



Non-IgE-mediated food allergy during infancy

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Purpose of review

Is to highlight the recent advances in the diagnosis and management of non-IgE-mediated food allergy which is a common consideration in primary care and in allergy and gastroenterology subspecialty practices evaluating infants.

Recent findings

The review focuses on food protein-induced enterocolitis syndrome (FPIES) and includes other non-IgE-mediated food allergy in nursing infants, food protein-induced allergic proctocolitis, and food protein-induced enteropathy. For FPIES, we review the 2017 International Consensus Guidelines that provided the first comprehensive framework for its diagnosis and management and that were supplemented by a 2019 position paper by the European Academy of Allergy and Clinical Immunology. We review recent reports that support FPIES as a diagnosis of primarily infants, highlight the problem of delayed diagnosis, reveal the need for improved biomarkers, emphasize new and common food protein triggers, and identify new approaches for evaluation of tolerance.

Summary

As formal diagnostic criteria for non-IgE-mediated food allergies are defined and prevalence data is increasingly reported, there will likely be improved recognition and evaluation of these conditions. Currently, large-scale prospective studies evaluating their incidence and prevalence, associated risk factors, and natural history are needed. Although avoidance of the suspected trigger food protein remains the cornerstone of management, additional studies of underlying pathophysiology and biomarkers of disease will likely reveal new avenues for therapeutics.

Keywords

eosinophilic esophagitis, food allergy, food protein-induced allergic proctocolitis, food protein-induced enterocolitis syndrome, food protein-induced enteropathy, IgE

INTRODUCTION

Non-IgE-mediated food allergy refers to any immune-mediated adverse food reaction whose pathophysiology does not involve IgE. Conditions in this category include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE), and others. These conditions most commonly affect the infant population hence the relevance of this review. Practice parameters and position papers providing evidence-based recommendations for the diagnosis and management of these conditions and their reported incidence and prevalence lay the framework for this review and are complemented by recent publications that have contributed to our improved understanding of these conditions (Table 1). It is important to note that while several primary research articles have been published on FPIES in recent years, recent primary research on FPIAP and FPE is limited. This review briefly touches

upon the manifestations, diagnosis, management, epidemiology, natural history, and underlying mechanism for each of these conditions and highlights in which there is an additional need for research to improve our understanding of non-IgE-mediated food allergy.

Food protein-induced enterocolitis syndrome

FPIES is a non-IgE-mediated food allergy first described in the 1970s and defined by delayed onset (1–4 h following ingestion), often recurrent emesis,

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KEY POINTS

- Acute FPIES is characterized by delayed-onset, repetitive, often violent emesis, lethargy, pallor, diarrhea, and, in severe cases, hypotension following consumption of a food protein. The most common triggers in infancy include cow's milk and soy.
- Food protein-induced allergic proctocolitis is a common cause of rectal bleeding in young infants. The symptom typically resolves with dietary cow's milk and/or soy removal and recurs with reintroduction.
- There is a need for an improved understanding of the epidemiology, diagnosis, management, natural history, and pathophysiology of non-IgE-mediated food allergies.

lethargy, pallor, and/or diarrhea that, in severe cases, may lead to hypotensive shock [1]. FPIES is traditionally classified as acute, chronic, or atypical depending on timing, symptoms, and the patient's clinical course. In acute FPIES, the onset of emesis is typically 1–4 h following ingestion of the suspected trigger food. Additional symptoms may include: lethargy, pallor, hypotension, hypothermia, and/or diarrhea (with typical onset several hours after emesis) [1]. The diarrhea only occurs in 20–50% of patients and may be more common in infants [2]. Patients with chronic FPIES manifest with symptoms of chronic emesis, diarrhea, and weight loss with or without dehydration and metabolic acidosis, a more smoldering and less dramatic process than acute FPIES [1,3]. Chronic FPIES is most commonly described in infants regularly consuming

Table 1. Reported incidence and/or prevalence of non-IgE-mediated food allergy

Authors	Study details	Age	Incidence/Prevalence
Mehr <i>et al.</i> [30]	Provider completed survey-based design identifying new FPIES diagnoses monthly in Australia	Median age of first reaction: 5 months (4–6)	15.4 new cases of FPIES per 100 000 births per year (230 infants over 29 months)
Katz <i>et al.</i> [31]	Prospective, population-based study of newborn infants in Israel	Mean age of FPIES onset: 57.8 ± 53.1 days	44 cases of cow's milk FPIES over a 2-year period (approximate prevalence of 0.34%) 21 cases of cow's milk induced proctocolitis over a 2-year period
Nowak-Węgrzyn <i>et al.</i> [9**]	Cross-sectional, US-based household survey		Estimated prevalence of FPIES in children was 0.51% Estimated prevalence of FPIES in children <1 year of age was 0.11%
Alonso <i>et al.</i> [11**]	Prospective birth cohort in Spain	Average age of FPIES onset: 7.6 months	Cumulative incidence of FPIES of 0.7% over 1-year period
Schoemaker <i>et al.</i> [32]	Prospective birth cohort in 9 European countries	Median age at diagnosis for IgE- and non-IgE-mediated cow's milk allergy: 10 (3–27) months	Adjusted incidence of non-IgE-mediated cow's milk allergy of 0.13–0.72% over 2-year period, depending on the country
Ludman <i>et al.</i> [33]	Retrospective review of all patients with FPIES diagnosis at UK-based referral center over a 3-year period	Median age of evaluation: 8 months (0.75–60 months)	FPIES diagnosis occurred in 54 of 14 800 referrals (0.36%)
Meyer <i>et al.</i> [34]	Retrospective review of Gastroenterology Department medical records from a single UK-based hospital over a 7-year period	Median age of symptom onset: 5 months (1–156 months) Average age of evaluation: 63 months (1–260 months)	12.6% diagnosed with a food protein induced gastrointestinal allergy
Martin <i>et al.</i> [19**]	Prospective cohort of epidemiology and clinical presentation of FPIAP in healthy infants at a single suburban pediatric practice	Median age of symptom onset: 26 days Median age of diagnosis: 35 days	7–17% incidence depending on method of diagnosis Lower rates of FPIAP in infants fed with both formula and breastmilk
Grimshaw <i>et al.</i> [35]	UK-based cohort of larger, prospective European-based birth cohort	Median age of child with any food allergy (IgE or non-IgE): 9.3 (5.7–17) months	Cumulative incidence of non-IgE-mediated food allergy of 2.4% over a 2-year period

FPIAP, food protein induced allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome.

cow's milk or soy-based formula, and often these are the culprit food(s) [4]. Chronic FPIES and FPE likely have significant overlap. Atypical FPIES is the likely diagnosis in subjects with a history consistent with acute FPIES, however, they also have presence of specific IgE to the trigger food (i.e., positive skin prick testing or serum-specific IgE) [1].

The diagnosis of FPIES is based largely on clinical history with no formal laboratory test to confirm the diagnosis. In acute FPIES, complete elimination of the suspected trigger food from the diet prevents the symptoms from recurring. In chronic FPIES, symptom resolution may take a few days following elimination of the suspected trigger food. The differential diagnosis of acute vomiting is extensive in the infant population, likely contributing to the pronounced delay in diagnosis that is seen in practice. Importantly, the identification of more specific clinical and laboratory biomarkers to assist in diagnosis acutely is needed. A recent retrospective study from Australia comparing cases of acute FPIES, sepsis, and infectious gastroenteritis presenting to an Emergency Department (ED) found that subjects with acute FPIES presented younger (median age: 6 months, IQR: 5–10 months) and more often presented with lethargy, floppiness, and pallor in addition to vomiting [5^{***}]. The median delay to FPIES diagnosis was 3 months and nearly 50% of subjects had multiple presentations to the ED prior to diagnosis [5^{***}]. In attempts to identify biomarkers utilizing basic laboratory tests that may have been performed whereas in the ED, subjects with FPIES more often had a normal CRP, normal electrolytes, elevated platelet count, lower mean platelet volume, and elevated albumin to globulin ratio compared with subjects with sepsis or gastroenteritis [5^{***}]. Further, a case series of three infants with acute FPIES undergoing diagnostic oral food challenge (OFC) or who experienced accidental exposure to their trigger found elevations in serum thymus and activation-regulated chemokine (TARC) measured approximately 24 h after the clinical reactions [6]. Significantly, TARC has also been shown to be elevated in other allergic conditions. Perhaps a scoring system using the aforementioned clinical presentation features and proposed biomarkers, such as TARC, could be developed for use in emergency rooms in cases where there is no clear infectious exposure. Indeed, in cases in which the FPIES diagnosis is less clear, the gold standard test for the diagnosis of FPIES is an OFC. There is no consensus regarding the exact protocol that should be utilized for an FPIES OFC. Currently, the FPIES consensus guidelines support the use of a protocol in which 0.3 g of the implicated food protein per kilogram of body weight is divided into three equivalent doses

that are administered over 30 min followed by an observation period of 4–6 h [1]. More recently, investigators in Italy retrospectively reviewed their use of a protocol in which 1/4 of the full dose (0.3 g of food protein per kilogram of body weight) of the suspected trigger food is administered followed by monitoring for 4 h, and, if no symptoms occur, the remainder of the dose is administered with another 4 h of observation [7^{*}]. In their study of 54 challenges in 48 subjects, all of the failed challenges occurred after the 25% dose, and the authors concluded that this protocol may be a safe and a more efficient alternative to other protocols published [7^{*}].

First-line management of FPIES, like most adverse food reactions, is avoidance of the trigger food. The majority of infants with cow's milk or soy-induced FPIES will tolerate an extensively hydrolyzed formula and a minority will require an amino acid-based formula. Due to a 30–40% risk of reactivity to both cow's milk and soy, use of these formulas in infants with cow's milk or soy FPIES is discouraged [4]. The FPIES international consensus guidelines encourage regular reassessment of patients to determine if the adverse food reaction has resolved and, in the United States, experts recommend consideration of an OFC 12–18 months after an individual's most recent reaction [1]. Wang *et al.* [8^{*}] retrospectively reviewed 169 FPIES OFCs performed between 2014 and 2017 at Children's Hospital of Philadelphia, in the USA. Historically in this cohort, the mean age at initial reaction was 7.9 months and the mean age at time of challenge, while it differed depending on the food, was 37.1 months. The challenge protocols utilized consisted of either a two-step feeding of a total of 1/4–1/3 of a serving size followed by observation or a single feeding of 1/3 of a serving size and observation for 4 h followed by a home dose-escalation protocol [8^{*}]. Approximately 18% of challenges were positive, of which five patients were transferred to the ED due to persistent symptoms refractory to intravenous hydration and ondansetron [8^{*}]. The mean age of passing an FPIES OFC ranged from 35 to 44.9 months, depending on the challenge food [8^{*}]. Of interest, no center has published a single serving size dose challenge approach (as opposed to graded challenge) perhaps out of safety concerns.

The exact incidence and prevalence of FPIES in the United States is unknown, however, based on parent proxy-reported survey data, an approximate prevalence among children is 0.51% [9^{***}]. Review of FPIES diagnoses, based on ICD-9/-10 coding and electronic medical record (EMR) evaluation, in a US-based pediatric primary care birth cohort, describes a possible increased incidence of FPIES from 2010–2014 to 2015–2018 [10]. The approximate incidence

of FPIES in a prospective, longitudinal birth cohort in Spain was 0.7% [11[■]]. Concomitant atopic disease and non-Hispanic race may be more frequent in children with FPIES [9[■],10]. This condition most commonly affects infants less than 12 months of age, however, as previously noted, there is often a considerable delay in time to diagnosis. A retrospective review of the EMR of 74 subjects with FPIES identified between 2015 and 2017 at Texas Children's Hospital in the USA found a median age at first presentation of 5 months (IQR: 4–6 months) and a median age at diagnosis of 11 months (IQR: 7–16 months) [12[■]]. Approximately 33% of patients had three or more FPIES episodes prior to their diagnosis and FPIES most commonly affected non-Hispanic white patients [12[■]]. In the infant population, cow's milk and soy are the most common FPIES triggers, however, solid food FPIES is also described, and rice and oats are the most commonly reported solid food FPIES triggers [2]. Significantly, more than 50% of patients may have more than one food trigger and, in the same study, 41% of subjects had identified both milk and a solid food trigger [12[■]]. A solid food FPIES trigger recently described as more common and previously considered to be a low-risk food is avocado [12[■],13].

The mechanism underlying FPIES is an area of active investigation. Utilizing RNA-sequencing and bioinformatics approaches, investigators examined the whole blood of children with a history of FPIES undergoing OFCs, prior to and during acute reactions [14[■]]. In individuals who reacted, a network of associated genes and pathways involved in granulocyte migration and triggering receptor expressed on myeloid cells 1 signaling was enriched and ultimately thought to be reflective of innate immune activation [14[■]]. Engagement of this network was not seen in subjects who did not react during OFC [14[■]]. Although endoscopy and colonoscopy are not routine components of the workup for FPIES, there are descriptions of FPIES patients undergoing these procedures with reports of colitis with eosinophilic and lymphocytic infiltrates, villous atrophy, and ulcerations and/or abscesses [15].

Food protein-induced allergic proctocolitis

There has been a paucity of primary literature in the recent years focused on FPIAP. The European task force on non-IgE-mediated allergy has sought to refine the diagnosis and management of non-IgE-mediated food allergies, including FPIAP [16[■]]. FPIAP typically presents in infancy as benign hematochezia at times associated with fussiness and loose, mucous-containing stools. It is most often

seen in breastfed infants and classically resolves with maternal dietary elimination of cow's milk and/or soy, which are the most common triggers. Maternal dietary elimination results in resolution of symptoms and with attempted maternal reintroduction, symptoms often recur, confirming the diagnosis. If the infant is formula fed and cow's milk-induced FPIAP is suspected, transition to an extensively hydrolyzed formula should result in symptom resolution. Egg and wheat have also been described as triggers [16[■]]. The diagnosis of FPIAP is clinical and there has been little investigation into biomarkers for diagnosis and prognostication. A small, retrospective study of 59 cases of FPIAP confirmed by OFC found mean platelet volume and mean plateletcrit at the time of diagnosis to be significantly higher in the FPIAP group compared with age-matched and sex-matched controls. These values were also significantly higher among subjects who did not develop tolerance to the suspected trigger food when compared with those who did [17]. Although colonoscopy is often not indicated in FPIAP, extensive infiltration by eosinophils through the mucosa is a hallmark [15].

Management algorithms have been proposed recommending that the decision to pursue an elimination diet be based on the duration of the hematochezia (<1 or ≥1 month) and emphasizing the importance of a trial of reintroduction of the suspected trigger food following elimination to confirm the diagnosis [18].

There have been more recent important epidemiologic studies that are worth highlighting. The exact prevalence of FPIAP has been unclear as estimates often include all non-IgE-mediated food allergies; nonetheless, it is likely one of the most common non-IgE-mediated food allergies with previous estimates reporting that FPIAP occurs in 5–15% of infants [19[■],20]. However, challenge confirmed studies have suggested rates as low as 2–5% and larger population assessments of milk allergy in infants have found even lower rates of FPIAP at 0.16% [20,21]. Importantly, as part of the Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) study, the first healthy infant cohort study examined the epidemiology and clinical presentation of FPIAP [19[■]]. The authors found a cumulative incidence of 17% for FPIAP. Significantly, only 7% ($n = 63$) had gross blood in the stool. Further, use of mixed feeding (breastmilk and formula) at any point in the first 4 months was associated with lower risk of FPIAP compared with exclusive formula-fed or breast-fed infants. There was no association with the development of IgE-mediated cow's milk allergy. Overall, the rates of FPIAP were much higher than expected likely due to not following formal national

diagnostic guidelines such as using fecal occult blood testing (not recommended formally) or not performing confirmatory challenges [19²²].

The cohort also found increased evidence of feeding dysfunction in FPIAP (e.g., gagging, irritability, and feeding refusal), but did not find an increased risk of growth failure, severe vomiting, or diarrhea. However, there was a clear association with eczema. A recent retrospective study of approximately 800 000 children in a Military Health System database found significant associations between the use of acid suppressive medications or antibiotics in infancy and the development of allergic disease [22,23]. Infants prescribed H₂-receptor antagonists and proton-pump inhibitors in the first 6 months exhibited hazard ratios of 2.2 and 2.6 for food allergy, respectively. Moreover, the use of acid suppression increased the risk of being diagnosed with milk allergy the most. The authors used ICD-9 codes to categorize specific allergic conditions which did not include codes that would delineate IgE versus non-IgE-mediated allergy [22]. It is likely a significant percentage of the milk allergy or other food allergy ICD-9 codes may have been used to diagnose FPIAP or other non-IgE-mediated food allergies by the providers in the database studied. One could hypothesize given the above findings of feeding dysfunction in the GMAP study that perhaps many of these children have undiagnosed FPIAP and are treated with acid suppression for presumed reflux prior to the elimination of milk and that there is no causative link. Significantly, the GMAP cohort did not find an association with the use of acid suppression or antibiotics and the development of FPIAP although the study was not powered to examine these relationships [19²²].

The natural history of FPIAP is favorable with the majority of affected infants outgrowing the condition within the first year of life [15]. It is important to note, however, that some studies have shown that affected patients may not develop tolerance until beyond 1 year of age [24]. A prospective study of 80 subjects with rectosigmoidoscopy-confirmed allergic proctocolitis found the prevalence of functional gastrointestinal disorders at 4 years of age to be higher among subjects with allergic proctocolitis compared with control subjects [25]. This highlights the notion that long-term outcomes and associations, despite resolution of the clinical condition, are not well known. Importantly, the GMAP cohort will be followed longitudinally; perhaps, this study will better characterize the long-term prognosis of FPIAP [19²²].

There has been little work further characterizing the underlying pathophysiology of FPIAP. Previous work of investigating colonic biopsy specimens

from 21 infants with FPIAP showed increased expression of TNF- α by lamina propria mononuclear cells compared with biopsy specimens of subjects with juvenile polyps. The authors suggested that this inflammatory cytokine may have a role in the underlying pathophysiology of FPIAP [26]. The aforementioned GMAP cohort will follow longitudinal metabolome and immune response analyses prospectively and should elucidate new insights into the disorder [19²²].

New insights into diagnosis and treatment are much needed as there is significant cost emotionally and financially with delayed or incorrect diagnoses. Indeed, increase use of acid suppression medications and hypoallergenic formulas lead to increased healthcare costs, and may predispose to the development of allergic disease, in the case of use of the former.

Food protein-induced enteropathy

FPE, also known as allergic enteropathy, presents in infancy with chronic diarrhea, vomiting, and failure to thrive [15,16²²]. Laboratory abnormalities may also be present including hypoalbuminemia and possible anemia [15,16²²]. As mentioned previously, this disorder likely overlaps with chronic FPIES although no work to date has investigated this relationship. Although a small intestine biopsy demonstrating villous damage, crypt hyperplasia, and increased intraepithelial lymphocytes is desired to make the diagnosis, clinical symptoms suggestive of enteropathy combined with resolution of symptoms with dietary elimination or transition to an elemental formula is likely also utilized for diagnosis [15]. The exact prevalence is unknown and the prognosis is favorable with most patients outgrowing the condition by 1–3 years of age [16²²]. Similar to FPIES and FPIAP, the most common implicated food proteins include cow's milk and soy.

Eosinophilic esophagitis

Eosinophilic esophagitis or EoE is a mixed IgE and non-IgE-mediated food allergy. In infancy, this may manifest as recurrent emesis or reflux, difficulty feeding, and/or failure to thrive [27]. Recently, studies have investigated risk factors in early life associated with the subsequent development of EoE. Identified risk factors include: maternal fever during pregnancy, preterm labor, C-section delivery, prematurity; use of proton pump inhibitors, H₂ receptor blockers and antibiotics in the first 6 months of life; atopic conditions (including milk protein allergy), gastroesophageal reflux (GER) or feeding difficulty, and erythema toxicum neonatorum [28,29]. EoE will be discussed in depth in other

articles in this edition of *Current Opinion in Allergy and Clinical Immunology*.

Other nonallergic feeding-associated concerns in infancy

Often dietary adjustments will be instituted by families for other common pediatric conditions affecting infants including GER, colic, irritable bowel syndrome, constipation, food aversions/refusal, or feeding difficulties. The role of particular food proteins in these conditions is difficult to elucidate given their often multifactorial nature. There is a need for further study of the role of food protein in these common conditions of infancy.

CONCLUSION

Physicians seeing infants for acute or persistent gastrointestinal concerns should consider a diagnosis of non-IgE-mediated food allergy. Although the prevalence of FPIES and FPE is likely lower than IgE-mediated food allergies, FPIAP may be more common and further studies are needed to clarify the true incidence and prevalence of these conditions. These entities are well defined clinically, however, tools outside of OFCs to support or confirm a diagnosis are limited. Future studies should be developed to improve the diagnosis and prognostication of non-IgE-mediated food allergy. With the development of these tools, insight will likely be gained regarding the underlying pathophysiology of these clinical entities.

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Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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