Allergy Asthma Immunol Res. 2022 Nov;14(6):587-603
https://doi.org/10.4168/aair.2022.14.6.587
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Review

Check for updates

Recent Update in Food Protein-Induced Enterocolitis Syndrome: Pathophysiology, Diagnosis, and Management

Mehr Mathew,[1] **Stephanie Leeds**,[1] **Anna Nowak-Węgrzyn**[2,3*]

[1]Department of Pediatrics, Yale School of Medicine, New Haven, CT, USA
[2]Department of Pediatrics, Hassenfeld Children's Hospital, NYU Grossman School of Medicine, New York, NY, USA
[3]Department of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn, Poland

OPEN ACCESS

Received: Aug 4, 2022
Revised: Sep 29, 2022
Accepted: Oct 7, 2022
Published online: Nov 21, 2022

Correspondence to
Anna Nowak-Węgrzyn, MD, PhD
Department of Pediatrics, Hassenfeld Children's Hospital, NYU Grossman School of Medicine, 160 E. 32nd Street, LM3, New York, NY 10016, USA.
Tel: +1-212-263-1255
Fax: +1-212-263-3606
Email: anna.nowak-wegrzyn@nyulangone.org

ORCID iDs
Mehr Mathew
https://orcid.org/0000-0002-5454-0753
Stephanie Leeds
https://orcid.org/0000-0002-3270-9108
Anna Nowak-Węgrzyn
https://orcid.org/0000-0002-0960-9854

Disclosure
There are no financial or other issues that might lead to conflict of interest.

ABSTRACT

Food protein-induced enterocolitis syndrome (FPIES), though first reported in the 1970s, remains poorly understood and likely underdiagnosed. It is a non-immunoglobulin E (IgE)-mediated food allergy syndrome, most commonly identified in infancy and childhood. It can manifest as a constellation of symptoms following food ingestion, including repetitive and projectile emesis (1–4 hours), accompanied by pallor, lethargy, muscular hypotonia, and diarrhea (5–10 hours). In more severe reactions, significant leukocytosis with neutrophilia, thrombocytosis, metabolic derangements, methemoglobinemia, anemia, low albumin, and total protein may be present. Hypotension and ultimately hypovolemic distributive shock may occur in up to 15%–20% of cases. The diagnosis of FPIES is challenging and providers continue to face difficulties in management. This review article aims to highlight the most recent updates in epidemiology, natural history, pathophysiology, potential diagnostic markers, and guidelines for the management of FPIES.

Keywords: Enterocolitis; food hypersensitivity; milk; soy; wheat; oat

OVERVIEW

Epidemiology

Food protein-induced enterocolitis (FPIES) is a non-immunoglobulin E (IgE)-mediated food allergy syndrome typically diagnosed in infancy and childhood.[1] FPIES, first described in the 1970s, is often under-reported, in part due to the lack of standardized diagnostic tests. The last several years, however, have seen some of the first population-based epidemiologic studies published, including multiple larger studies, to determine its incidence and prevalence. With more reliable published data, FPIES, initially believed to be rare, is in fact the most common non-IgE mediated food allergy disorder globally.[2] The cumulative incidence rates estimated in the United States, Israel, Australia, and Spain range from 0.015% to 0.7%.[2-6] The first population-based survey in the US, accounting for more than 900,000 people based on the 2016 United States Census, reported an estimated FPIES lifetime prevalence of 0.51% in those under the age of 18 years old and 0.22% in adults.[6] More

recently, Cianferoni[2] estimated that the incidence of FPIES in the US ranges from 0.14% to 0.28%. A population-based study in Australia has reported lower incidence rates but relied on voluntary reporting by pediatricians. Moreover, the Australian study only captured acute but not chronic FPIES, also likely contributing to underestimation.[4] Nevertheless, acute FPIES was significantly more reported in Australia than very early onset of inflammatory bowel disease in the first 2 years and eosinophilic esophagitis under 18 years.

The mean age of FPIES onset varies depending on the triggering food and the timing of food introduction. Classically, FPIES begins early in infancy, with patients presenting within 1 to 4 weeks of cow's milk or soy protein introduction. The age of onset of solid-food FPIES, however, tends to be later given that these foods are first introduced at around 6 months of age, with the most commonly reported triggers of infant cereal grains (oat, rice, wheat), vegetables (sweet potato, carrot), and fruit (avocado, banana, apple).[7] In an Israeli population-based cohort study of 13,019 patients over 2 years, approximately 44 (0.34%) had cow's milk FPIES and developed FPIES within the first 6 months of life.[3] Of note, males appear to be at a slightly increased risk of developing childhood-onset FPIES compared to females, with the male majority ranging from 52% to 62% in multiple studies.[3,5,7]

Though FPIES typically presents within the first year of life, it has also been diagnosed in the adult population. The US population-based survey mentioned earlier found that FPIES has a prevalence of 0.22% in adults aged 18 years or older.[6] Despite similarities in presentation, including delayed symptom onset with a predominance of gastrointestinal symptoms, there are some noteworthy differences in adult-onset compared to childhood-onset FPIES. In adults with FPIES, seafood is the most frequently implicated trigger rather than cow's milk or soy protein.[8-11] Moreover, unlike in childhood-onset FPIES, females are more likely than males to be affected with adult-onset FPIES, with a median age of onset of 29 years old.[9-11] As reports of FPIES in adults increase, additional differences may be appreciated.

Natural history

As previously mentioned, FPIES can present as either an acute or chronic phenotype. The acute form presents as repetitive, projectile emesis typically within 1 to 4 hours of trigger food ingestion. Patients may also develop diarrhea within 6 to 8 hours.[12] This acute onset is typically in the setting of intermittent ingestion of the offending food protein in small amounts, with resolution of symptoms within 24 hours. On presentation, these patients can appear ill due to signs of pallor, hypotonia, hypotension, and/or hypothermia; however, they are usually well between episodes, demonstrating otherwise appropriate growth and development.[1]

The chronic form of FPIES results in poor weight gain, weight loss, anemia, hypoproteinemia, and hypoalbuminemia.[12] Typically, these patients ingest the offending food protein frequently, *i.e.*, daily feedings with cow's milk- or soy-based formula. These patients experience frequent watery diarrhea that is occasionally bloody or mucousy, as well as worsening emesis over the course of days to weeks. They often require longer periods of food avoidance, usually for days to weeks, prior to experiencing symptom resolution.[1] Given that chronic FPIES is largely observed in formula-fed infants, it is believed to be underdiagnosed in nations where there are numerous alternative/hypoallergenic formulas since patients are often switched to these prior to the development of fulminant chronic FPIES.[2]

The median age of onset of acute FPIES is older (approximately 6 months old) compared to that of chronic FPIES (less than 1 month old).[13] This, in part, can be explained by the fact that

https://doi.org/10.4168/aair.2022.14.6.587

the acute form of FPIES can also present in the setting of chronic FPIES. Acute onset can be seen followed by the chronic phase in the setting of reingestion of the triggering food after it has been eliminated from the diet.[7] This is often the case when the trigger is solid food, depending on the frequency of ingestion.

In general, most patients with FPIES develop tolerance to their food triggers by school age.[1] The age of resolution appears to be strongly influenced by food, country, and study design. A prospective study from South Korea, in which sequential oral challenges were utilized to confirm diagnosis and resolution of FPIES in 23 infants, reported tolerance rates to cow's milk of 27.3% and soy of 75% at 6 months of age, 41.7% and 90.9% at 8 months and 63.6% and 91.7% at 10 months, respectively.[14] In the Israeli cohort with an FPIES incidence of 0.34%, approximately 40/44 patients (90%) experienced complete resolution by age 3.[3]

Caubet *et al.*[15] found that on retrospective chart review of 160 FPIES patients, the median age of tolerance for oat was 4 years, rice was 4.7 years, cow's milk in those with no milk-specific IgE was 5.1 years, and soy was 6.7 years. In contrast to the Israeli population birth cohort, Caubet *et al.*[15] reported resolution rates among pre-selected children presenting to a tertiary referral center. In a cohort of 81 Spanish children with FPIES whereby fish was the primary trigger, 75% of patients experienced resolution by 5 years of age.[16] In a retrospective study of children with acute FPIES who underwent oral food challenges (OFCs) from 1995 to 2015 in Australia, 100% of those with cow's milk FPIES experienced resolution by age 20 months, and 90% of those with rice FPIES and 75% of those with grain FPIES experienced resolution by age 3 years. Moreover, tolerance was achieved at a significantly younger age in patients with rice and cow's milk FPIES compared to those with fish and egg FPIES.[17] These findings were echoed in a large French multicenter retrospective study of 179 patients, whereby the median age of resolved cow's milk FPIES was 2 years old and the resolution of FPIES to fish occurred later, at a median age of 2.9 years.[18] Wang *et al.*[19] found that in 119 patients with FPIES in a large referral center in the US, the mean age of tolerance to cow's milk was 35 months, to grains was 35.7 months, and to soy was 38.4 months. A recent six-year German retrospective survey found that time to tolerance was significantly shorter in chronic FPIES at age 16.5 months than in acute FPIES at age 19.5 months.[20]

Though uncommon, cases of atypical FPIES evolving into IgE-mediated food allergy have also been reported.[1,18,20] A subset of patients with FPIES can develop positive skin prick test and/or detectable serum levels of food-specific IgE to their FPIES trigger, termed atypical FPIES. Approximately 25% of those with atypical FPIES can transition from an FPIES phenotype to an IgE-mediated allergic reaction, and it is unclear what role IgE may play in the remaining patients with evidence of sensitization.[1] In these cases, one can either see initial development of tolerance to a food trigger followed by intolerance in the setting of an IgE mediated reaction, or no development of tolerance at all.[15,18,21] As was appreciated by Caubet *et al.*,[15] those with cow's milk FPIES and detectable cow's milk-specific IgE often do not outgrow their FPIES. Though once believed that IgE sensitization to an FPIES trigger portended a longer duration of FPIES and delay in achieving tolerance, emerging data shows that this may not actually be the case.[18]

Food triggers

In FPIES of infancy, cow's milk is the most common trigger, followed by soy, in countries that utilize infant soy formulas.[12,22] Anywhere from 45%–55% of patients diagnosed with FPIES in the setting of cow's milk or soy ingestion will also react to the other.[22,23] Moreover, children

https://doi.org/10.4168/aair.2022.14.6.587

with cow's milk or soy FPIES are at higher risk for having solid food FPIES.[23] Interestingly, cow's milk FPIES is rare in exclusively breastfed infants.[1,4,24] These infants typically don't develop the complete FPIES phenotype, suggesting a protective role of breast milk perhaps due to the presence of pre- and partially-digested food antigens as well as transforming growth factor-β and IgA.[1]

Though there is some geographic variation in common culprit foods, oat and rice are usually the 2 most commonly reported triggers of solid food FPIES.[7,12] Approximately 60% of all patients with reported solid food FPIES also had milk and/or soy FPIES. Furthermore, those with FPIES to one grain have a 50% chance of developing FPIES to another grain.[24] Typically, patients with solid food FPIES tend to have more severe reactions as well as longer time to tolerance. Moreover, the risk of multiple-food FPIES is almost 80% in infants with solid food or soy protein FPIES. Other relatively common solid food triggers include egg and seafood.[22] In regions like the eastern Mediterranean, egg is actually the most common trigger, followed by fish and only then cow's milk.[25] In Japan, the rates of egg FPIES have increased dramatically in recent years.[26] In the US, peanut and tree nuts have emerged as solid food triggers, possibly due to the encouragement of early introduction in infancy.[27,28]

In adult-onset FPIES, the most common food trigger is shellfish.[10] Interestingly, adult patients often report tolerating the offending food regularly prior to the acute development of symptoms, making it unclear whether there is an inciting event that provokes adult-onset FPIES.[1]

Risk factors

Currently, there is no convincing data indicating that prenatal or perinatal maternal/paternal risk factors are associated with the development of FPIES. The Israeli birth population cohort of 13,019 patients showed a weak association between Cesarean delivery and milk FPIES, but no association with gestational age, maternal age, number of siblings, or maternal dairy consumption.[3] This is further underscored by the findings of the Healthy Start study, which examined a pre-birth cohort of mother and offspring dyads and showed that there was no association between maternal dietary intake during pregnancy and multiple allergic diseases in offspring.[29] Recently, a cross-sectional survey of parents or guardians of allergy-free infants and infants with FPIES aged 12 months or younger demonstrated increased prenatal maternal antibiotic use in the FPIES group.[30] It is possible that alterations to the maternal microbiome could increase an infant's risk for developing FPIES, though more data is needed to support this hypothesis. Other interesting reports have looked at a potential association between Down syndrome and FPIES, speculating that a surgical history of colostomy and postoperative nutrition of cow's milk formula might put these patients at higher risk for FPIES.[31]

Comorbidities

Multiple retrospective studies over the last decade showed that both personal and familial histories of atopy are significantly associated with FPIES. Compared to healthy individuals, up to 55% of patients with FPIES can demonstrate any form of atopy, the most common form being atopic dermatitis (AD).[15,24,32,33] After AD, the other most common co-morbid atopic conditions in order of prevalence are IgE-mediated food allergy, allergic rhinitis, and asthma.[15,33,34] This predilection to atopy is also reflected in adults with FPIES.[6]

Reports of FPIES in siblings are rare, with most cases reported in twins, both fraternal and identical.[24,35] Though reported family history of FPIES is uncommon in patients with FPIES, reported atopy and food allergy in extended family is very common, with up to 70% of first-

https://doi.org/10.4168/aair.2022.14.6.587

degree relatives reporting some degree of atopy in multiple studies.[15,33] Certain non-atopic medical conditions were also reported more frequently amongst first and second degree relatives of patients with FPIES, including migraines (15%–18%), gastroesophageal reflux disease (12%–16%), and inflammatory bowel disease (2%–5%).[33] Of note, the association of FPIES with IgE-mediated food allergies often results in significant diet restriction in patients and extends to multiple food groups.[2] Dietary restriction is observed more so in FPIES patients with a first-degree relative with FPIES.[2,32]

PATHOPHYSIOLOGY

The past decade has seen a significant expansion in our understanding of the underpinnings of this disease, which, in turn, contributed to the first international consensus guidelines on diagnosing and managing FPIES published in 2017.[12] As stated earlier, though it has been established that FPIES is not an IgE-mediated process, it is still not clear how specific food triggers induce the symptoms with which patients present. It was initially believed that FPIES was a type IV or cell-mediated hypersensitivity.[1] More recent studies, however, challenge this notion, and perhaps point towards the innate immune system as a major driver of the FPIES reaction.[36,37]

Innate immunity

Goswami *et al.*[36] evaluated the molecular changes associated with positive or negative OFCs to determine whether a patient's FPIES was active or outgrown, respectively. Through mass cytometry, they demonstrated profound activation of the innate immune system in the absence of an abnormal, antigen-specific T cell response in subjects with positive OFCs. They further confirmed this pattern of activation in a larger cohort using peripheral blood samples to build a transcriptional profile through RNA sequencing. The group's findings are summarized by 3 major observations. First, in samples obtained prior to performing OFCs, there was increased monocyte activation in those with active FPIES compared to those who outgrew their FPIES. Specifically, there was increased gene expression of *CEACAM1*, primarily expressed by neutrophils, and upregulation of CD163 protein production, a monocyte-specific membrane marker. Interestingly, there was a significant reduction in this response post-positive OFC, highlighting that these cells are activated during food-elicited reactions in FPIES. Second, increased activation marker expression of eosinophils, neutrophils, and natural killer (NK) cells was appreciated, suggesting increased expansion of those cells. Moreover, increased circulating neutrophils were not seen in those who outgrew their FPIES, unlike in those with active FPIES. Finally, a loss of circulating lymphocytes and upregulation of the monocyte activation maker, CD69, was noted in the positive OFC group. This observation suggests that innate immune cell activation induces T cell extravasation from circulation.[36] Though Goswami *et al.*[36] appreciated normal levels of allergen-specific T cells in peripheral blood samples of both groups, this does not necessarily rule out the role of cell-mediated immunity in the FPIES reaction. The loss of lymphocytes in the circulation they appreciated could be due to their localization elsewhere, for example the intestinal mucosa, especially given multiple studies demonstrating mucosal barrier disruption and altered permeability.[38-40]

Mehr *et al.*[37] expanded upon these findings, highlighting the systemic immune response as central to the FPIES reaction. The group evaluated the transcriptional profile of 36 patients with a known history of FPIES, of which 10 had active FPIES. In samples from

https://doi.org/10.4168/aair.2022.14.6.587

those 10 patients, increased expression of genes involved innate immune signaling, namely interleukin (*IL*)*-10* and *TREM1*, as well as those involved in granulocyte adhesion and diapedesis. Other studies have also demonstrated this pattern of increased innate immunity. In patients with active FPIES, increased IL-8 levels have been appreciated in multiple studies, underscoring the increased recruitment and involvement of neutrophils observed.[38,40,41] Moreover, significant eosinophilia has been appreciated in the cord blood of infants who went on to develop FPIES and eosinophil-derived products have been appreciated in fecal samples of FPIES patients.[42,43] Pecora *et al.*[44] have postulated that the FPIES reaction resembles the innate immune response to bacterial infection given that the presentation and time course of these reactions mirror those of foodborne illnesses. It is worth considering that those with FPIES could have an inappropriate innate response to specific foods or exaggerated response to dysbiosis of gut microbiota, discussed further below.

Adaptive immunity

Though it may be that the innate immune response primarily drives the FPIES reaction, as touched upon earlier, the cell-mediated response likely also contributes. The extent of this contribution, however, is still not well understood. Goswami *et al.*[36] observed pan-T cell activation and redistribution from circulation in those with active FPIES and not in those who had outgrown their FPIES. In those with a negative OFC, fewer allergen-responsive T cells were appreciated and a skewed T helper 2 (Th2) response was noted. This finding was replicated by the increased CD4+ T cell proliferation and Th2 cytokine production in cow's milk FPIES patients observed in a study by Caubet *et al.*[40] Interestingly, Berin *et al.*[38] appreciated non-conventional T cell populations that were preferentially activated in FPIES patients. Though it is clear that there is a T cell response to food antigens in FPIES, this response is not significantly different from those with IgE-mediated food allergy or those who have outgrown their FPIES, making a cell-mediated response likely less central to the FPIES reaction.[40]

The importance of the cell-mediated response in FPIES could lie in the fact that it amplifies and/or even initiates the innate immune response. Kimura *et al.*[41] reported a cytokine profile in FPIES patients that included increased expression of IL-2 and IL-5, both of which are secreted by activated T cells to enhance NK cell activity and promote eosinophil maturation, respectively. Berin *et al.*[38] observed a significant elevation in IL-17 in FPIES patients, which is primarily released by Th17 cells and links T cell activation with neutrophil activation and de-margination. This effect, however, likely only plays a small role peripherally as IL-23, a potent promoter of Th17 expansion, was well below detectable levels.[38] One of the more interesting links between the innate and cell-mediated response in FPIES was demonstrated by Caubet *et al.*[40] They found that the baseline level of IL-10, a cytokine secreted by cells implicated in both immune responses, was higher prior to OFC in individuals with resolved FPIES when compared to those with active FPIES.[40] Given that IL-10 is a potent anti-inflammatory cytokine that limits host immune response, this finding suggests that it plays a role in achieving tolerance to one's FPIES trigger.

It should be noted that the humoral or antibody-mediated response appears to play little to no role in the pathophysiology of FPIES. Goswami *et al.*,[36] Caubet *et al.*,[40] and Berin[45] observed no specific immunoglobulins to food antigens in patients with FPIES.

Autonomic dysfunction and the gut microbiome

Given the range of non-specific systemic symptoms with which FPIES patients can present, it is thought that autonomic dysfunction might contribute to pathogenesis in some capacity.

https://doi.org/10.4168/aair.2022.14.6.587

Signs of nausea, vomiting, hypotension, and hemodynamic instability are part and parcel of autonomic instability.[46] It is uncertain, however, whether this autonomic response in FPIES might be secondary to gastrointestinal abnormalities or neuroimmune interactions. The use of ondansetron, a central selective serotonin receptor antagonist, as a mainstay of symptom management and the ability of immune cells to synthesize and/or process serotonin support the notion of a neuroimmune-mediated response.[39] Moreover, serotonin can stimulate intestinal peristalsis, vasodilation, and perception of pain and nausea in the gut as well as serve as a chemotactic factor for eosinophils, likely partially accounting for the histological finding of eosinophilic infiltration on intestinal biopsy in FPIES patients.[39,46]

As with many food allergy syndromes, there is increasing interest in the role of the intestinal microbiome in FPIES. Boyer and Scuderi appreciated a statistically significant difference in the constitution of the gut microbiota of FPIES infants when compared to allergy-free infants.[47] Infants with FPIES had significantly more *Gammaproteobacteria* (primarily *Escherich-Shigella* and *Balneatrix*) and *Porphyromonadaceae* (primarily *Parabacteroides*) whereas control infants had significantly more *Prevotella*. Moreover, Boyer *et al.*[30] subsequently appreciated that antibiotic use was higher in infants with FPIES compared to their control counterparts.

These observations support the paradigm of a gut-immune-brain axis with the intestinal microbiome as a key component. The proposed mechanism is that dysbiosis and a subsequent imbalance of metabolites can stimulate enterochromaffin or enteroendocrine cells of the GI tract to produce serotonin, resulting in gut dysmotility locally and food aversion, nausea, and vomiting due to its central effects.[39]

DIAGNOSIS

Diagnostic criteria

FPIES poses a significant diagnostic challenge to providers given variability in symptom presentation, clinical similarity to other disease processes, and lack of a clearcut diagnostic test or biomarker. As a result, misdiagnosis and delays in diagnosis are common and often result in patients undergoing unnecessary evaluations.[7] When FPIES was first identified as a unique entity, Powell developed diagnostic criteria using a group of infants less than 3 months old and highlighted poor growth, diarrhea, and fecal leukocytosis in the setting of cow's milk or soy protein ingestion that was verified on repeat oral food challenges, consistent with what is now considered chronic FPIES.[48] Sicherer *et al.*[49] expanded upon Powell's criteria to include children up to 9 months old, patients with acute-onset symptoms, those with solid food triggers, and those that had detectable IgE levels to their trigger. They were also the first to include the main symptom of FPIES, repetitive vomiting, in their criteria. In addition to what Powell[48] and Sicherer *et al.*[49] proposed, Leonard and Nowak-Węgrzyn[50] recommended additional criteria requiring the occurrence of at least two episodes. Subsequently, Miceli Sopo *et al.*[51] were the first to introduce the concept of an acute FPIES episode and describe the varying severity of those episodes. They explained that in addition to repetitive vomiting, one would expect to see pallor and lethargy, as well as potential diarrhea that often presents after vomiting. Miceli Sopo *et al.*[51] also maintained that two episodes were necessary to diagnose FPIES but increased the age limit for initial presentation to up to 2 years of age. In 2015, Leonard and Nowak-Węgrzyn[52] revised their criteria to remove the age limit for initial presentation and were the first to delineate major and minor criteria. Finally, in 2017 Nowak-Węgrzyn *et al.*[12] published the first set of international consensus guidelines identifying one major and nine minor criteria.

https://doi.org/10.4168/aair.2022.14.6.587

As it stands, acute FPIES is diagnosed if the one major and at least 3 minor criteria are met (**Table 1**).[12] Clinical features can vary between mild-to-moderate and severe acute reactions, namely with regards to the extent of dehydration, lethargy, and the level of intervention required. Laboratory findings that can be seen during a mild-to-moderate acute episode include leukocytosis with a neutrophilic predominance, thrombocytosis, as well as fecal leukocytes or eosinophils. In a severe acute episode, one can also see metabolic acidosis and methemoglobinemia.[12] For chronic FPIES, the most important diagnostic criterion is that a patient experiences resolution of their symptoms within days of eliminating the trigger food and experiences acute recurrence upon reintroduction. Laboratory findings could demonstrate anemia secondary to chronic blood loss in the stools and hypoalbuminemia.[12,53]

A major limitation of the most recent guidelines is that they may not capture variable phenotypes of an acute FPIES reactions. In Japan, for example, fever has been noted in some patients presenting with an acute reaction and this fever has been reproducible on oral food challenge.[54] These observations do suggest a potential ethnic or geographic variation in clinical presentation, but more global studies are needed to clarify this.

Oral food challenges

Clinical history is often enough to diagnose FPIES with particular attention to timing of symptoms after ingestion and the triggering food; however, when history alone is not enough, especially in the setting of chronic FPIES, supervised OFCs are warranted and considered the gold standard for diagnosis.[12] Without a confirmatory OFC, the diagnosis of chronic FPIES is only a presumptive one. The OFC is considered diagnostic for FPIES if 2 or more minor criteria as well as the major criterion are met (**Table 1**). Another common use of OFC in FPIES

Table 1. FPIES diagnostic criteria

FPIES diagnostic criteria	Description
Acute FPIES: Diagnosis requires meeting the major criterion and ≥ 3 minor criteria	
Major criterion	Vomiting 1 to 4 hrs after ingestion of suspected food trigger and absence of typical IgE-mediated allergic skin or respiratory symptoms
Minor criteria	1. ≥ 2 repetitive episodes of vomiting after ingestion of suspected food trigger 2. Repetitive vomiting 1 to 4 hrs after eating a different food 3. Extreme lethargy with any suspected reaction 4. Need for emergency department with any suspected reaction 5. Need for intravenous fluid support with any suspected reaction 6. Diarrhea within 24 hrs (typically within 5 to 10 hrs) 7. Hypotension 8. Hypothermia
Chronic FPIES	The most important criterion for diagnosis is resolution of symptoms within days of elimination of offending foods and acute recurrence of symptoms when the food is reintroduced with: - Vomiting within 1 to 4 hrs - Diarrhea within 24 hrs (typically within 5 to 10 hrs) Milder presentation: lower doses of food trigger result in intermittent vomiting ± diarrhea, as well as poor weight gain/failure to thrive Severe presentation: daily ingestion of food trigger result in intermittent but progressive vomiting and diarrhea ± blood ± dehydration ± metabolic acidosis
Oral food challenge: Diagnostic of FPIES (positive) if major criterion and ≥ 2 minor criteria are met	
Major criterion	Vomiting 1 to 4 hrs after ingestion of suspected food trigger and absence of typical IgE-mediated allergic skin or respiratory symptoms
Minor criteria	1. Lethargy 2. Pallor 3. Diarrhea within 5 to 10 hrs after suspected food trigger ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of ≥ 1,500 cells/mL above baseline count

Modified from Nowak-Węgrzyn *et al*.[12]
FPIES, food protein-induced enterocolitis syndrome; IgE, immunoglobulin E.

https://doi.org/10.4168/aair.2022.14.6.587

patients is to determine whether tolerance to a food trigger has developed. In the US, OFC is typically performed between 12 to 18 months from the last documented reaction.[12] In the aforementioned French multi-center study, Lemoine *et al.*[18] found that performing an OFC within a year of being diagnosed results in increased risk of failing the OFC.

Currently, there is no standardized protocol for performing OFCs in patients with FPIES (**Table 2**).[3,15,16,19,55] Moreover, there is no consensus on when to allow introduction of trigger foods at home. Up to 45% to 95% of reported OFC reactions have required intervention with intravenous fluids, steroids, or both.[12] Given the difficulty in risk stratifying patients in anticipation of an OFC, the international consensus guidelines recommend that peripheral intravenous venous access be established prior to an OFC in anticipation of a severe reaction.[12] Though it is likely in the best interest of the patient to complete an OFC with physician supervision, shared decision-making about home introduction is encouraged if being considered.

Recently, Sultafa *et al.*[56] proposed a modified OFC protocol where exposure to a trigger food is conservatively up-titrated with physician supervision to allow for close monitoring of delayed or chronic FPIES presentations. Current guidelines recommend introducing 0.06 to 0.6 g/kg of food protein in 3 equivalent doses administered every 15 to 30 minutes over a 30- to 60-minute period.[12] If no symptoms develop within 2 to 3 hours, a full serving is administered, followed by another 4 hours of monitoring and subsequently continued at home in the absence of adverse effects, of course. Sultafa *et al.*[56] recommend introducing food protein at 1% of the target serving followed by 4 hours of monitoring. They then recommend that the patient continue to ingest this dose at home for 4 weeks before returning to trial 5% of the target dose, followed by 10%, 20%, 30%, 40%, 60%, 80%, and finally 100% of the target dose with the aim of increasing the dose every 4 weeks with physician supervision.

Table 2. Comparison of various oral food challenge protocols in FPIES

Author	Country	Setting	Dose interval	Total dose	Post-OFC observation	Comments
Katz *et al.* (2011)[3]	Israel	Inpatient (n = 24)	Dose 1–2: 10 min Dose 2–3: 20 min Dose 3–4: 20 min Dose 4–5: 45 min Dose 5–6: 45 min	385 mL (11.55 g) cow's milk	3 hrs	Median cumulative reactive dose was 385 mL
Caubet *et al.* (2014)[15]	USA	Inpatient (n = 180)	3 equal doses over 45 min	0.3 g protein/kg with max of 3 g	4–8 hrs	74/180 OFCs positive If subject had IgE to food trigger, OFC administered in incrementally increasing doses every 15 min
Vazquez-Ortiz *et al.* (2017)[16]	Spain	Inpatient (n = 81)	3 equal doses every 90 min 7 equal doses every 90 min	0.3 g protein/kg	-	36% reacted to 2nd dose 51% reacted to 3rd dose
Wang *et al.* (2019)[19]	USA	Outpatient (n = 169)	Single dose	One third of full serving for age	4 hrs	Full dose titration at home 17/169 positive OFCs 13/152 reactions at home during titration to full dose Diarrhea and vomiting in 1 patient that required ED evaluation
Infante *et al.* (2019)[55]	Spain	Inpatient (n = 75)	Method 1: 4 doses given over 30 min Method 2: only doses 2–4 given, 1 dose every 48 hrs	Doses of Fish: - Dose 1: ⅛ - Dose 2: ¼ - Dose 3: ½ - Dose 4: Full serving	Method 1: - After dose 4, 2 hrs Method 2: - After dose 2, 4 hrs - After dose 3, 4 hrs	Method 1: 95% reacted after full dose reached - 18.6% mild, 42% moderate, 39.5% severe reactions Method 2: 81% reacted after receiving ¼ of full serving - 69% mild, 18.8% moderate, 2.5% severe reactions

FPIES, food protein-induced enterocolitis syndrome; OFCs, oral food challenges; IgE, immunoglobulin E; ED, emergency department.

https://doi.org/10.4168/aair.2022.14.6.587

The stark contrast between the two proposed protocols highlights the need for international standardization of the approach to OFCs in FPIES and the importance of identifying specific patient characteristics that would indicate when home introduction is appropriate.

Potential diagnostic markers

As previously mentioned, no reliable serological markers currently exist for the diagnosis of FPIES. An emerging diagnostic marker that is showing promise, however, is thymus and activation-regulated chemokine (TARC).[57,58] TARC is a Th2 chemokine, often seen at elevated levels in other allergic diseases like AD, that appears to be differentially elevated in patients presenting with symptoms of FPIES. Makita *et al.*[57] appreciated significantly higher post-emetic TARC levels in patients with solid food FPIES compared to those presenting with infectious gastroenteritis. Given the high association of atopy, especially AD, with FPIES, elevated TARC levels may not always be specific; however, the post- to pre-OFC TARC ratio might help increase specificity. Okura *et al.*[58] observed in patients with FPIES, the median TARC ratio was significantly higher in the positive OFC group than in the negative OFC group irrespective of the presence of AD in patients. Though more studies are needed to further evaluate the sensitivity and specificity of TARC as a biomarker for FPIES, these initial findings show promise.

Cord blood eosinophilia and fecal eosinophil-derived neurotoxin can also be used to support a diagnosis of FPIES with the appropriate corresponding history and presentation, however, neither alone are specific to an FPIES diagnosis.[42,43]

Differential diagnosis

Two other forms of non-IgE-mediated food allergy should be considered in patients with high suspicion for FPIES. Food protein-induced allergic proctocolitis (FPIAP) is the least severe form of the non-IgE-mediated syndromes and causes chronic, blood-streaked stools that spontaneously resolve by approximately 1 year of age in otherwise normally growing and developing infants.[59] Food protein-induced enteropathy (FPE) presents with chronic, non-bloody diarrhea that results in failure to thrive and, in some, malabsorption with spontaneous resolution by 2 years old. It can develop after infectious gastroenteritis and result in secondary lactose intolerance causing the protracted diarrhea.[60,61] FPIES is the most severe of the non-IgE-mediated food allergy syndromes and often presents acutely or with acute on chronic findings that can mimic both FPIAP and FPE; however, the acute FPIES presentation involves vomiting, which is not typically seen in FPIAP or FPE. In addition, the age of resolution tends to be later in FPIES.

Sometimes, abnormal abdominal gas patterns seen on imaging in preterm infants with FPIES can be confused for necrotizing enterocolitis (NEC).[59] A study by Kim *et al.*[61] found that symptomatic presentation of preterm infants with FPIES compared to those with NEC did not significantly differ. In fact, they found that pneumatosis intestinalis on ultrasonography was more common among preterm patients with FPIES than those with NEC. Qi *et al.*[62] proposed that IL-27 can potentially be used to distinguishing between FPIES and necrotizing enterocolitis, as IL-27 levels are significantly higher in patients with NEC. More studies, however, are needed to validate the sensitivity and specificity that the group determined for IL-27 as a potential biomarker for NEC.[62] Given these findings, radiographic testing in the routine work-up of suspected FPIES is strongly discouraged.[12]

With an acute FPIES episode, the differential diagnosis frequently includes viral gastroenteritis, sepsis, and anaphylaxis given the systemic findings on presentation. In the

https://doi.org/10.4168/aair.2022.14.6.587

case of severe episodes, methemoglobinemia appreciated on laboratory work up can also be seen in inborn errors of metabolism, which must be considered given that patients often present in infancy.[59] Other diagnoses to consider include lactose intolerance, gastrointestinal reflux disease, eosinophilic gastrointestinal disorders, immune enteropathies, congenital or acquired causes of bowel obstruction, metabolic disorders, and primary immunodeficiencies (**Table 3**).[12,59,60,63]

MANAGEMENT

In the case of an acute FPIES reaction, supportive care is the mainstay of treatment.[12] If a reaction were to occur at home, oral rehydration should be attempted if there has been minimal vomiting (1–2 times) and no associated lethargy; however, should vomiting be repetitive (> 3 times) with associated moderate to severe lethargy, seeking emergency medical care to initiate intravenous hydration and, in patients older than 6 months, ondansetron is recommended.[12] For patients with severe symptoms consistent with shock (significant lethargy, hypotension), fluid resuscitation with intravenous fluid boluses followed by maintenance fluids should be administered, as well as IV ondansetron.[64] Though there is no evidence supporting the benefit of corticosteroid use during a severe FPIES reaction, it is often given for presumed gastrointestinal inflammation.[53] Vital signs and mental status should be monitored closely, blood pressure support should be initiated if indicated, and

Table 3. Differential diagnoses to consider in FPIES

Condition	Distinguishing clinical features
Infectious	
1. Gastroenteritis (viral, bacterial)	1. Fever, presence of sick contacts
2. Sepsis	2. Positive bacterial/viral cultures and tests, improvement with antibiotics, lack of spontaneous resolution following food withdrawal
3. Necrotizing enterocolitis	3. Presentation in neonatal period (particularly in preterm infants), presence of pneumatosis intestinalis, fever, absence of peripheral blood eosinophilia
Allergic/Immunologic	
1. IgE-mediated food allergy/anaphylaxis	1. Immediate onset after food exposure, positive serum IgE or skin testing, associated respiratory and cutaneous symptoms
2. FPIAP	2. Primarily blood ± mucus in stool, typical resolution by 1 year of age[59]
3. FPE	3. Chronic non-bloody diarrhea that can be triggered by gastroenteritis, resolves by 2 years of age[59,60]
4. Inflammatory bowel disease	4. Chronic abdominal symptoms, often associated family history of autoimmunity
5. Primary immunodeficiency	5. Frequent, severe, and opportunistic infections
Gastrointestinal	
1. Lactose intolerance	1. Gas, bloating, and diarrhea with milk exposures
2. Gastroesophageal reflux disease	2. Frequent spit up, difficulty feeding, weight loss
3. Celiac disease	3. Nutritional deficiencies from malabsorption, including anemia
4. EGID	4. Mixed IgE and cell-mediated process not related to specific food intake, likely presence of food-specific IgE, inappropriate accumulation of eosinophils in gastrointestinal tract on biopsy resulting in organ dysfunction *i.e.*, dysphagia, less severe vomiting[70]
Anatomic	
1. Hirschsprung disease	1. Delayed passage of meconium, significant abdominal distension
2. Obstruction (*i.e.*, volvulus, malrotation)	2. Bilious vomiting
Metabolic	
1. Mitochondrial disorders 2. Pyruvate dehydrogenase deficiency 3. Fructose intolerance 4. Ketothiolase deficiency	1. Developmental delay, progressive neurological deterioration, organomegaly, seizures, electrolyte derangements triggered by infection/stressors
Behavioral	
1. Food aversion	1. Associated with neurodevelopmental disorders, psychosocial stressors

Adapted from Nowak-Węgrzyn *et al.*[12]
FPIES, food protein-induced enterocolitis syndrome; IgE, immunoglobulin E; FPIAP, food protein induced allergic proctocolitis; FPE, food protein-induced enteropathy; EGID, eosinophilic gastrointestinal disorders.

https://doi.org/10.4168/aair.2022.14.6.587

electrolyte abnormalities should be corrected as needed.[64] Counseling families on trigger food avoidance, reviewing signs of dehydration and shock, and potentially providing a prescription for oral ondansetron is recommended in the case of accidental ingestion or encounter with a new trigger food in patients with FPIES. Of note, epinephrine is not indicated for the treatment of acute FPIES treatment. Though patients with atypical FPIES have trigger food-specific IgE, anaphylaxis in these patients is rare.[64]

Infants with cow's milk or soy protein FPIES can often tolerate breastfeeding; however, for formula-fed infants, extensively hydrolyzed casein-based formula is typically recommended.[12] There have, however, been cases reported of these formulas exacerbating a patient's acute FPIES or persistent failure to thrive in the setting of chronic FPIES.[65,66] Among these infants, 10%–20% require an amino acid-based formula (AAF).[12] A recent double-blind multi-center randomized controlled trial found that using a synbiotic-containing AAF in patients with cow's milk FPIES resulted in higher levels of bifidobateria and lower ratio of *Eubacterium rectale* to *Clostridium coccoides* in their feces, similar to those seen in healthy breastfed infants.[67] For patients with severe FPIES, an AAF might be a better initial formula choice.

In general, children with FPIES, especially those with multiple food FPIES, are at an increased risk for developing food aversion, poor weight gain, and nutritional deficiencies.[7] The psychosocial burden of this is high for caregivers, especially in light of the coronavirus disease 2019 (COVID-19) pandemic.[68] Dietary management currently entails avoiding allergens, advancing complementary foods to encourage normal growth and development, and providing families with detailed individualized feeding plans to ease the burden on caregivers when possible.[69] Another option that shows promise is oral desensitization, often utilized in the dietary management of IgE-mediated food allergy. Miceli Sopo *et al.*[70] performed oral desensitization in a 9-year-old patient with persistent, acute FPIES to egg whose skin prick tests were negative in the setting of 6 failed OFCs. Approximately 13.5 months after initiating desensitization, the patient was able to tolerate the equivalent of one entire raw egg. One month after the patient stopped ingesting egg upon completing the desensitization protocol, an OFC was performed with one raw egg and was negative with no adverse reactions. Large randomized controlled trials are needed to clarify the role of oral desensitization in different FPIES phenotypes with various food triggers, but the possibility of inducing tolerance sooner in FPIES provides exciting avenues for advancing management and patient quality of life.

CONCLUSION

In summary, FPIES is a non-IgE-mediated food allergy syndrome with an incidence and prevalence higher than was once believed.[2] Though a variety of foods can trigger FPIES, the most common triggers are cow's milk and soy protein.[12,22] The risk of multiple food FPIES is significantly higher in those with solid food or soy protein FPIES.[24] Reassuringly, the majority of FPIES cases resolve by school age.[1] The mechanism of disease appears to be primarily driven by the innate immune response, with contributions from the adaptive immune system.[36,37] Emerging studies also highlight the significance of the central nervous system and the gut microbiome in the pathogenesis of FPIES, identifying them as potential therapeutic targets.[39,46,47]

Major and minor diagnostic criteria highlighted in the international consensus guidelines from the American Academy of Allergy, Asthma & Immunology help guide the diagnosis of

https://doi.org/10.4168/aair.2022.14.6.587

FPIES.[12] An FPIES episode is distinct from an IgE-mediated food allergy, mainly due to the absence of cutaneous and respiratory findings. When clinical history and presentation alone are not enough for diagnosis, especially given that an FPIES episode can mimic other disease processes, oral food challenges are available as the diagnostic gold standard. Though no diagnostic markers are officially available to diagnose FPIES, measuring TARC levels could aid in diagnosis.[57,58] In addition to trigger avoidance, the mainstay of FPIES treatment is supportive care, primarily rehydration and anti-emetics.[12] In the case of severe episodes with concern for shock, intensive care with intravenous fluid deficit repletion and continuous maintenance hydration, blood pressure support, and electrolyte corrections might be indicated.

Caring for a child with FPIES places undue burden on caregivers, especially highlighted by the recent COVID-19 pandemic.[69] The need for specialized formulas and avoidance of allergenic foods can be challenging and costly, not to mention result in poor weight gain and food avoidance in patients.[12,68] Oral desensitization, often employed in the dietary management of IgE-mediated food allergies, shows potential as a means for promoting tolerance to a food trigger in patients with FPIES.[70]

Though the last 10 to 15 years have seen a significant expansion in our understanding of FPIES, there is still more that needs to be discovered about this unique disease process. In addition to identifying more therapeutic targets, criteria for diagnosis and positive oral food challenges remain controversial and require further validation and standardization. Moreover, larger randomized clinical trials are needed to optimize current management practices. As highlighted in this review, avenues for future research are vast and the upcoming decade holds great promise in lifting the veil on FPIES.

REFERENCES

1. Nowak-Wegrzyn A, Berin MC, Mehr S. Food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract 2020;8:24-35.
PUBMED | CROSSREF
2. Cianferoni A. Food protein-induced enterocolitis syndrome epidemiology. Ann Allergy Asthma Immunol 2021;126:469-77.
PUBMED | CROSSREF
3. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. J Allergy Clin Immunol 2011;127:647-653.e1.
PUBMED | CROSSREF
4. Mehr S, Frith K, Barnes EH, Campbell DE; FPIES Study Group. Food protein-induced enterocolitis syndrome in Australia: a population-based study, 2012-2014. J Allergy Clin Immunol 2017;140:1323-30.
PUBMED | CROSSREF
5. Alonso SB, Ezquiaga JG, Berzal PT, Tardón SD, San José MM, López PA, et al. Food protein-induced enterocolitis syndrome: increased prevalence of this great unknown-results of the PREVALE study. J Allergy Clin Immunol 2019;143:430-3.
PUBMED | CROSSREF
6. Nowak-Wegrzyn A, Warren CM, Brown-Whitehorn T, Cianferoni A, Schultz-Matney F, Gupta RS. Food protein-induced enterocolitis syndrome in the US population-based study. J Allergy Clin Immunol 2019;144:1128-30.
PUBMED | CROSSREF
7. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. Pediatrics 2009;123:e459-64.
PUBMED | CROSSREF

8. Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. J Allergy Clin Immunol 2012;130:1199-200.
PUBMED | CROSSREF
9. Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. J Allergy Clin Immunol Pract 2014;2:355-357.e1.
PUBMED | CROSSREF
10. Du YJ, Nowak-Węgrzyn A, Vadas P. FPIES in adults. Ann Allergy Asthma Immunol 2018;121:736-8.
PUBMED | CROSSREF
11. Du YJ, Gonzalez-Delgado P, Vadas P. Food protein-induced enterocolitis syndrome: not just in children. Ann Allergy Asthma Immunol 2021;127:291-2.
PUBMED | CROSSREF
12. Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K, et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: executive summary-Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2017;139:1111-1126.e4.
PUBMED | CROSSREF
13. Su KW, Patil SU, Stockbridge JL, Martin VM, Virkud YV, Huang JL, et al. Food aversion and poor weight gain in food protein-induced enterocolitis syndrome: a retrospective study. J Allergy Clin Immunol 2020;145:1430-1437.e11.
PUBMED | CROSSREF
14. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. Arch Dis Child 2009;94:425-8.
PUBMED | CROSSREF
15. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol 2014;134:382-9.
PUBMED | CROSSREF
16. Vazquez-Ortiz M, Machinena A, Dominguez O, Alvaro M, Calvo-Campoverde K, Giner MT, et al. Food protein-induced enterocolitis syndrome to fish and egg usually resolves by age 5 years in Spanish children. J Allergy Clin Immunol Pract 2017;5:512-515.e1.
PUBMED | CROSSREF
17. Lee E, Campbell DE, Barnes EH, Mehr SS. Resolution of acute food protein-induced enterocolitis syndrome in children. J Allergy Clin Immunol Pract 2017;5:486-488.e1.
PUBMED | CROSSREF
18. Lemoine A, Colas AS, Le S, Delacourt C, Tounian P, Lezmi G. Food protein-induced enterocolitis syndrome: a large French multicentric experience. Clin Transl Allergy 2022;12:e12112.
PUBMED | CROSSREF
19. Wang KY, Lee J, Cianferoni A, Ruffner MA, Dean A, Molleston JM, et al. Food protein-induced enterocolitis syndrome food challenges: experience from a large referral center. J Allergy Clin Immunol Pract 2019;7:444-50.
PUBMED | CROSSREF
20. Lange L, Gernert S, Berger M, Arens A, Rache L, Delissen J, et al. Different patterns of foods triggering FPIES in Germany. J Allergy Clin Immunol Pract 2022;10:1063-9.
PUBMED | CROSSREF
21. Onesimo R, Dello Iacono I, Giorgio V, Limongelli MG, Miceli Sopo S. Can food protein induced enterocolitis syndrome shift to immediate gastrointestinal hypersensitivity? A report of two cases. Eur Ann Allergy Clin Immunol 2011;43:61-3.
PUBMED
22. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. J Allergy Clin Immunol Pract 2013;1:343-9.
PUBMED | CROSSREF
23. Jarvinen-Seppo KM, Sickles L, Nowak-Wegrzyn AH. Clinical characteristics of children with food protein-induced enterocolitis (FPIES). J Allergy Clin Immunol 2010;125:AB85.
CROSSREF
24. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. Pediatrics 2003;111:829-35.
PUBMED | CROSSREF
25. Ocak M, Akarsu A, Sahiner UM, Soyer O, Sekerel BE. Phenotypes and natural history of food protein-induced enterocolitis syndrome in the east Mediterranean region. Allergy Asthma Proc 2020;41:420-7.
PUBMED | CROSSREF

26. Akashi M, Hayashi D, Kajita N, Kinoshita M, Ishii T, Tsumura Y, et al. Recent dramatic increase in patients with food protein-induced enterocolitis syndrome (FPIES) provoked by hen's egg in Japan. J Allergy Clin Immunol Pract 2022;10:1110-1112.e2.
PUBMED | CROSSREF

27. Baldwin S, Werther R, Hargrove A, Anagnostou A, Mehr S. Food protein-induced enterocolitis syndrome to nuts: an increasing phenomenon. Ann Allergy Asthma Immunol 2021;126:464-6.
PUBMED | CROSSREF

28. Lopes JP, Cox AL, Baker MG, Bunyavanich S, Oriel RC, Sicherer SH, et al. Peanut-induced food protein-induced enterocolitis syndrome (FPIES) in infants with early peanut introduction. J Allergy Clin Immunol Pract 2021;9:2117-9.
PUBMED | CROSSREF

29. Venter C, Palumbo MP, Glueck DH, Sauder KA, O'Mahony L, Fleischer DM, et al. The maternal diet index in pregnancy is associated with offspring allergic diseases: the Healthy Start study. Allergy 2022;77:162-72.
PUBMED | CROSSREF

30. Boyer J, Sgambelluri L, Yuan Q. Association of antibiotic usage with food protein-induced enterocolitis syndrome development from a caregiver's survey. JPGN Rep 2021;2:e132.
PUBMED | CROSSREF

31. Okazaki F, Wakiguchi H, Korenaga Y, Takahashi K, Yasudo H, Fukuda K, et al. Food protein-induced enterocolitis syndrome in children with down syndrome: a pilot case-control study. Nutrients 2022;14:388.
PUBMED | CROSSREF

32. Maciag MC, Bartnikas LM, Sicherer SH, Herbert LJ, Young MC, Matney F, et al. A slice of food protein-induced enterocolitis syndrome (FPIES): insights from 441 children with FPIES as provided by caregivers in the International FPIES Association. J Allergy Clin Immunol Pract 2020;8:1702-9.
PUBMED | CROSSREF

33. Banerjee A, Wood R, Dantzer J, Dunlop J, Isola J, Keet C. The association of food protein-induced enterocolitis syndrome (FPIES) with personal and familial co-morbidities. J Allergy Clin Immunol 2022;149:AB206.
CROSSREF

34. Ruffner MA, Wang KY, Dudley JW, Cianferoni A, Grundmeier RW, Spergel JM, et al. Elevated atopic comorbidity in patients with food protein-induced enterocolitis. J Allergy Clin Immunol Pract 2020;8:1039-46.
PUBMED | CROSSREF

35. Shoda T, Isozaki A, Kawano Y. Food protein-induced gastrointestinal syndromes in identical and fraternal twins. Allergol Int 2011;60:103-8.
PUBMED | CROSSREF

36. Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Węgrzyn A, Berin MC. Systemic innate immune activation in food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2017;139:1885-1896.e9.
PUBMED | CROSSREF

37. Mehr S, Lee E, Hsu P, Anderson D, de Jong E, Bosco A, et al. Innate immune activation occurs in acute food protein-induced enterocolitis syndrome reactions. J Allergy Clin Immunol 2019;144:600-602.e2.
PUBMED | CROSSREF

38. Berin MC, Lozano-Ojalvo D, Agashe C, Baker MG, Bird JA, Nowak-Wegrzyn A. Acute FPIES reactions are associated with an IL-17 inflammatory signature. J Allergy Clin Immunol 2021;148:895-901.e6.
PUBMED | CROSSREF

39. Su KW, Shreffler WG, Yuan Q. Gastrointestinal immunopathology of food protein-induced enterocolitis syndrome and other non-immunoglobulin E-mediated food allergic diseases. Ann Allergy Asthma Immunol 2021;126:516-23.
PUBMED | CROSSREF

40. Caubet JC, Bencharitiwong R, Ross A, Sampson HA, Berin MC, Nowak-Węgrzyn A. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. J Allergy Clin Immunol 2017;139:572-83.
PUBMED | CROSSREF

41. Kimura M, Ito Y, Shimomura M, Morishita H, Meguro T, Adachi Y, et al. Cytokine profile after oral food challenge in infants with food protein-induced enterocolitis syndrome. Allergol Int 2017;66:452-7.
PUBMED | CROSSREF

42. Suzuki H, Tsutsumi Y, Morita H, Motomura K, Umehara N, Sago H, et al. Cord blood eosinophilia precedes neonatal onset of food-protein-induced enterocolitis syndrome (FPIES). Allergol Int 2021;70:262-5.
PUBMED | CROSSREF

43. Wada T, Toma T, Muraoka M, Matsuda Y, Yachie A. Elevation of fecal eosinophil-derived neurotoxin in infants with food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2014;25:617-9.
PUBMED | CROSSREF

44. Pecora V, Prencipe G, Valluzzi R, Dahdah L, Insalaco A, Cianferoni A, et al. Inflammatory events during food protein-induced enterocolitis syndrome reactions. Pediatr Allergy Immunol 2017;28:464-70.
PUBMED | CROSSREF

45. Berin MC. Advances in understanding immune mechanisms of food protein-induced enterocolitis syndrome. Ann Allergy Asthma Immunol 2021;126:478-81.
PUBMED | CROSSREF

46. Hoffmann NV, Ahmed A, Fortunato JE. Food protein-induced enterocolitis syndrome: dynamic relationship among gastrointestinal symptoms, immune response, and the autonomic nervous system. Ann Allergy Asthma Immunol 2021;126:498-505.
PUBMED | CROSSREF

47. Boyer J, Scuderi V. Comparison of the gut microbiome between food protein-induced enterocolitis syndrome (FPIES) infants and allergy-free infants. Ann Allergy Asthma Immunol 2017;119:e3.
CROSSREF

48. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr 1978;93:553-60.
PUBMED | CROSSREF

49. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr 1998;133:214-9.
PUBMED | CROSSREF

50. Leonard SA, Nowak-Węgrzyn A. Clinical diagnosis and management of food protein-induced enterocolitis syndrome. Curr Opin Pediatr 2012;24:739-45.
PUBMED | CROSSREF

51. Miceli Sopo S, Greco M, Monaco S, Tripodi S, Calvani M. Food protein-induced enterocolitis syndrome, from practice to theory. Expert Rev Clin Immunol 2013;9:707-15.
PUBMED | CROSSREF

52. Leonard SA, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome. Pediatr Clin North Am 2015;62:1463-77.
PUBMED | CROSSREF

53. Leonard SA, Pecora V, Fiocchi AG, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: a review of the new guidelines. World Allergy Organ J 2018;11:4.
PUBMED | CROSSREF

54. Kimura M, Ito Y, Tokunaga F, Meguro T, Shimomura M, Morishita H, et al. Increased C-reactive protein and fever in Japanese infants with food protein-induced enterocolitis syndrome. Pediatr Int 2016;58:826-30.
PUBMED | CROSSREF

55. Infante S, Marco-Martín G, Zubeldia JM, Fuentes-Aparicio V, Alvarez-Perea A, Cabrera-Freitag P, et al. Oral food challenge in food protein-induced enterocolitis syndrome by fish: is there any room for improvement? Int Arch Allergy Immunol 2019;179:215-20.
PUBMED | CROSSREF

56. Sultafa J, McKibbon L, Roberts H, Sarraj J, Kim H. Modified oral food challenge protocol approach in the diagnosis of food protein-induced enterocolitis syndrome. Allergy Asthma Clin Immunol 2022;18:8.
PUBMED | CROSSREF

57. Makita E, Kuroda S, Itabashi K, Sugawara D, Ichihashi K. Evaluation of the diagnostic accuracy of thymus and activation-regulated chemokine to discriminate food protein-induced enterocolitis syndrome from infectious gastroenteritis. Int Arch Allergy Immunol 2021;182:229-33.
PUBMED | CROSSREF

58. Okura Y, Shimomura M, Takahashi Y, Kobayashi I. Usefulness of thymus and activation-regulated chemokine in solid food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2022;33:e13677.
PUBMED | CROSSREF

59. Suresh R, Kim SL, Sicherer SH, Ciaccio CE. Food allergy. In: Guandalini S, Dhawan A, editors. Textbook of pediatric gastroenterology, hepatology and nutrition. 2nd ed. Cham: Springer; 2022. 345-59.

60. Iyngkaran N, Robinson MJ, Sumithran E, Lam SK, Puthucheary SD, Yadav M. Cows' milk protein-sensitive enteropathy. An important factor in prolonging diarrhoea of acute infective enteritis in early infancy. Arch Dis Child 1978;53:150-3.
PUBMED | CROSSREF

61. Kim YI, Joo JY, Jung YH, Choi CW, Kim BI, Yang HR. Differentiation of food protein-induced enterocolitis syndrome misleading to necrotizing enterocolitis. Ann Allergy Asthma Immunol 2022;128:193-8.
PUBMED | CROSSREF

62. Qi Y, Liu C, Zhong X, Ma X, Zhou J, Shi Y, et al. IL-27 as a potential biomarker for distinguishing between necrotising enterocolitis and highly suspected early-onset food protein-induced enterocolitis syndrome with abdominal gas signs. EBioMedicine 2021;72:103607.
PUBMED | CROSSREF

63. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol 2004;113:11-28.
PUBMED | CROSSREF

64. Leonard SA, Miceli Sopo S, Baker MG, Fiocchi A, Wood RA, Nowak-Węgrzyn A. Management of acute food protein-induced enterocolitis syndrome emergencies at home and in a medical facility. Ann Allergy Asthma Immunol 2021;126:482-488.e1.
PUBMED | CROSSREF

65. Kabuki T, Joh K. Extensively hydrolyzed formula (MA-mi) induced exacerbation of food protein-induced enterocolitis syndrome (FPIES) in a male infant. Allergol Int 2007;56:473-6.
PUBMED | CROSSREF

66. Joshi SR, Bird JA. Cow's milk-associated chronic food protein-induced enterocolitis syndrome exacerbated by extensively hydrolyzed formula. Ann Allergy Asthma Immunol 2018;120:532-3.
PUBMED | CROSSREF

67. Candy DC, Van Ampting MT, Oude Nijhuis MM, Wopereis H, Butt AM, Peroni DG, et al. A synbiotic-containing amino-acid-based formula improves gut microbiota in non-IgE-mediated allergic infants. Pediatr Res 2018;83:677-86.
PUBMED | CROSSREF

68. Trogen B, Jin H, Cianferoni A, Chehade M, Schultz F, Chavez A, et al. A survey examining the impact of COVID-19 on food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract 2022;10:312-314.e3.
PUBMED | CROSSREF

69. Groetch M, Durban R, Meyer R, Venter C, Nowak-Wegrzyn A. Dietary management of food protein-induced enterocolitis syndrome during the coronavirus disease 2019 pandemic. Ann Allergy Asthma Immunol 2021;126:124-6.
PUBMED | CROSSREF

70. Miceli Sopo S, Sinatti D, Gelsomino M. Oral desensitization in egg acute food protein-induced enterocolitis syndrome. Eur Rev Med Pharmacol Sci 2021;25:5766-8.
PUBMED | CROSSREF