



Non-IgE-mediated gastrointestinal food allergies

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Purpose of review

We focus on recent advances regarding the epidemiology, physiopathology, diagnosis and managements of non-IgE-mediated gastrointestinal food allergies (non-IgE-GI-FAs), particularly food protein-induced enterocolitis syndrome (FPIES).

Recent findings

The first international FPIES diagnostic and management guidelines have been recently published. Although FPIES largely remains a diagnosis of exclusion, it may be more prevalent than previously thought. Ondansetron has emerged as a major tool for the treatment of FPIES acute reactions. Recent data also suggest an important role for innate immune cells in FPIES pathogenesis.

Summary

Despite major advances in the diagnosis and management of non-IgE-GI-FAs, particularly FPIES, the lack of specific diagnostic tests and biomarkers to guide clinical management remains challenging.

Keywords

food protein-induced allergic proctocolitis, FPIAP, food protein-induced enterocolitis syndrome, FPIES, food protein-induced enteropathy, FPE, non-IgE-mediated gastrointestinal food allergy

INTRODUCTION

Food allergy constitutes one of the main causes of pediatric consultations with an estimated prevalence ranging from 3 to 8% in childhood [1,2]. Although most of the current studies include prevalence estimate of IgE-mediated food allergies, major interest has recently focused on non-IgE-mediated gastrointestinal food allergies (non-IgE-GI-FAs) due to the potential severity of reactions [3]. Lack of awareness regarding these disorders among primary care physicians, but also allergists, is responsible for a frequently delayed diagnosis [4]. On the other hand, over-diagnosis is also common due to the lack of a definitive diagnostic biomarker and non-specific gastrointestinal manifestations attributed to food allergy [5]. An incorrect diagnosis may result in unnecessary restrictive diet with a negative impact on quality of life and potentially severe consequences on the patient's health due to nutrient deficiency and feeding disorders/food aversion [6].

In this review, we will discuss major advances regarding the epidemiology, physiopathology, diagnosis and management of non-IgE-GI-FAs based on recent publications, focusing particularly on food protein-induced enterocolitis syndrome (FPIES).

NON-IGE-MEDIATED GASTROINTESTINAL FOOD ALLERGIES CLASSIFICATION

In contrast to IgE-mediated food allergies, non-IgE-GI-FAs are characterized by subacute and/or chronic gastrointestinal symptoms and include FPIES, food protein-induced allergic proctocolitis (FPIAP) and food protein-induced enteropathy (FPE). Celiac disease and cow milk allergy-induced iron-deficiency anemia are also classified as non-IgE-GI-FAs, but will not be discussed in this review [7,8]. In addition, the role of food is often questioned during pediatric consultations in a subset of children with constipation, gastroesophageal reflux disease, colic and apparent nonceliac wheat (or gluten) sensitivity. Although these disorders cannot be classified as

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KEY POINTS

- FPIES has emerged as the most actively studied non-IgE-GI-FAs probably due to the potential severity of acute reactions.
- Recent studies have strongly suggested that FPIES is much more common than previously thought, although accurate epidemiologic data are still needed.
- International evidence-based guidelines have been recently published providing important particularly new diagnostic criteria and guidelines for food introduction and nutritional support of FPIES patients.
- The role of T cell has been increasingly questioned in regard to the pathophysiology of FPIES, with new evidence for a major role by innate immune cells, especially neutrophils, monocytes and eosinophils cells.
- Ondansetron has emerged as a major tool for the treatment of those FPIES patients during the acute phase of the reaction, although further studies are still needed to confirm its efficacy and safety.

non-IgE-GI-FAs, because a specific immunologic mechanism has not been clearly demonstrated, symptomatic improvement after specific food protein elimination and recurrence upon re-exposure support a major role of food in a subset of patients, especially those with severe symptoms refractory to optimal medical management (reviewed in [9[¶]]). In the case of irritable bowel syndrome (IBS), major interest has focused on the potential involvement of fermentable oligosaccharides, disaccharides, monosaccharides and polyols, and there is some evidence for this mechanism underlying IBS in children, such that their elimination may lead to symptomatic improvement [9[¶],10]. We have included mention of these disorders as they are common in pediatric population, but it is important to note that the role of food in these functional disorders remains highly debated and further well conducted studies are needed in the paediatric population.

CLASSICAL NON-IGE-MEDIATED GASTROINTESTINAL FOOD ALLERGIES

The different types of disorders included in non-IgE-GI-FAs have overlapping clinical features, but can be distinguished based on their typical clinical characteristics, severity, age of onset and natural history [11].

Food protein-induced allergic proctocolitis and food protein-induced enteropathy

Despite the lack of prevalence studies, FPIAP is thought to be the most common non-IgE-GI-FAs,

with an estimated prevalence ranging widely between 0.16 and 64% of isolated rectal bleeding in infants [12–14]. FPIAP emerges also as the most benign form of non-IgE-GI-FAs, characterized by a limited rectal and lower digestive tract inflammation induced by ingested food proteins. The typical clinical manifestation of this disorder is blood-streaked stools appearing usually in the first few weeks–months of life in otherwise healthy infants fed with breast milk or infant formula (i.e. milk or soy formulas) [7,12,15–20]. The exact pathologic mechanism of FPIAP remains unknown, but biopsies show typically an eosinophil-dominated inflammation [21]. The diagnosis is mainly based on typical clinical manifestations and resolution of symptoms 1–10 days after withdrawal of the trigger food(s). Although elimination of the incriminated food(s) from the maternal diet in exclusively breastfed infants is usually sufficient to resolve symptoms, an extensively hydrolyzed or amino acid-based formula might be necessary in a minority of patients [22]. Of note, extensively hydrolyzed formulas might cause FPIAP in up to 10% of cases [13,17,22]. It is important to note that rectal bleeding may resolve spontaneously in about 20% of breastfed infants, without any changes in the diet [13,23]. Recently, probiotic *Lactobacillus rhamnosus* GG, used as a monotherapy or as an adjunctive therapy to hydrolyzed formula, has been reported to accelerate symptom resolution [24–26]. However, this treatment is currently not recommended in routine management, as the evidence remains low and may require further investigations. Reintroduction of the suspect food after 4–8 weeks of elimination can be performed usually at home and documented with a symptoms diary [27]. Endoscopy with biopsies is rarely performed to confirm histologic diagnosis, but might be useful to exclude others causes of bleeding in case of worsening. In the vast majority of cases, FPIAP has a favorable prognosis, and food tolerance is achieved before 1 year of age [19,20,28] but may take longer in infants with multiple food allergies [18].

Concerning FPE, the prevalence remains largely unknown, and seems to have declined, or even has disappeared over the past few decades [29]. FPE is characterized by chronic diarrhea, that may lead to failure to thrive (FTT), typically occurred between 2 and 9 months of age, and the most common foods involved are cow milk, followed by soybean, egg and wheat [30,31]. Diagnosis is based on the typical clinical history, and endoscopy with biopsies is usually needed to confirm the diagnosis typically showing damage to the villous architecture [32]. Similar to FPIAP, removal of the offending food is usually required, followed by reintroduction at

home 4–8 weeks after to confirm the recurrence of symptoms [29]. FPE is also a transient disorder resolving around 1–3 years [33,34].

Food protein-induced enterocolitis syndrome

Probably because of the potential severity of reactions, FPIES received an increased interest over the past decade and emerged currently as the most actively studied non-IgE-GI-FAs [7]. Several recent studies provided major insights regarding different aspects of FPIES. Although FPIES was considered to be a rare disorder, a prospective population-based birth cohort reported a cumulative incidence of 3 per 1000 newborns over 2 years for cow milk-FPIES, close to the one reported for IgE-mediated cow milk allergy in the same Israeli population [3]. In a recent Australian study, the incidence of FPIES in children was lower at 15,4/100 000/year, probably underestimated by the methodology used (i.e. based on voluntary reporting system) [35^{***}]. Accurate epidemiologic data in different countries are still needed to estimate the true prevalence of FPIES.

Regarding the pathophysiology, FPIES has been classified as non-IgE-mediated food allergy [7,36–38,39^{***}] and is usually considered to be T-cell-mediated. Nevertheless, the role of T cells has been questioned, particularly by the fact that neither peripheral blood mononuclear cell proliferation nor patch tests can be used as a diagnostic tool at an individual level [5,40–48]. In addition, the role of T cells has been further challenged by recent data showing similar CD4 T-cell-proliferative responses after casein stimulation in cow milk-FPIES patients to those with IgE-mediated cow milk allergy and those tolerating cow milk [39^{***},49,50]. However, CD4⁺CD25⁺ regulatory T cells might be incriminated in tolerance acquisition, particularly by a suppressive action via cell-to-cell contact and by the production of transforming growth factor- β and interleukin 10 [44,49]. Recently, data have suggested a major role of innate immunity in the pathophysiology of FPIES, particularly by incriminating neutrophils, monocytes and eosinophil cells [51–53]. In addition, a potential role of mast cells has been suggested, but these data need to be confirmed by further studies. A systemic inflammatory mechanism in children with FPIES is supported by a significant increase of C-reactive protein (CRP) levels in FPIES children compared with FPIAP infants; elevation of CRP at the onset of FPIES also has a poor prognosis of FPIES if CRP is high at the onset [54,55]. In addition, a significant increase of CRP levels after challenge, in FPIES children has been found supporting an inflammatory mechanism during FPIES reactions [56,57]. Finally, recent findings show

excellent efficacy of treatment of acute FPIES reactions with ondansetron, a serotonin 5Hydroxytryptamine receptor antagonist that reduces peripheral and central vagal nerve activity, suggesting the potential role of neuroendocrine mechanism [58^{*},59,60,61^{*}]. Although major advances have been made, further studies are still needed to have a better understanding of FPIES pathophysiology.

In 2017, the first international evidence-based guidelines have been published to improve diagnosis and management of FPIES that is often difficult [62^{***}]. As a first step, features for clinical phenotyping of FPIES have been proposed [36,63–65]. Thus, different clinical forms with various degrees of severity can be distinguished and are mainly determined by the frequency and the dose of the trigger food, as well as the phenotype and age of the patient [60,66,67]. The most common form is the acute FPIES, which is characterized by repetitive protracted vomiting, typically occurring 1–4 h after food ingestion, associated with lethargy and pallor [9^{*},10]; watery diarrhea may follow within 24 h [3,9^{*},10,27,65,67,68]. Severe cases of FPIES may lead to dehydration with hemodynamic instability (up to 15% of the cases), requiring intravenous hydration and hospitalization [63,69]. Chronic FPIES is less well described but is classically characterized by intermittent vomiting, chronic watery diarrhea with malabsorption responsible for FTT and occurs with daily ingestion of triggering food, with onset usually by 4 months of age in children feeding with cow milk or soy-based formula [9^{*},10]. After a period of avoidance, re-exposure to the incriminated food leads to acute FPIES symptoms (i.e. acute-on-chronic form of FPIES).

Similar to other non-IgE-GI-FAs, diagnosis of FPIES is based on clinical criteria, including typical characteristic signs and symptoms resolving after avoidance of the offending food [70,71]. These diagnostic criteria have been recently revised and are listed in Table 1 [70,71]. Exclusion of other causes is important as the differential diagnosis is broad and FPIES is often misdiagnosed [9^{*},35^{***}]. Oral food challenge (OFC), which is considered the gold standard, might be useful to confirm diagnosis but is no longer mandatory, particularly in patients with several typical reactions (Table 1) [62^{***},72]. In contrast, diagnosis of chronic FPIES, which is often over diagnosed and less well recognized, requires an OFC [62^{***}]. As for other types of allergies, the OFC should be performed in an appropriate setting with a trained team [71]. Intravenous access is usually recommended because of high risk of potential severe reaction. The food is usually administered in three equal doses over 30 min (0.06–0.3 g of food protein/kg of body weight). It is important to note that coassociation with atopic

Table 1. Diagnostic criteria for food protein-induced enterocolitis syndrome and diagnostic criteria for interpretation of positive oral food challenge in food protein-induced enterocolitis syndrome patients

Acute FPIES	
1 Major criterion+	≥3 Minor criteria
Vomiting in the 1–4 h after ingestion of the suspect food and absence of IgE-mediated allergic symptoms	>1 Episode to the same food
	Repetitive vomiting to a different food
	Lethargy
	Pallor
	Emergency department visit
	Need for intravenous fluid support
	Diarrhea in 24 h
	Hypotension
	Hypothermia
Chronic FPIES	
Milder: intermittent vomiting and/or diarrhea, with FTT, without dehydration	Resolution of symptoms within days after elimination of the offending food(s), with acute symptoms upon reintroduction, is the most important criterion. OFC is required to confirm diagnosis
Severe: intermittent vomiting and diarrhea (possible with blood), lead to potential dehydration, when the offending food is regularly consumed	
Positive criteria for OFC	
1 Major criterion+	≥2 Minor criteria
Vomiting in the 1–4 h after ingestion of the suspect food and absence of IgE-mediated allergic symptoms	Lethargy
	Pallor
	Diarrhea 5–10 h
	Hypotension
	Hypothermia
	Increase of neutrophils levels of ≥1500 above the baseline level

FPIES, food protein-induced enterocolitis syndrome; FTT, failure to thrive; OFC, oral food challenge. Adapted with authorization from [62^{***}].

disease, including eczema or food IgE-sensitization, has been reported frequently in FPIES children [37,67]. Furthermore, specific IgE to the offending food may be found either at the onset or subsequently in up to 30% of FPIES (atypical FPIES), and has been associated with increased risk of developing an IgE-mediated allergy to the incriminated food and a more protracted course [3,5,65,67,71]. Skin prick tests and/or specific IgE should be measured before performing the OFC to adapt the protocol, as well as in patients with atopic background (atopic dermatitis, IgE-mediated food allergy). Interpretation criteria of a positive OFC have also been recently revised and are described in Table 1 [62^{***}].

Management of FPIES includes emergency treatment during the acute phase, avoidance of the

offending food, monitoring of resolution and nutritional management including complementary food introduction [62^{***}]. The treatment of acute-FPIES depends on the severity of the reaction and may require aggressive isotonic fluid resuscitation (10–20 ml/kg boluses of normal saline 0,9%), repeated as needed, whereas oral hydration may be sufficient in mild-to-moderate FPIES reaction [3]. Recently, administration of intravenous or intramuscular ondansetron has been recommended as an adjunctive therapy for the management of acute FPIES reaction, although the evidence remains limited [59,60,61[■]]. After the diagnosis is established, removal of the incriminated food is the rule. Recent epidemiologic studies have provided important data regarding the frequency of different trigger foods. Cow milk and soy followed by grains (rice and oat) are the most commonly reported

triggers of FPIES in Western Europe and the United States of America [3,66,67,73], whereas in Australia, rice is the most commonly incriminated food [35,65,74]. Fish is the most common solid food trigger in Spain and Italy. It is important to note that FPIES has been described in these past decades with a large variety of foods, including foods that are usually considered as hypoallergenic, and this may explain partly delayed diagnosis of FPIES in many cases [11,36,37,65,67,73–84]. Differences between countries regarding the incriminated foods may be explained by geographic variations in dietary practices, prevalence of atopic diseases and probably specific genetic factors [3,66,79]. In infants with cow milk- or soy -based formula FPIES, breast-feeding should be continued when possible until 6–12 months of age, unless acute or chronic symptoms are observed and attributed to the food protein in the maternal diet [85]. Otherwise, extensively hydrolyzed formula is recommended, although up to 20% of FPIES children need an amino acid-based formula [36,37,64,67,86,87]. Probably according to the earlier introduction of cow milk and/or soy, onset of FPIES to these foods occurs at younger ages compared with FPIES to solid foods [37,68]. Although, the majority of FPIES patients will react to a single food (65–80%), up to 10% will react to more than three different foods [5,67]. An association between cow milk- and soy -FPIES has been described in up to 40% of children with FPIES to soy and cow milk, respectively. In addition, almost one-third of cow milk- and/or soy -FPIES patients will also react to solid food(s) [5,36,64,71]. Similarly, patients with solid-FPIES have a higher risk to react to multiple solid foods, particularly combined FPIES to rice/oat have been reported in United States of America and Australia [37,65,67]. Due to the risk of coreactivity, it is suggested to avoid cow milk and/or soy in children with FPIES to soy and/or cow milk, respectively, during the first 6 months of life, after which there may be acceptable dietary alternatives. Cautious introduction of these foods is recommended, usually by performing an OFC, particularly in children with severe initial reactions. Regarding solid-FPIES, avoidance of foods from the same category, like grains, poultry or legumes, is usually recommended. Of note, there is no recommendation to delay the introduction of complementary foods past 6 months of age [8,88,89]. Thus, parents may introduce solid foods at about 6 months of age at home, by starting with fruits and vegetables, followed by other complementary foods. If the past FPIES reactions were severe, supervised introduction in the office may be advisable. Of note, there are no data regarding primary FPIES prevention.

The natural history of FPIES depends on the trigger food, the sequence of introduction, as well

as the atopic status and country of origin. Infants with cow milk- or soy- FPIES may develop tolerance earlier than solid food-FPIES. Indeed, cow milk-FPIES was reported to resolve around 1–2 years of age in average, although it can occur at a later age according to large recent cohorts [3,19,37,65–67,90,91]. Atypical FPIES, defined as detectable specific IgE to the trigger food is associated with older age of tolerance [67]. Regarding resolution of solid food-FPIES, there is less robust data, but average age of resolution was reported around 5 years of age [67]. Thus, the optimal timing of reintroduction of the offending food has not been well studied but seems to be considerably variable. Reintroduction of the food that caused FPIES is recommended under physician supervision as an OFC and is usually considered 12–18 months since the most recent reaction [10], although it may be delayed based mainly on the type of food involved, and the severity of previous reactions.

SUMMARY

Non-IgE-GI-FAs include a wide range of disorders, with FPIES being the most severe. Non-IgE-GI-FAs are more common than previously appreciated. The first international evidence-based FPIES guidelines have been recently published, providing important recommendations regarding patient diagnosis and management, which is often difficult. However, further large multicentric studies are still needed to better characterize these disorders, to further improve management. In addition, a better understanding of the pathophysiology is needed to develop new biomarkers, which will lead eventually to the development of new diagnostic tests and treatment modalities.

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Conflicts of interest

There are no conflicts of interest.

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