.[41] Other stool testing such as occult blood was used to help in diagnosing FPIES but found to be non-specific as it can present in other diseases such as FPIAP.[12] Fecal calprotectin which indicates inflammation of the gut mucosa can be elevated in patients with FPIAP and FPIES.[54,55] However, data are scarce, and unavailability of validated normal ranges for infants makes its utility in diagnosing these conditions limited.[56] Therefore, the routine use of stool tests is not recommended.[56]

Endoscopic Evaluation and Biopsy

This test is used to support the diagnosis of FPE. Histology findings include jejunal villous atrophy, crypt hyperplasia and inflammation. These findings tend to be less severe than those seen in celiac disease.[57,58] Biopsy is not indicated in FPIES and FPIAP unless there is uncertainty in the diagnosis. However, biopsies were taken from patients with FPIAP shown eosinophilic infiltration in the lamina propria and epithelium.[2] Furthermore, multiple biopsies might be necessary because FPIAP is often a patchy disease.[59]

Allergy Testing

This includes skin prick testing and the detection of serum food-specific IgE, which are usually negative. These tests are not requested for patients with non-IgE-mediated food allergy, unless there are associated severe atopic dermatitis or immediate allergic reaction to ingested food.[3,43] However, approximately 25–30% of the patients with FPIES can have atypical FPIES and might develop IgE to the food trigger.[2,43,60] Hence, these patients are under risk of developing significant allergic reaction to the culprit food; therefore, allergy testing may be considered prior to OFC to exclude atypical FPIES.[43,61] Recent studies suggest higher rate of atypical FPIES than previously reported rates; in the USA, it has been found to be 24% of 160 patients[27] and 33% of 52 patients in the UK.[62]

Oral Food Challenge Tests (OFC)

The OFC is considered the gold standard to diagnose FPIES, FPIAP, and FPE after symptoms resolution under dietary elimination. In addition, it is performed to assess the development of tolerance to the culprit food.[2,27] In FPIES, OFC should be supervised by a physician in an appropriately monitored situation because of potential severe reactions occurrence and need for intervention. While in FPIAP and FPE, reintroduction of trigger food 4–8 weeks after elimination can safely be performed at home.[2]

Management

Elimination Diet

The mainstay of the management of non-IgE-mediated food allergy is the removal of offending foods from the diet. Identification of triggers relies on clinical history. Cow's milk is the most common trigger for FPIES, FPIAP, and FPE.[43] An oral food challenge is recommended when an infant's history is unclear, such as the absence of a clear trigger, atypical symptoms, or lack of resolution with trigger food elimination.[63] The most common approach is to avoid causal foods without broad restrictions. Avoiding a wider variety of foods may be considered in severe cases of FPIES, when failure to thrive, and dehydration are present. For such cases, it is recommended to begin with an elemental diet, then be sequentially introduced to new foods while being closely monitored for the recurrence of symptoms.[43] It is usually unnecessary to avoid products with precautionary labeling (eg, "can contain traces of").[41] While most children with IgE-mediated allergies tolerate baked products, there is limited data to support tolerance to baked food in patients with FPIES.[28] In a multicenter, retrospective research included 61 children with egg FPIES, the average time to achieve tolerance to cooked egg was reported to be 30.2 months, and 43.9 months for raw eggs.[64] While guidelines suggest strict avoidance of triggers, some patients have tolerated baked products. Tolerance is preferably established under a physician's supervision.[28] Breastfeeding is recommended in FPIES and routine maternal dietary elimination of triggers is not recommended; unless if an allergic reaction occurs after breastfeeding, or/and exclusively breastfed infants are

failing to thrive.[65] In cow's milk/soy-induced FPIES, extensively hydrolyzed (eHF) or amino acid-based formulas (AAF) have been recommended.[65,66] As cross-reactivity between cow's milk and soy-based formulas is low, such that soy-based formula can be considered as an alternative for feeding infants with cow's milk allergy and FPIES who are over 6 months of age.[15] As more infants with non-IgE-mediated than IgE-mediated cow's milk allergy react to eHF, which is likely due to residual cow's milk protein; it was suggested by many experts that hydrolyzed rice formulas can be recommended as a first-line alternative to cow's milk-based eHF or AAF, where available, in the dietary management of infants with cow's milk allergy.[67] When a diagnostic elimination diet is indicated, hydrolyzed rice formula can be used.[67]

Most exclusively breastfed infants with FPIAP respond to the maternal elimination of milk products. Cow's milk elimination does not typically resolve FPIAP caused by other triggers, such as eggs, which can be removed from the maternal diet.[63] The European Academy of Allergy and Clinical Immunology (EAACI) recommends 2–4 weeks of maternal elimination diet, followed by an attempt to re-introduce food to confirm the diagnosis.[68] Clinical bleeding typically resolves within 1–2 weeks with the elimination of the offending item from the mother's diet. Most cases resolve within 72–96 hours; however, if symptoms prolong for at least 2 weeks, it is necessary to check the mother's adherence and, if necessary, eliminate soy and egg from the diet.[69] Occasional recurrence of bleeding is common in breastfed infants, most likely due to small intakes of triggering protein. If bleeding is infrequent, small in amount, and self-limited, then no further intervention is needed, and the mother can maintain the current level of dietary restriction.[69] Some have suggested a "watch-and-wait" approach for a month before starting an elimination diet.[70,71] The infant and mother can continue a regular diet without elimination if asymptomatic. Twenty percent of the patients with FPIAP are thought to resolve without maternal dietary elimination spontaneously.[70,71] In those with symptoms for over a month, hemoglobin levels should be assessed.[43] Some infants, about 12%, continue to have persistent bleeding with changes in the maternal diet.[69] Moreover, Lozinsky et al found that the majority of children with non-IgE-mediated allergy had improvement of symptoms within 4 weeks; however, data were mainly based on non-breastfed children.[72]

When exclusive breastfeeding is not possible or failure of symptom resolution when dairy (±soy) is eliminated from the maternal diet, guidelines recommend extensively hydrolyzed formula (EHF) for mild cases and amino-acid-based formula (AAF) for severe cases. AAFs are recommended when symptoms do not resolve with EHF, failure to thrive, multiple food allergies, and eosinophilic esophagitis.[73,74] The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) recommended avoiding soy-based formulas due to a high risk of co-reactivity with cow's milk. In addition, there are concerns based on animal data regarding the phytoestrogen content in soy-based formula and the potential risk for infants, especially premature and infants with congenital hypothyroidism (CH).[75] Therefore, soy-based formula is not recommended before the age of 6 months in infants with cow's milk-induced FPIES who are premature or diagnosed with CH.[65] Soy formula can be used in infants older than 6 months if EHF is not tolerated, is too expensive, or guardian preferences (vegan diet).[76] It is recommended to re-introduce the offending food to the mother or infant's diet after 6 months of elimination or at 12 months of age.[69] In cases of failure, the trigger should be removed, and new attempts can be made after 6 months.[43] There is currently insufficient evidence to recommend the routine use of formulas enriched with pre/pro/postbiotics and synbiotics in managing children with cow's milk allergy.[77,78]

Most infants outgrow FPIAP by 1 year and can ingest food without restriction.[79] Infants with uncomplicated FPIAP may not require an allergy referral. However, further evaluation may be warranted if the trigger cannot be identified, or symptoms do not resolve with trigger elimination. Sigmoidoscopy or colonoscopy with biopsies may be necessary for patients that require further evaluation. They are recommended for patients with atypical symptoms, severe rectal bleeding, or anemia despite a cow's milk elimination diet trial.[69] FPIAP is a benign transient medical condition; however, in small percentage of patients, resolution of the allergy can be delayed up to age of 3 years.[52,70] Therefore, an evaluation of late tolerance risk factors can help reduce the stress of long-term maternal dietary elimination.[52] Cetinkaya et al in their prospective study that included 185 infants with FPIAP, non-IgE-mediated multiple-food allergies, using cow's milk formula before the symptoms emerged, concomitant IgE-related food allergy, and delay in timing of complementary feeding were reported as predictors for late tolerance development.[18]

Acute Management

FPIES

Management of acute FPIES reactions is based on the severity of symptoms. Oral rehydration and close monitoring for 4–6 hours at home are suggested for mild symptoms. For moderate-to-severe symptoms, emergency care or hospitalization may be required.[41] Acute FPIES can cause dehydration, leading to hemodynamic instability and a medical emergency. Aggressive isotonic fluid resuscitation may be required (10–20 mL/kg boluses of normal saline). In severe reactions, patients may require supplemental oxygen or mechanical ventilation for respiratory failure, vasopressors for hypotension, bicarbonate for acidemia, and methylene blue for methemoglobinemia.[41] Epinephrine autoinjectors are not recommended for FPIES unless the patient has an IgE-mediated allergy and is at risk for food-induced anaphylaxis. IV corticosteroids (methylprednisolone 1 mg/kg; maximum 60–80 mg) can be considered for severe reactions, although efficacy has not been established.[63] Ondansetron, a 5HT3 receptor antagonist with an anti-serotoninergic effect, can be considered. Ondansetron can reduce or prevent nausea and vomiting and the development of diarrhea.[80] It is recommended to administer 0.1–0.15 mg/kg IV or intramuscularly.[80] There is a lack of studies comparing ondansetron parenteral vs enteral route for FPIES-induced emesis. Although current data suggest that intravenous and intramuscular ondansetron forms have better efficacy, it is impractical in the home setting.[81] The International FPIES Association suggested in 2020, during the coronavirus disease 2019 (COVID-19 pandemic), to consider prescribing oral ondansetron to be used at home in case of an acute reaction.[81] After an acute episode, an emergency treatment plan that includes diagnosis and management should be provided to patients and parents that can be shown to physicians in emergencies. Educating caregivers is vital to avoid misdiagnosis of future episodes. Discussions should include the elimination of offending food protein, breastfeeding, formula choice, and time of reintroduction of the offending food.[80]

FPIAP

Generally, patients with FPIAP have normal physical examination and blood testing. No acute intervention is usually required.[63]

Long-Term Management

FPIES

Primary management consists of eliminating the trigger food from the infant's diet (Table 3). Clinical history often helps identification of the trigger food. In contrast to FPIAP, FPIES is rare in breastfed infants. Most infants with FPIES tolerate allergens through breastfeeding without needing a maternal elimination diet.[82] Breastfeeding is encouraged, and maternal avoidance of the allergen is not recommended. Extensively hydrolyzed formulas are recommended for FPIES

Table 3 Food Triggers for FPIES, from Most to Least Common

Food Category	Specific Food	Rates (%)
Milk		67
Soy		41
Grains	Rice>Oat>Wheat>Corn>Barley	25.3
Egg		11
Meats/Fish	Chicken>Turkey>Beef>Pork>Lamb>Salmon>Crab	<10
Vegetables	Sweet potato>Pea>Potato>Carrot>Squash>Kidney bean>Green bean	<10
Fruits	Banana>Apple>Pear>Peach>Plum>Strawberry>Watermelon>Avocado	<10
Peanut/Tree nut	Peanut>Tree nut	<10

Note: Data from Ruffner et al.[61] Used with permission of Oxford University Press - Journals, from Non-IgE-mediated food allergy: Evaluation and management, Canadian Paediatric Society, 26, 3, 1996; permission conveyed through Copyright Clearance Center, Inc.[63]

patients who can no longer breastfeed, have mild-to-moderate symptoms, and in the absence of faltering growth.[76] It is recommended to initiate with EHF, and if failing to resolve symptoms within 2 weeks, to switch to AAF.[80] For patients with severe symptoms, such as failure to thrive, AAF is the optimal initial choice.[80]

For exclusively symptomatic FPIES occurring in breastfed infants, a maternal elimination diet of suspected trigger food should be implemented if reactions occur after breastfeeding or if an infant has failure to thrive.[41] The mother should consult with an allergy specialist and dietician. A hypoallergenic formula should be considered if a maternal elimination diet does not resolve symptoms.[41]

There is no diagnostic testing for FPIES other than an oral food challenging test (OFCs), which would be recommended if the history is uncertain for a clear trigger food, or no symptom resolution with trigger food avoidance.[41] OFCs for FPIES are recommended every 12–18 months after the latest reaction to determine if the allergy has resolved.[43] OFCs should be done periodically to evaluate if the patient has developed tolerance to offending foods. For patients with FPE or FPIAP, foods can be gradually re-introduced at home. In FPIES, foods should be re-introduced under medical supervision due to the risk of hemodynamic instability.[2]

For complementary feeding in FPIES, guidelines suggest introducing low-risk foods such as fruits and vegetables.[41] Foods of different colors, textures, and flavors should be continuously offered to avoid aversive feeding behaviors. It is recommended that caregivers introduce a new food as a single ingredient and wait at least 4 days before introducing another food to observe for development of a reaction.[41] Iron-rich foods should also be encouraged as FPIES patients are vulnerable to anemia.[83] The success of an elimination diet will depend on working with a dietitian, parental resources, number of allergens to avoid. Patients can benefit from nutritional guidance to avoid nutritional deficiencies like calcium, iron, and vitamin D.[80] A multidisciplinary approach in management that includes an allergist, dietician, nutritionist, and psychologist is the most successful way to ensure the growth and health of patients.[84]

FPE

Management of FPE is the elimination of the offending food(s), which results in disease resolution within a few weeks.[28] EHF is the most appropriate formula choice with proved efficacy and cost-effectiveness.[85] However, if there is a severe reaction, failure to thrive or multiple allergies, then AAF should be considered.[28,86] Infants should be rechallenged at 12 months of age, and most cases resolve within 1–3 years of age.[28]

Tolerance Induction Strategies in Food Allergies

Oral tolerance induction has been explored in the contexts of prevention and treatment of food allergy. Early introduction of allergenic foods (ie, egg and peanut) in the diet of infants, before allergic sensitization occurs, has shown to be beneficial. Guidelines have changed to recommend the introduction of these allergenic foods by 6 months of age.[87]

Although some guidelines suggest delaying introduction of additional common allergens empirically to prevent FPIES, this approach is not recommended.[88] Because IgE-mediated food allergy is more prevalent and generally more difficult to outgrow, the risk of developing an IgE-mediated allergy to foods such as peanut or egg outweighs the benefit of delayed introduction to manage or prevent FPIES. Rather, introducing commonly allergenic solids at around 6 months of age (and not before 4 months), especially if the child is at risk for IgE-mediated allergy, is recommended.[88]

Tolerance induction strategies in food allergies through immunomodulatory treatments (like food oral immunotherapy (OIT), sublingual or epicutaneous immunotherapy) have been studied, but mainly in the context of Ig-mediated food allergy. So far, the efficacy of immunomodulatory treatments has been variable, with actual oral tolerance induction achieved in only a small proportion of allergic patients and side effects hampering further development or patients' adherence to existing options. It remains to be proven whether immunotherapy can lead to long-term oral tolerance, where individuals may consume the food at any frequency in any amount without developing any allergic symptoms. A greater understanding of the immune mechanisms involved in food allergy and oral tolerance may lead us to a better efficacy and safety profile for future disease-modifying therapeutic approaches.[87,89]

Prognosis

The prognosis of FPIES, FPIAP, and FPE is generally good, with most of patients achieving tolerance during early childhood.[2] Patients with acute FPIES usually resolve within a few hours of rehydration. Patients with chronic FPIES improve within a few days to 2 weeks. The overall remission rate of FPIES ranges between 50% and 90% by the age of 6 years.[11] Atypical FPIES patients are at a considerable risk of developing IgE-mediated food reaction and can have a more protracted course.[90] Symptoms related to FPIAP, generally improve within 3 days of food elimination, but stool may completely normalized after 2 weeks.[31]

On the other hand, FPE-related symptoms, in comparison to FPIES and FPIAP, take longer time to completely resolve. Malabsorption resulted from villous injury can serious and can take weeks to completely resolve following the offending protein elimination.[11] Long-term prognosis, however, is good: tolerance to the offending protein was achieved in the majority of infants by 2–3 years.[25]

Conclusion

Although non-IgE-mediated food allergies are less common than IgE-mediated food allergies, these disorders are being increasingly recognized in children. FPIES, FPIAP, and FPE are the most common non-IgE-mediated food allergies seen in children. Generally, these disorders have a favorable prognosis; however, severe presentation such as shock as in acute form of FPIES or failure to thrive as in a chronic form of FPIES and FPE can be experienced. These disorders can cause significant healthcare burden and allergists should provide an accurate diagnosis with a clear therapy plan, and reassurance regarding the prognosis which is for most of the non-IgE-mediated conditions is excellent. A multidisciplinary team involving general pediatricians, dieticians, speech pathologists, and allergists/gastroenterologists is recommended when managing complex cases.

Abbreviations

FA, food allergy; IgE, immunoglobulin E; non-IgE-GI-FA, non-IgE-mediated gastrointestinal food allergic disorders; FPIES, food protein-induced enterocolitis syndrome; EoE, eosinophilic esophagitis; FPIAP, food protein-induced allergic proctocolitis; FPE, food protein-induced allergic enteropathy; OFC, oral food challenge; EHF, extensively hydrolyzed formula; AAF, amino acid-based-formula.

Disclosure

The authors report no conflicts of interest in this work.

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