# Food protein-induced enterocolitis syndrome (FPIES): Beyond the guidelines

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## ABSTRACT

**Background:** *Food protein–induced enterocolitis syndrome (FPIES) is a non–immunoglobulin E (IgE) cell mediated food allergy that can cause severe symptoms and is considered an allergic emergency.*

**Objective:** *To describe FPIES epidemiology and appraise the approach to diagnosis and management.*

**Methods:** *A review of the relevant articles published in the peer-reviewed journals since the publication of the First International FPIES Consensus Guidelines in 2017.*

**Results:** *FPIES is estimated to affect 0.51–0.9% of children and 0.22% of adults in the United States. It typically presents with protracted, projectile vomiting, which occurs within 1–4 hours of ingesting culprit foods, sometimes followed by diarrhea within 24 hours of ingestion. In ~15–20% of severe cases, patients go into hypovolemic or distributive shock. In chronic FPIES, infants may have failure to thrive and weight loss. The most common triggers include cow's milk, oat, rice, and avocado, with egg and peanut being more frequently reported. Examples of other common fruit and vegetable triggers include banana, apple, and sweet potato. FPIES can be classified into acute, chronic, adult-onset, or atypical subtypes. FPIES is associated with comorbid atopic conditions of IgE-mediated food allergy, atopic dermatitis, asthma, allergic rhinitis, and eosinophilic esophagitis. The natural history of infantile FPIES is generally favorable, with the exception of fish FPIES. Seafood FPIES in adults has low rates of resolution over 3–5 years. Correctly identifying FPIES can be challenging because there are no specific biomarkers for diagnosis and the constellation of symptoms may mimic those of infectious enteritis or sepsis. Management relies on dietary food avoidance, periodic re-evaluations for tolerance with oral food challenges, and management of acute reactions with rehydration and antiemetic ondansetron. Although the pathophysiology of FPIES remains poorly understood, underlying mechanisms such as cytokine release, leukocyte activation, and impaired gastrointestinal mucosal barrier function may act as cornerstones for further research.*

**Conclusion:** *Prevention, laboratory diagnostic testing, and strategies to accelerate tolerance development are urgent unmet needs in FPIES.*

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Food protein-induced enterocolitis syndrome (FPIES) is a non–immunoglobulin E (IgE) cell-mediated food allergy.[1] FPIES affects ~375,000 children in the United States (0.51% of the pediatric population) and 550,000 adults (0.22% of the U.S. adult population).[2] The more recent data from the Gastrointestinal Microbiome and Allergic Proctocolitis birth cohort in the suburban Boston reported the cumulative incidence of FPIES in the first 3 years of life as 0.9%, which highlights the possibility of an even higher or increasing prevalence of FPIES in infancy.[3] FPIES can be classified into acute, chronic, adult onset, or atypical subtypes. The most common subtype is acute FPIES, which affects an estimated 90% of patients.[4] It typically presents with protracted, projectile vomiting, which occurs within 1–4 hours of ingesting culprit foods, and diarrhea, which occurs within 24 hours of ingestion. Patients may also present with lethargy and pallor; of note, reactions are with the notable absence of typical cutaneous and respiratory allergy symptoms.[5] In more severe cases, FPIES can lead to significant dehydration, metabolic derangements, and inflammatory states reflected with elevated C-reactive protein, leukocytosis with neutrophilic predominance, and thrombocytosis. In chronic states, patients develop low albumin and

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total protein, anemia, weight loss, and failure to thrive.[6] In ~15–20% of severe cases, patients go into hypovolemic or distributive shock. Correctly identifying FPIES can be challenging because there are no specific biomarkers for diagnosis, and the constellation of symptoms may mimic those of infectious enteritis or sepsis. Although the pathophysiology remains poorly understood, recent studies conducted during oral food challenges (OFC) have shown a link between activation of the purine pathway and serotonin release, with a constellation of adaptive and innate immune responses likely contributing to the predominant gastrointestinal symptoms.[7–9] FPIES is managed by dietary food avoidance and emergency treatment of reactions. The aim of this review is to provide current information about the epidemiology, pathophysiology, diagnosis, and management of FPIES.

## Brief History

FPIES was first identified in the literature starting early in 1960s and 1970s; however, these were isolated case reports in which the constellation of symptoms involved in FPIES were identified.[4] More specifically, infants were found to develop acute enterocolitis after ingestion of cow's milk or soy milk.[10,11] In 1998, the first clinical features of FPIES were described with solid food triggers and atypical FPIES was identified.[12] In 2017, the first international consensus guidelines for the diagnosis and management of FPIES were published.[1] Since then, substantial progress has been made in getting FPIES recognized by the medical community, including attaining an *International Classification of Diseases, Tenth Revision* code (https://icd.who.int/), the virtual National Institutes of Health FPIES workshop in June 2022, and inclusion of FPIES and other non–IgE-mediated food allergies in the National Institutes of Health National Institute of Allergy and Infectious Diseases funding opportunities.[4]

## Phenotypes

*Acute FPIES.* Acute FPIES, which occurs in ~90% of cases of infants, is characterized by acute onset emesis, typically within 1–4 hours of ingesting the offending agent. This may also be associated with lethargy, pallor, hypotonia, with or without diarrhea.[5] Symptoms typically resolve within 24 hours and patients tend to remain asymptomatic between episodes; reactions manifest again with intermittent ingestion of trigger foods.

*Chronic FPIES.* Chronic FPIES occurs in ~10% of patients and is characterized by frequent episodes of vomiting or diarrhea, which develop over the period of days to weeks.[13] Chronic FPIES develops when food is ingested regularly, and symptoms resolve within days to weeks after food elimination. Chronic FPIES is usually diagnosed in infants < 4 months old who are fed cow's milk or soy formulas; to date, only one case of chronic FPIES in an adult has been documented.[10,11,14] Chronic FPIES may be associated with weight loss or failure to thrive.

*Atypical Food Protein–Induced Enterocolitis.* Approximately 25% of patients have a positive skin-prick test result and/or detectable serum IgE to the trigger agent.[15,16] When patients have detectable food-specific IgE as well as a clinical history consistent with FPIES, atypical FPIES is diagnosed. Approximately one in three of these patients might progress to IgE-mediated allergy, which triggers potentially dangerous immediate reactions, *e.g.,* anaphylaxis, especially noted in those with cow's milk allergy. Patients with atypical FPIES may also have a more protracted course, with longer times until resolution.[12,15]

*Adult Food Protein–Induced Enterocolitis.* Historically, FPIES has believed to have been a disorder that primarily affected infants and young children; however, more recently, FPIES has been reported in teenagers and adults. FPIES to seafood, fish, and shellfish can start in older children, teenagers, and adults.[17,18] There have also been reported cases of FPIES in patients attributed to dairy, wheat, and egg.[19,20] The most common presentation is new symptoms to patients who had previously tolerated these trigger foods. Symptoms are often dramatic, severe abdominal pain, nausea, with vomiting and diarrhea. Limited information remains with regard to the prevalence, risk factors, history, and comorbid conditions implicated in adult FPIES.[21] However, one prospective study conducted from 2007 to 2016 at a single center in Spain identified FPIES that occurred to seafood at a median age of 25 years ($N = 25$). Most of these patients presented with abdominal pain and emesis, and, notably, all had tolerated the trigger food. Sixty percent of these patients reacted to crustaceans as a single food group. Another significant finding was that 88% of these patients were female.[21]

The approach to adult patients remains variable. Diagnostic modalities most often used by clinicians for adult FPIES include skin-prick testing, OFC, or specific IgE testing in descending order. The anticipatory guidance to adults has also varied, with most patients being told to avoid the specific foods to which they reacted, whereas some patients are told to avoid the whole group of foods that caused a reaction. There is also inconsistency with regard to the prognosis of the condition due to limited data. Given the variability in diagnostic testing and guidance, there is a clear indication of the need for specific guidelines for adults, which have not yet been estabi-shed.

### Food Protein–Induced Enterocolitis Triggers

A retrospective study of ~410 members of the International FPIES Association, which implicated insights from the caregivers of ~441 children identified common food groups that were avoided.[22] The food groups most avoided were grains (60.0%), cow's milk (52.4%), vegetables (42.7%), and fruits (38.0%).[22] Of these children, 69.4% avoided multiple food groups (median number of food groups avoided, 3), and there was an association between those who avoided multiple food groups and those who had first-degree relatives with FPIES.[22] Emerging food triggers in the United States include peanut, tree nut, and egg based on various published studies.[23–25] In our unpublished experience at New York University, egg was responsible for ~30%; peanut,15%; and tree nuts, 9.8% of the cases in patients over the past 36 months. Similar observations have been reported recently, with egg and peanut being the third and fourth most common triggers in infants in another large academic U.S. center.[26] Global triggers seem to be similar, with cow's milk, rice, soy, and seafood remaining common triggers.[27] An apparent increase in peanut and egg FPIES raises concerns as to whether early introduction of these foods is a risk factor for developing FPIES. This association remains speculative, and further investigation is required. However, in our opinion, weighing the risk of developing IgE-mediated peanut and egg allergy compared with FPIES, early introduction of peanut and egg is preferred for all infants.

### Food Protein–Induced Enterocolitis Diagnosis

Given the limited insights into the pathophysiology of FPIES and the lack of biomarkers to confirm the diagnosis, FPIES is currently recognized as a constellation of symptoms; this frequently leads to a delayed diagnosis, especially in adults. Currently, patients are required to meet one major criterion and three or more minor criteria (Table 1) for acute FPIES diagnosis.[1] FPIES is diagnosed clinically but can be confirmed by OFC. OFC is usually performed after a period of food avoidance to evaluate for resolution of FPIES. These OFCs, depending on the nutritional value and social importance of the food, are typically done 6–24 months after the most recent FPIES reaction. The timing of FPIES OFC involves shared decision-making between the physician and patient. The diagnosis of chronic FPIES is less well defined and is delineated in Table 2. Without food challenge, the diagnosis of chronic FPIES remains presumptive based on clinical symptoms.[6,28] Of note, atypical FPIES is more likely in infants with atopic dermatitis with IgE-mediated food allergy to another food(s). In those patients, skin-prick or blood testing may be considered at diagnosis and/or before attempted reintroduction of the food; however, in most patients' food allergy testing is negative because FPIES is not IgE mediated. Although not evidence based, we would also consider testing for those FPIES triggers that are common allergens in IgE-mediated food allergy: egg, peanut, tree nuts, sesame, fish, shellfish, especially in patients with atopic comorbidities such as AD, wheezing or IgE-mediated food allergy to other foods.

Currently, there is no universally accepted protocol for the standardization of FPIES OFC protocol.[1,29]

Table 1 **Diagnostic criteria for acute FPIES***

| Acute FPIES Diagnostic Criteria |
|---|
| One major criterion: vomiting 1–4 hours after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms, and |
| One or more minor criteria |
| Lethargy |
| Pallor |
| Need for an emergency department visit with any suspected reaction |
| Need for intravenous fluid support with any suspected reaction |
| Diarrhea in 24 hours (usually 5 to 10 hours) |
| Hypotension |
| Hypothermia |
| Additional or recurrent episodes of vomiting after eating the same suspect food |
| Repetitive vomiting episode 1 to 4 hours after eating a different food |

*FPIES = food protein-induced enterocolitis syndrome; IgE = immunoglobulin E.*

**The presence of neutrophilia and/or thrombocytosis supports the diagnosis of acute FPIES; however, these laboratory values are only present in ~50% of cases (from Ref. 5); these laboratory values may also be seen in other clinical syndromes, such as sepsis or gastroenteritis, which makes them less reliable as markers for acute FPIES.*

Table 2 **Diagnostic criteria for chronic FPIES**

| Chronic FPIES Diagnostic Criteria |
|---|
| Resolution of symptoms within days after elimination of offending food |
| Acute recurrence of symptoms when food is reintroduced |
| Typically with emesis within 1–4 hours of ingestion and diarrhea within 24 hours |

*FPIES = Food protein–induced enterocolitis syndrome.*

Table 3 **Protocol for FPIES food challenge**

| | Classic FPIES IgE-Negative | Atypical FPIES IgE-Positive |
|---|---|---|
| Peripheral IV access* | Secured before OFC | Secured before OFC |
| Medications at bedside | Oral rehydration solution; 0.9% NS; ondansetron p.o., i.m., IV; methylprednisolone; oral analgesic (acetaminophen) | For treatment of both IgE-mediated (anaphylaxis) and delayed FPIES symptoms |
| Total dose# | 0.06–0.3 mg of food protein per kg body weight, maximum 3 g or 30% of the age-appropriate serving size | 0.06–0.3 mg of food protein per kg body weight, maximum 3 g or 30% of the age-appropriate serving size |
| Dosing increments (% of the total dose) | Single dose or 3 equal portions over 30 minutes | 1st dose: 10%; 2nd dose: 15%; 3rd dose: 25%; 4th dose: 50% |
| Dosing interval | Once or over 30 minutes | Every 20 minutes |
| Observation period | 4 Hours if no symptoms or longer until resolution of symptoms; discharge home when tolerating liquids by mouth and voiding | 4 Hours if no symptoms or longer until resolution of symptoms; discharge home when tolerating liquids by mouth and voiding |

*FPIES = Food protein–induced enterocolitis syndrome; IgE = immunoglobulin E; IV = intravenous; OFC = oral food challenge; NS = normal saline; p.o. = per os (oral); i.m. = intramuscular.*

**Peripheral IV access should be secured for patients with previous severe reactions to the challenge food, e.g., treated with IVF in the emergency department or when/hospitalized.*

*#If the initial feeding was well tolerated, then the patient will gradually increase to a full serving at home; alternatively, a second session of supervised OFC to a full serving could be scheduled; the feeding of cereal grains and foods with low protein content should be based on the typical serving sizes for patient's age.*

OFCs usually occur under the supervision of a physician in the inpatient or outpatient setting, given that it is a potentially high-risk procedure and requires immediate availability of fluid resuscitation. Food can be administered gradually in three equal portions over 30 minutes or with a single-dose administration of food protein of 0.06–0.6 g/kg body weight. A total of 3 g of food protein should not be exceeded.[30] It should be noted that this protein dose may not be relevant in low protein foods, *e.g.,* rice, and, in these patients, normal portions of food should be used for OFC. In the United States, the initial supervised OFC is followed by a gradual dose increase at home, up to the full serving size for age. Approximately 50% of positive challenges require

Table 4 **Proposed criteria for a positive supervised FPIES OFC and suggested treatment**

| Grade | Severity | Symptoms of a Positive Challenge Result | Treatment |
|---|---|---|---|
| I | Mild | 1–2 episodes of vomiting, normal activity level | Oral rehydration, oral antiemetic |
| II | Moderate | ≥3 Episodes of vomiting or abdominal pain and/or cramping score > 8 on a scale of 0–10 or pain interfering with normal behavior and/or appetite/activities | Oral or IV rehydration; parenteral antiemetic oral analgesic |
| III | Severe | Hypotension with or without other symptoms* | IV rehydration, with or without overnight observation, in addition to the above treatments |
| IV | Potentially life-threatening | Persistent hypotension or shock, with or without other symptoms | Hospital admission for life support, in addition to the above treatments |

*FPIES = Food protein–induced enterocolitis syndrome; OFC = oral food challenge; IV = intravenous.*

**Hypotension: a systolic blood pressure (mm Hg): ages 1–10: systolic <70+(age in years x 2); ≥11 years: <90 mm Hg.*

treatment; the patient may be discharged 6 hours after reaction if he or she is tolerating oral intake well. If no reaction occurs, then the patient is usually discharged 4 hours later. Due to the delayed nature of symptoms, this OFC procedure does not lend itself to identifying the threshold dose for the FPIES reaction. Studies conducted FPIES OFC over several days and reported that, for many patients, the FPIES threshold was < 3 g of food protein and that OFCs with a lower partial dose tend to induce milder symptoms.[31,32] This approach has been tested at Children's Hospital of Philadelphia, where supervised OFC with one third of the typical portion of food for age occurred in the hospital, and the patients were discharged with instructions for a gradual home titration (Table 3).[33] Of the 169 FPIES OFCs, 30 challenge results were positive

Table 5 **Empiric approach to reintroduction of the FPIES food trigger***

| Factor | Home Introduction | Office Introduction | Hospital Introduction | Comments |
|---|---|---|---|---|
| Severity of the past reaction | | | | |
| Mild-moderate | Can be considered | Can be considered | Usually not necessary | Shared decision, provide specific instructions for food dosing and management of FPIES acute reactions, prescribe ondansetron |
| Severe | No | No | Yes | Not appropriate for home or office |
| IgE status | | | | |
| IgE– (classic) FPIES | Can be considered | Can be considered | Depends on the severity of the past reaction, IV access advisable | Typical FPIES challenge protocol in the office; home introduction might follow a gradual protocol, starting from a low dose, e.g., 1/4 teaspoon and doubling the amount every feeding until the regular serving dose is reached; monitor for gastrointestinal symptoms of diarrhea, abdominal discomfort, reflux, vomiting |
| IgE+ (atypical) | Can be considered if low risk of anaphylaxis | Can be considered if low risk of anaphylaxis | Yes, depends on the severity of the past reaction, IV access advisable | No asthma and/or wheezing, no anaphylaxis to other food; dosing per IgE food challenge protocol, observation per FPIES protocol, at least 4 hours |
| Caregiver comfort level with regard to management of FPIES reactions | | | | |
| Low | No | No | Yes | Shared decision |
| High | Yes | Yes | Yes, if severe past reaction | Shared decision, provide specific instructions for food dosing and management of FPIES acute reactions, prescribe ondansetron |

*FPIES = Food protein–induced enterocolitis syndrome; IgE = immunoglobulin E; IV = intravenous.*
**This is an empiric approach based on the clinical practice of one of us (A.N.W.); this approach has not been validated by rigorous studies; in case of any doubts, proceed with a supervised food reintroduction as formal FPIES food challenge.*

(17%): 17 of these were during the initial hospital phase and 13 were during home dose titration. Most of the patients had tolerable reactions during the hospital OFC phase; however, five patients had intractable vomiting and/or lethargy and two were found to be hypotensive. Fourteen of these patients (7.1%) received intravenous fluids (IVF) and 12 patients (6.1%) received ondansetron. As per the home reactions, 13 patients had reactions at home but had tolerated the initial challenge in the hospital. The reactions seemed to be milder, with most having delayed diarrhea. This study concluded that 1-dose protocol followed by dose titration can be considered safe and that early IVF or ondansetron administration may prevent progression to severe symptoms.[33] However, the frequency of reactions during OFC that requires treatment with intravenous fluids may be overestimated by the reports from the large, academic referral centers that attract patients with more severe phenotype and usually secure intravenous peripheral access before OFC.[34] Many mild and moderate FPIES reactions may be successfully managed with oral rehydration and oral or intramuscular ondansetron (Table 4). As with any food allergy, the decision to rechallenge is at the discretion of the physician, patient, and caregivers, the timing of which depends on the nutritional and social value of the food. Prolonged avoidance of the food and delayed introduction may increase the risk of IgE sensitization and feeding difficulties.[35,36] An empirical approach to reintroduction of the FPIES food trigger is presented in Table 5.

### Management of Food Protein–Induced Enterocolitis

*Dietary*. The key to minimizing the risk of further episodes of FPIES is strict avoidance of the offending food. However, there is no need for avoidance with cross-contamination when foods are labeled as "may contain" (Table 6).[37] Patients should avoid baked milk or egg unless tolerated. Most infants react to one or two foods.[26] In a subset of patients with mild FPIES phenotype, baked egg and milk may be tolerated and introduction of baked foods would improve nutritional choices for the patient who is affected.[38,39] If breast-feeding, the maternal diet does not need to be restricted unless the infant is symptomatic with acute or chronic symptoms or not thriving. In cow's milk or soy FPIES, hypoallergenic formula (Extensively Hydrolyzed Formula or Amino Acid) (up to 40%) may be used. In rice FPIES, there are no data on the use of extensively hydrolyzed rice formula (eHRF) in FPIES. The eHRF is not available in the United States; however, eHRF used widely in parts of Europe (France and Germany). An eHRF may be an option in milk FPIES but not for rice FPIES. Plant-based infant formulas such as soy-based formula are based on intact plant protein. There is ~50% co-reactivity to cow's milk and soy formula in infants

Table 6 **Practical dietary management of FPIES**

| Question | Guidance |
|---|---|
| Degree of dietary food avoidance | Avoid all forms of food (cooked and raw), no need for avoidance of traces and foods with precautionary allergy label |
| Introduction of baked milk or egg | Generally under supervision, unless previously tolerated; unknown what percentage of infants with milk/egg FPIES tolerate baked milk/baked egg |
| Avoidance of the food that cause FPIES on direct feeding to the infant in the maternal diet during breast-feeding | Usually not necessary, unless ongoing symptoms of acute or chronic FPIES attributed to transfer of food protein *via* breast milk, failure to thrive |
| Choice of infant formula in cow's milk or soy FPIES or in multiple food FPIES | Majority tolerate extensively hydrolyzed casein- or whey-based hypoallergenic formula, all tolerate amino acid–based formula |
| Use of soy formula in infants with cow's milk FPIES | Introduce carefully, preferably under supervision, especially in the first 6 months of life, due to ~40% co-reactivity |
| Choosing new foods for introduction after FPIES reaction | Generally select a food from a different food group, introduce the first food from the food group more gradually, if well tolerated, subsequent related foods are introduced more liberally |
| Timing of reintroduction of the known FPIES food trigger | Variable, usually between 6 and 24 months after the most recent acute FPIES reaction to this food; shared decision between the physician and the patient and family |

*FPIES = Food protein–induced enterocolitis syndrome.*

< 6 months of age and, therefore, soy formula is generally not recommended as the first choice for infants with cow's milk FPIES.[1] If soy formula is preferable for reasons other than allergenicity, then the introduction should be done under a physician's supervision. Generally, extensively hydrolyzed casein or whey-based infant formulas are recommended. So-called plant milks are not nutritionally suitable for infants and should not be used instead of infant formula. These plant-based beverages may be suitable for children ages > 1 year, under registered dietitian supervision to aid in lifestyle changes and to ensure adequate nutrition.[37] When choosing a new food for introduction after an acute FPIES reaction, it is prudent to select a food from a different food group to minimize the risk of potential cross-reactivity (Fig. 1). In all cases, growth charts in pediatric patients should be monitored.

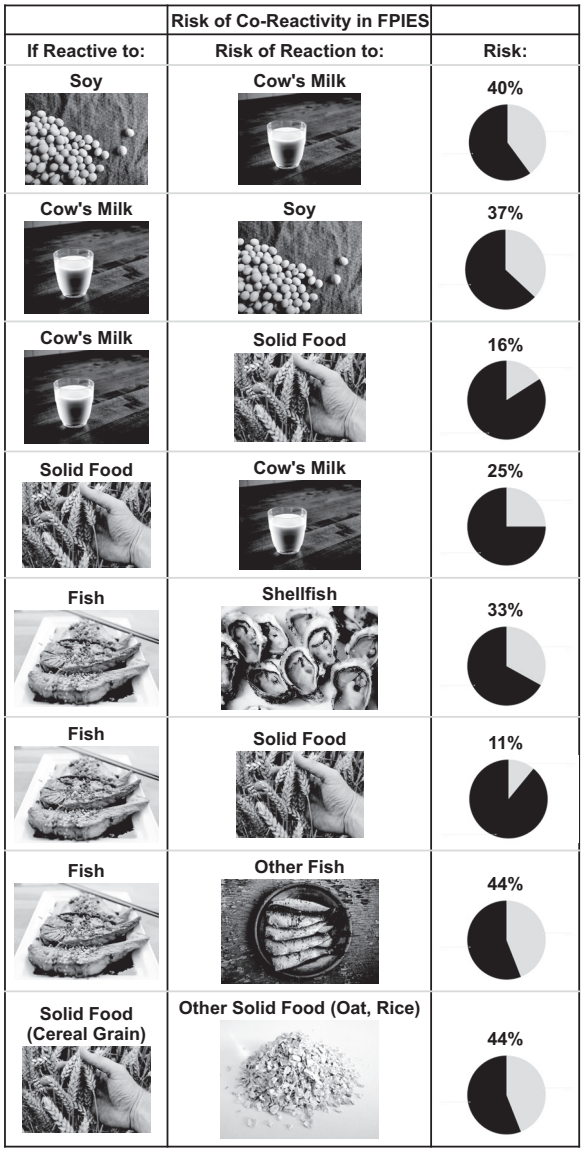


***Figure 1.*** *Patterns of cross and co-reactivity in FPIES. These estimates are limited by the low quality of evidence and they are most applicable to ages < 12 months because onset of FPIES after age 12 months is generally uncommon. Exception is FPIES to seafood, which can start in older children and adults. FPIES = Food protein–induced enterocolitis.*

*Emergency Management of Mild-Moderate FPIES.* In cases in which foods that caused past mild reactions were definitely ingested or if the patient is showing signs of an FPIES reaction, they should be monitored for symptoms.[40] If symptoms occur, then administer ondansetron orally for patients > 6 months (dosing 0.15 mg/kg, maximum 8 mg).[41] This dose may be repeated if the patient has emesis within 10 minutes of the first dose. In patients in whom there has been no vomiting for 20–30 minutes, oral rehydration should be attempted in small amounts with clear liquids or breast milk. Patients should be carefully monitored for dehydration through tears, saliva, and urine with oral rehydration advanced as tolerated.

*Emergency Management of Severe FPIES.* In some patients when the reaction is severe, emergency services should be contacted immediately.[1,40,42] If the patient is found to be somnolent or unresponsive, then they should be placed in the recovery position to prevent aspiration. In patients who require evaluation in the emergency department, aggressive fluid resuscitation might occur because ~15% of patients may develop hypovolemic shock. Intravenous fluid resuscitation may be used in conjunction with parenteral ondansetron to help with vomiting and methylprednisolone to alleviate intestinal inflammation. There is currently no role for an epinephrine autoinjector unless there is concern for anaphylaxis.[43]

### Food Protein–Induced Enterocolitis Comorbidities

The association of FPIES with atopic disorders and eosinophilic esophagitis has been noted.[16,44] For

Table 7 **Immunopathophysiology of FPIES**

| Immune Response in Acute FPIES |
|---|
| Cell-mediated response innate and adaptive |
| Pan activation of T lymphocytes, in particular $T_H17$ lymphocytes |
| Cytokine activation (particularly IL-17A, IL-17C, CCL20) |
| Monocyte activation IL-6, IL-10, oncostatin M, leukemia inhibitor factor, TNF $\alpha$ |

*FPIES = Food protein–induced enterocolitis syndrome; TH17 = T helper 17 cells; IL = Interleukin; CCL = Chemokine Ligand 20; TNF = Tumor Necrosis Factor.*

example, the odds ratio (OR) of atopic dermatitis to FPIES was 2 (95% confidence interval [CI], 1.5–2.7; $p < 0.0001$); IgE food allergy was OR 7.6 (95% CI, 5.5–10.4; $p < 0.0001$), asthma was OR 1.6 (95% CI, 1.2–2.2; $p < 0.0001$), and allergic rhinitis was OR 1.9 (95% CI, 1.9–2.6; $p < 0.0001$). As noted previously, a small proportion of patients with chronic cow's milk FPIES also developed IgE cow's milk allergy, and 14 were found to have allergies to other foods. Another study found 19.11% of eosinophilic esophagitis patients to have FPIES.

## Natural History

The natural history and progression of FPIES seems, overall, to be favorable in infants, in whom many patients had resolution of FPIES induced by a specific trigger within months.[5,15,31,45] Atypical FPIES (IgE+) in infants may be associated with a more protracted course.[15] The cumulative probability of recovery from cow's milk FPIES at ~2 years was 89% in a prospective population-based study in Israel.[46] Most other food groups also are tolerated well at varying ages. The exception to this is fish FPIES, which only 30% of patients were able to tolerate at 4 years of age.[47,48] In adults, the natural history remains less favorable, in which < 50% are able to achieve tolerance after 2.5–3.5 years.[17,21]

## Pathophysiology of Food Protein–Induced Enterocolitis

The pathophysiology of FPIES remains poorly understood. There is no detectable humoral response

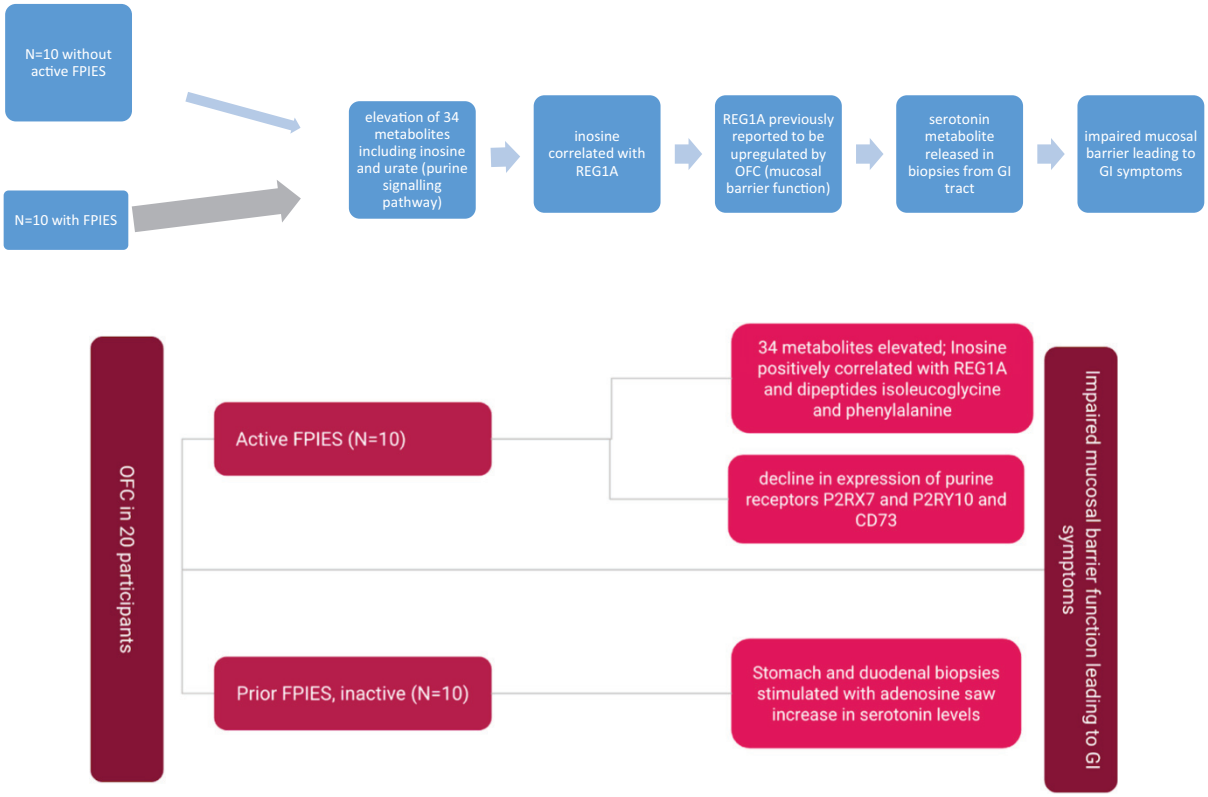


***Figure 2.*** *Metabolomics approach after OFC to identify pathways that underlie FPIES reactions. The levels of a total of 34 metabolites were elevated in patients during OFC, including inosine and urate of the purine signaling pathway in patients with symptomatic FPIES compared with patients who were asymptomatic. Inosine was found to be significantly and positively correlated with REG1A ($p = 0.0004$). REG1A has previously been reported to be upregulated after OFC and acts as a regulator of mucosal barrier function. Inosine was also significantly correlated with dipeptides isoleucoylgylcine and phenylalanine that likely represent impaired barrier function. There also was a notable decline of expression of purine receptors (P2RX7 and P2RY10) and CD73 in peripheral blood after OFC in patients who were symptomatic. Given that symptoms predominantly originate from the GI tract, stomach and duodenal biopsy specimens from non-FPIES donors were stimulated* in vitro *with adenosine, and serotonin levels were measured by immunoassay. Correspondingly, the FPIES-free biopsy specimens stimulated by adenosine also saw an increase in serotonin. There was a notable release of a serotonin metabolite also found after OFC in patients who were symptomatic (from Ref. 9). OFC = Oral food challenge; FPIES = food protein–induced enterocolitis; REG1A = regenerating islet-derived 1 alpha; GI = gastrointestinal.*

Table 8 **Unmet needs and future directions in FPIES**

| Unmet Need | Future Directions |
|---|---|
| Epidemiology: limited data with regard to prevalence | Population-based studies to determine the burden of FPIES in all ages, the prevalence of FPIES to emerging food triggers: peanut and tree nuts; the natural history of FPIES in adults; establishing a FPIES registry |
| Diagnosis: lack of noninvasive biomarkers | Laboratory diagnostic biomarkers for acute and chronic FPIES that identify specific food triggers without the need for oral challenges; revised diagnostic criteria to accurately capture FPIES in adults |
| Management: lack of strategies to accelerate tolerance | Research focused on gut microbiome, mechanisms of tolerance development, baked milk and egg diet; use of food ladders in FPIES; oral immunotherapy for FPIES |
| Prevention: lack of prevention strategies | Identify risk factors for FPIES and approaches to reduce risk |

*FPIES = Food protein–induced enterocolitis syndrome.*

to the conventional food protein antigens.[49] Acute FPIES reactions in the setting of supervised OFC are cell mediated, with the evidence of activation of $T_H17$ lymphocytes and their cytokines as well as an innate immune compartment, summarized in Table 7.[7] The mechanism of symptom presentation and immune activation is poorly understood. In a recently published study, an untargeted metabolomics approach was used to identify pathways that underlie FPIES reactions.[9] Serum samples were obtained from 10 children with FPIES and 10 controls who were asymptomatic (outgrew FPIES) during and after OFC. The findings are outlined in Fig. 2. Analysis of these data suggests that purine pathway signaling is involved in serotonin release, which causes classic symptoms such as vomiting.

## SUMMARY/KEY MESSAGES

Despite the gradual progress made in the past 2 decades, there remain many unmet needs (Table 8). FPIES is a condition that affects patients from childhood to adulthood. Given the crossover between FPIES and other clinical conditions, *e.g.*, sepsis, as well as the lack of biomarkers for diagnosis, FPIES remains difficult to diagnose without delay. Although recognized decades ago, FPIES has been gaining more recognition in the literature over the past few years. Now with a formal *International Classification of Diseases, Tenth Revision* (*icd.who.int*) code and outlined diagnostic criteria, acute FPIES may be diagnosed more frequently and with increasing awareness. On the contrary, adult-onset FPIES has limited information; in some studies, it is believed to be caused more frequently by seafood and occur at higher rates in females. The management of FPIES remains to avoid the trigger food. Although the pathophysiology of FPIES remains poorly understood, underlying mechanisms such as cytokine release, leukocyte activation, and impaired gastrointestinal mucosal barrier function may act as cornerstones for further research.

## REFERENCES


1. Nowak-Węgrzyn A, Chehade M, Groetch ME, 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.
2. Nowak-Wegrzyn A, Warren CM, Brown-Whitehorn T, et al. Food protein-induced enterocolitis syndrome in the US population-based study. J Allergy Clin Immunol. 2019; 144:1128–1130.
3. Su K-W, Cetinbas M, Martin VM, et al. Early infancy dysbiosis in food protein-induced enterocolitis syndrome: a prospective cohort study. Allergy. 2023; 78:1595–1604.
4. Bartnikas LM, Nowak-Wegrzyn A, Schultz F, et al. The evolution of food protein-induced enterocolitis syndrome: from a diagnosis that did not exist to a condition in need of answers. Ann Allergy Asthma Immunol. 2021; 126:489–497.
5. Nowak-Wegrzyn A, Berin MC, Mehr S. Food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract. 2020; 8:24–35.
6. Weinberger T, Feuille E, Thompson C, et al. Chronic food protein-induced enterocolitis syndrome: characterization of clinical phenotype and literature review. Ann Allergy Asthma Immunol. 2016; 117:227–233.
7. Goswami R, Blazquez AB, Kosoy R, et al. Systemic innate immune activation in food protein-induced enterocolitis syndrome. J Allergy Clin Immunol. 2017; 139:1885–1896.e9.
8. Berin MC, Lozano-Ojalvo D, Agashe C, et al. Acute FPIES reactions are associated with an IL-17 inflammatory signature. J Allergy Clin Immunol. 2021; 148:895–901.e6.
9. Lozano-Ojalvo D, Chen X, Dunkin D, et al. Untargeted serum metabolomic analysis reveals a role for purinergic signaling in FPIES. J Allergy Clin Immunol. 2023; 151:797–802.
10. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr. 1978; 93:553–560.
11. Powell GK. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance. J Pediatr. 1976; 88:840–844.
12. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr. 1998; 133:214–219.

13. Su K-W, Patil SU, Stockbridge 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.
14. Gonzalez-Delgado P, Ruano-Zaragoza M, Gutierrez A, et al. Chronic adult food protein-induced enterocolitis syndrome. Ann Allergy Asthma Immunol. 2020; 125:716–717.
15. Caubet JC, Ford LS, Sickles L, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol. 2014; 134:382–389.
16. Ruffner MA, Wang KY, Dudley JW, et al. Elevated atopic comorbidity in patients with food protein-induced enterocolitis. J Allergy Clin Immunol Pract. 2020; 8:1039–1046.
17. Crespo J, Pérez-Pallise ME, Skrabski F, et al. The natural course of adult-onset food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract. 2022; 10:2986–2992.
18. Gonzalez-Delgado P, Caparrós E, Moreno MV, et al. Food protein-induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood. J Allergy Clin Immunol Pract. 2019; 7:670–672.
19. Du YJ, Nowak-Węgrzyn A, Vadas P. FPIES in adults. Ann Allergy Asthma Immunol. 2018; 121:736–738.
20. Du YJ, Gonzalez-Delgado P, Vadas P. Food protein-induced enterocolitis syndrome: not just in children. Ann Allergy Asthma Immunol. 2021; 127:291–292.
21. González-Delgado P, Muriel J, Jiménez T, et al. Food protein-induced enterocolitis syndrome in adulthood: clinical characteristics, prognosis, and risk factors. J Allergy Clin Immunol Pract. 2022; 10:2397–2403.
22. Maciag MC, Bartnikas LM, Sicherer SH, 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; 8:1702–1709.
23. Lopes JP, Cox AL, Baker MG, et al. Peanut-induced food protein-induced enterocolitis syndrome (FPIES) in infants with early peanut introduction. J Allergy Clin Immunol Pract. 2021; 9:2117–2119.
24. Robbins KA, Ackerman OR, Carter CA, et al. Food protein-induced enterocolitis syndrome to peanut with early introduction: a clinical dilemma. J Allergy Clin Immunol Pract. 2018; 6:664–666.
25. Baldwin S, Werther R, Hargrove A, et al. Food protein-induced enterocolitis syndrome to nuts: an increasing phenomenon. Ann Allergy Asthma Immunol. 2021; 126:464–466.
26. Hua A, El-Zataari M, Hudson E, et al. Evolution of food protein-induced enterocolitis syndrome (FPIES) index trigger foods and subsequent reactions after initial diagnosis. J Allergy Clin Immunol Pract. 2023; 11:3179–3186.e2.
27. Cianferoni A. Food protein-induced enterocolitis syndrome epidemiology. Ann Allergy Asthma Immunol. 2021; 126:469–477.
28. Polk BI, Nowak-Wegrzyn A. A 2-month-old child with hypovolemic shock. J Allergy Clin Immunol Pract. 2022; 10:3339–3340.e10.
29. Nicolaides R, Bird JA, Cianferoni A, et al. Oral food challenge for FPIES in practice—a survey: report from the Work Group on FPIES Within the Adverse Reactions to Foods Committee, FAED IS, AAAAI. J Allergy Clin Immunol Pract. 2021; 9:3608–3614.e1.
30. Bird JA, Leonard S, Groetch M, et al. Conducting an oral food challenge: an update to the 2009 Adverse Reactions to Foods Committee Work Group Report. J Allergy Clin Immunol Pract. 2020; 8:75–90.e17.
31. Katz Y, Goldberg MR, Rajuan N, et al. 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.e1-3.
32. Infante S, Marco-Martín G, Zubeldia JM, et al. Oral food challenge in food protein-induced enterocolitis syndrome by fish: is there any room for improvement? Int Arch Allergy Immunol. 2019; 179:215–220.
33. Wang KY, Lee J, Cianferoni A, et al. Food protein-induced enterocolitis syndrome food challenges: experience from a large referral center. J Allergy Clin Immunol Pract. 2019; 7:444–450.
34. Bird JA, Barni S, Brown-Whitehorn TF, et al. FPIES oral food challenge: time for a change? Ann Allergy Asthma Immunol. 2021; 126:506–515.
35. Martin VM, Virkud YV, Phadke NA, et al. Increased IgE-mediated food allergy with food protein-induced allergic proctocolitis. Pediatrics. 2020; 146:e20200202.
36. Flom JD, Groetch M, Kovtun K, et al. Feeding difficulties in children with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract. 2023; 11:2939–2941.e3.
37. Groetch M, Durban R, Meyer R, et al. Dietary management of food protein-induced enterocolitis syndrome during the coronavirus disease 2019 pandemic. Ann Allergy Asthma Immunol. 2021; 126:124–126.
38. Miceli Sopo S, Romano A, Bersani G, et al. Cooking influence in tolerance acquisition in egg-induced acute food protein enterocolitis syndrome. Allergol Immunopathol (Madr). 2019; 47:221–226.
39. Faitelson Y, Yoffe S, Segal N, et al. Tolerability of baked milk consumption in children with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol Pract. 2023; 11:329–331.
40. Leonard SA, Sopo SM, Baker MG, et al. Management of acute FPIES emergencies at home and in a medical facility. Ann Allergy Asthma Immunol. 2021; 126:482–488.e1.
41. Holbrook T, Keet CA, Frischmeyer-Guerrerio PA, et al. Use of ondansetron for food protein-induced enterocolitis syndrome. J Allergy Clin Immunol. 2013; 132:1219–1220.
42. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update—2014. J Allergy Clin Immunol. 2014; 134:1016–1025.e43.
43. Fernandes BN, Boyle RJ, Gore C, et al. Food protein-induced enterocolitis syndrome can occur in adults. J Allergy Clin Immunol. 2012; 130:1199–1200.
44. Cianferoni A, Warren CM, Brown-Whitehorn T, et al. Eosinophilic esophagitis and allergic comorbidities in a US-population-based study. Allergy. 2020; 75:1466–1469.
45. Ruffner MA, Ruymann K, Barni S, et al. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. J Allergy Clin Immunol Pract. 2013; 1:343–349.
46. Katz Y, Goldberg MR. Natural history of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol. 2014; 14:229–239.
47. Vila L, García V, Rial MJ, et al. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. J Allergy Clin Immunol Pract. 2015; 3:621–623.
48. González-Delgado P, Caparrós E, Moreno MV, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. Pediatr Allergy Immunol. 2016; 27:269–275.
49. Caubet JC, Bencharitiwong R, Ross A, et al. Humoral and cellular responses to casein in patients with food protein-induced enterocolitis to cow's milk. J Allergy Clin Immunol. 2017; 139:572–583. □