CME review article

Food protein–induced enterocolitis syndrome: an update on natural history and review of management

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Objectives: To review the clinical features, pathophysiology, and management of food protein–induced enterocolitis syndrome (FPIES) and to discuss new observations in epidemiology and natural history.

Data Sources: PubMed searches were performed for articles published between 1978 and May 2011 using the keywords *food-induced enterocolitis* and *FPIES*.

Study Selection: Articles were selected based on their relevance to the topic of this review. The newest developments in FPIES were defined by articles published in the past 3 years.

Results: FPIES is a non–IgE-mediated gastrointestinal food hypersensitivity thought to be cell-mediated, although the exact pathophysiologic mechanism requires further study. In a recent birth cohort, the incidence of cow's milk FPIES was 0.34% in the first year of life compared with 0.5% for IgE-mediated cow's milk allergy. FPIES typically presents before 6 months of age in formula-fed infants with repetitive emesis, diarrhea, dehydration, and lethargy 1 to 5 hours after ingesting the offending food. Four cases of FPIES in breastfed infants have recently been reported. The most common offending foods are cow's milk, soy, and rice. Diagnosis is based primarily on clinical history and, when unclear, physician-supervised oral food challenges. FPIES is usually outgrown by school age. Although management remains avoidance of the offending food, observations that natural history varies for different foods has redefined the timing of reintroduction.

Conclusion: Early recognition of FPIES and removal of the offending food are imperative to prevent misdiagnosis and mismanagement of symptoms that may mimic other causes. Close follow-up is required to determine when foods may be added back into the diet.

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INTRODUCTION

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, often with diarrhea, that leads to acute dehydration and lethargy, or weight loss and failure to thrive if chronic.[1] Although FPIES has been established as a distinct clinical entity, certain features overlap with food protein–induced enteropathy and proctocolitis. In addition, affected children are often mismanaged as having acute viral gastrointestinal illness or sepsis, delaying diagnosis of FPIES for many months. We review the clinical features, pathophysiology, and management of FPIES and discuss new observations in epidemiology and natural history. For our review, we conducted a PubMed search using the

keywords *food-induced enterocolitis* and *FPIES*. We included relevant studies published between 1978 and May 2011, with the newest developments reflected in publications from the past 3 years.

EPIDEMIOLOGY

Gastrointestinal immune reactions to cow's milk proteins that are T cell-mediated with or without the contribution of milk-specific IgE are estimated to account for up to 40% of cow's milk protein hypersensitivity in infants and young children.[2] In a large birth cohort of 13,019 infants conducted in Israel, 0.34% were diagnosed as having FPIES in the first year of life, whereas the incidence of IgE-mediated milk allergy was established at 0.5%.[3] There is a slight male predilection in FPIES (52%–60%).[3–5] Approximately 30% of infants with FPIES develop atopic diseases, such as atopic dermatitis (25%–65%), asthma (3%-20%), or allergic rhinitis (20%).[4,6,7] Family history of atopic diseases is present in 40% to 80% of patients, including a family history of food allergy in approximately 20%.[6]

CLINICAL FEATURES

Clinical features of FPIES are summarized in Table 1. FPIES manifests as profuse, repetitive vomiting and diarrhea in young, formula-fed infants. The disease is most commonly triggered by cow's milk or soy, with several studies showing that more than 50% react to both foods.[8,9] In a recent birth cohort study conducted in Israel, however, none of the 44 infants diagnosed as having cow's milk FPIES showed sensitivity to soy.[3] This difference could be attributed to a milder phenotype reported from a nonselected birth cohort compared

with a more severe phenotype reported from allergy and gastroenterology referral populations. Symptoms of "classic" FPIES usually begin in early infancy (1–3 months but up to 1 year of age) within 1 to 4 weeks after introduction of cow's milk or soy protein. In the Israeli birth cohort, all 44 infants with cow's milk FPIES presented with symptoms within the first 6 months of life.[3] Delayed introduction of cow's milk or soy in breastfed infants may result in later onset. FPIES to cow's milk and soy in exclusively breastfed infants is extremely rare, suggesting a protective role of breastfeeding.[5] To the best of our knowledge, only 4 cases of exclusively breastfed infants with cow's milk FPIES have been reported in the literature.[10,11]

FPIES may be induced by solid food, such as rice, oats, barley, chicken, turkey, egg white, green pea, peanut, sweet potato, white potato, fruit protein, fish, and mollusks.[5,6,12,13] Mean age at onset of solid food FPIES tends to be later than that of cow's milk and soy FPIES, typically presenting when these foods are first introduced between the ages of 4-7 months.[4,14] Rice is the most common solid food inducing FPIES.[7] The development of FPIES up on introduction of foods after 1 year of age is rare, although onset of FPIES to fish and shellfish has been observed in older children and adults.[14] Those with a history of FPIES to one grain have a 50% chance of developing FPIES to other grains. However, wheat FPIES has not been reported in infants with oat or rice FPIES, presumably because significantly delayed introduction of wheat in these cases avoids the "window of physiologic susceptibility."[2,5] Interestingly, egg is a very rare trigger of FPIES. However, in one series of 10 young infants with milk or soy FPIES, 30% developed acute symptoms during an egg oral food challenge (OFC) (intended to be a negative control for milk and soy) at a median age of 5.5 months.[8] Subsequently, to our knowledge, no more cases of egg FPIES were published, suggesting that the natural history of FPIES is likely modified by a common practice of delaying the introduction of potentially allergenic foods or foods from the same food group (eg, wheat in a patient with rice FPIES).

Among infants with solid food FPIES, 80% reacted to more than 1 food, 65% were previously diagnosed as having cow's milk and/or soy FPIES, and 35% were breastfed.[5] Delayed diagnosis of solid food FPIES in particular may be due to the perception that grains, such as rice and oats, and vegetables have low allergenic potential and are not usually suspected as triggers of allergic reactions.

Symptoms of FPIES may be chronic while the food is a staple of the diet, such as with cow's milk- or soy-based formula, or present acutely either after the food has been removed from the diet and then reintroduced, or if the food is ingested intermittently. In the most severe cases, symptoms of intermittent vomiting, bloody diarrhea, lethargy, dehydration, abdominal distension, weight loss, and metabolic acidosis may begin within the first days of life. Laboratory studies may reveal anemia, hypoalbuminemia and an elevated white blood cell count with a left shift and eosinophilia. In 65% of those with a recorded white blood cell count, thrombocytosis (platelet count $>500 \times 10^9$/L) was also seen.[4] Intramural gas

Table 1. Clinical Features of Food Protein–Induced Enterocolitis Syndrome

Chronic	Acute
Symptoms	*Symptoms*
Intermittent, chronic emesis	Repetitive emesis onset 1–3 hours after ingestion
Chronic, watery diarrhea with blood/mucus	Diarrhea onset about 5 hours after ingestion
Lethargy	Lethargy
Dehydration	Pallor
Abdominal distension	Dehydration
Weight loss	Hypotension
Failure to thrive	Hypothermia
Laboratory	Abdominal distension
Anemia	*Laboratory*
Hypoalbuminemia	Elevated neutrophil count
Elevated white count:	Thrombocytosis
left shift	Metabolic acidosis
eosinophilia	Methemoglobinemia
Metabolic acidosis	Fecal leukocytes and eosinophils
Methemoglobinemia	Frank or occult fecal blood
Stool-reducing substances	Increased carbohydrate content in stool
Radiology	Elevated gastric juice leukocytes
Intramural gas	
Air-fluid levels	

may be seen on abdominal radiographs, prompting a diagnosis of necrotizing enterocolitis. Transient methemoglobinemia was reported in approximately one-third of infants with severe reactions and acidemia, with some requiring methylene blue and bicarbonate treatment.[15] Methemoglobinemia may be caused by severe intestinal inflammation and reduced catalase activity, resulting in increased nitrites.

Overall, approximately 75% of infants with FPIES symptoms appear acutely ill, and 15% develop hypotension and require hospitalization.[6] Infants presenting with chronic symptoms usually improve within 3 to 10 days of switching to a casein hydrolysate–based formula with or without temporary intravenous fluids. In our experience from a food allergy referral center, severe chronic FPIES is uncommon nowadays, likely due to ready availability if hypoallergenic formulas. Early introduction of hypoallergenic formula for mild, non-specific gastrointestinal symptoms may prevent the expression of full FPIES. Food reintroduction induces acute symptoms, typically emesis beginning within 1 to 3 hours and diarrhea within 2 to 10 hours (mean onset, 5 hours) of ingestion, with stool containing blood, mucus, sheets of leukocytes and eosinophils, and increased carbohydrate content.[16] Peripheral blood neutrophil counts are usually elevated in patients with positive challenge results and peak at 6 hours. Not all patients with acute reactions develop diarrhea. In a study of 66 acute episodes in 35 children, emesis was present in 100% of episodes, lethargy in 85%, pallor in 67%, diarrhea in 24%, and hypothermia (temperature <36°C) in 24%.[4]

PATHOPHYSIOLOGY

It is hypothesized that ingestion of food allergens causes local inflammation leading to increased intestinal permeability and fluid shift, which results in the symptoms of emesis, diarrhea, dehydration, and lethargy that are characteristic of FPIES.[17] One study showed that baseline intestinal absorption is normal and does not predispose patients to FPIES.[18] The diagnosis of FPIES is based on clinical criteria; endoscopy and biopsy studies are not routinely performed. In previous studies, however, endoscopic evaluations and biopsies in infants with FPIES identified diffuse colitis with variable degrees of ileal involvement.[6] Activated peripheral blood mononuclear cells, increased tumor necrosis factor-α, and decreased expression of transforming growth factor-β receptors in the intestinal mucosa may be involved in the intestinal inflammation.[6]

Food specific IgE antibodies are typically not detected in FPIES. There is a potential role for intestinal mucosal IgE antibody in facilitating antigen uptake and local intestinal inflammation, but this requires further study. A decrease in serum food specific IgG$_4$ antibody and an increase in serum food specific IgA levels have been noted in 1 study.[19]

DIFFERENTIAL DIAGNOSIS

FPIES is considered the most severe of the non–IgE-mediated gastrointestinal food hypersensitivities, where food protein–induced proctocolitis represents the least severe end of the spectrum and food protein–induced enteropathy exists in between. Proctocolitis is a benign transient condition, which typically begins in the first few months of life with blood-streaked stools in well-appearing infants. Most infants (>50%) with proctocolitis are exclusively breastfed. Mild anemia and, rarely, hypoalbuminemia may be present. Occasionally, peripheral eosinophilia may be seen, whereas eosinophilic infiltration of colonic biopsy specimens is prominent. Food protein–induced enteropathy is a syndrome of small bowel injury causing malabsorption, intermittent emesis, diarrhea, failure to thrive, and, rarely, blood stools; symptoms similar to celiac disease although less severe. These infants are usually formula-fed. Anemia and hypoalbuminemia may be present but not methemoglobinemia or acidemia. Cow's milk and soy are the most common food proteins implicated in these non–IgE-mediated gastrointestinal food hypersensitivities. In addition, the results of food skin prick test and serum food-allergen IgE tests are typically negative.

Acute vomiting, diarrhea, and dehydration may mimic a gastrointestinal viral illness or food poisoning. The absence of fever and sick contacts will be seen in cases of FPIES, although this may also occur in acute viral illness. Often it is the reoccurrence of repetitive emesis hours after ingestion of a particular food that points to food intolerance and not an acute microbial illness. Acute dehydration and lethargy may also mimic sepsis on presentation to an acute care facility. Hypotension and/or an elevated white blood cell count with a left shift lends support to this diagnosis; hydration and antibiotic therapy are often started. Specific to FPIES is the rapid recovery of the child to baseline after vigorous rehydration alone. Anaphylaxis can present with acute vomiting and diarrhea; however, symptoms usually begin within 30 minutes or infrequently up to 2 hours after ingestion, whereas FPIES symptoms typically begin 1 to 3 hours after ingestion. In addition, IgE-mediated symptoms involving the skin (flushing, urticaria, angioedema) or respiratory system (congestion, wheezing, coughing) are not present in FPIES, and anecdotally, epinephrine has not been helpful in the resolution of FPIES symptoms. In newborns, the combination of acute abdominal symptoms, signs of shock, and intramural gas on abdominal radiograph may mimic necrotizing enterocolitis. There are reports of exploratory laparotomy performed when acute FPIES was mistaken for ileus.[20] Metabolic disorders may also be considered if metabolic acidosis is present, or even congenital methemoglobinemia if methemoglobin levels are elevated.

DIAGNOSIS

Infants often present with multiple reactions and extensive evaluations before the diagnosis of FPIES is considered, especially when FPIES is caused by solid foods.[5,7] The non-specific symptoms and lack of definitive diagnostic tests may also contribute to a delay in diagnosis. Even some variation in the clinical presentation based on which food triggers the reaction may complicate diagnosis. In 1 study, infants with rice FPIES had severe symptoms and were more likely to receive fluid resuscitation on presentation than those with

milk or soy FPIES (42% vs 15%, *P* = .02).[7] In adults, shellfish (crustacean and mollusks) and fish FPIES may provoke a similar presentation with severe nausea, abdominal cramps, protracted vomiting, and diarrhea.[14]

Diagnosis of FPIES is based on history, clinical symptoms, exclusion of other causes, and, if necessary, results of an OFC. Most patients (>90%) have negative skin prick test results and undetectable food-specific IgE at diagnosis, although detectable food-specific IgE antibodies have been noted in some patients at the time of or after diagnosis of FPIES. In total, 21% with solid food FPIES and 18% to 30% with cow's milk or soy FPIES had detectable food-specific IgE.[3,5,21] Those with detectable food-specific IgE antibodies tended to have a more protracted course of FPIES and the potential for developing symptoms of IgE-mediated allergy.

Atopy patch testing (APT) was performed in 19 infants aged 5 to 30 months with challenged-confirmed FPIES.[22] APT predicted 28 of 33 outcomes of OFCs, and all patients with positive OFC results had a positive APT result, although 5 patients with positive APT results did not react on OFC. These results have not been confirmed by other studies; thus, further evaluation is required to determine the role of APT in the diagnosis of FPIES.

Although OFC is the criterion standard for diagnosis of FPIES, infants do not usually require confirmatory challenges for initial diagnosis if they have a classic history and symptoms resolve after removal of the offending food from their diet. Physician-supervised OFCs are necessary if the history is unclear, and to determine whether FPIES has resolved before a food is reintroduced into the diet.

In young infants with chronic symptoms, hypoalbuminemia and weight gain of less than 10 g/d were identified as independent predictors of cow's milk FPIES.[23] Results from stool examination in the context of chronic diarrhea were nonspecific, showing occult blood, polymorphonuclear neutrophils, eosinophils, Charcot-Leyden crystals, and reducing substances. Before establishment of the clinical diagnostic criteria, endoscopies performed in symptomatic infants with cow's milk and/or soy FPIES revealed friable mucosa with rectal ulceration and bleeding. Biopsy specimens showed varying degrees of villous atrophy, tissue edema, crypt abscesses, increased lymphocytes, eosinophils, and mast cells.[6] Immunohistochemical studies showed IgM- and IgA-containing plasma cells.

Radiologic findings in infants with chronic diarrhea, rectal bleeding, and/or failure to thrive showed air-fluid levels, nonspecific narrowing and thumb-printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid. If laparotomy was performed because of suspected ileus, distension of small bowel loops and thickening of the wall of jejunum distal to the Treitz ligament with diffuse subserosal bleeding were reported.[20] Resolution of radiologic abnormalities after dietary restriction has been documented.[6]

ORAL FOOD CHALLENGES

OFCs can be used to establish the diagnosis of FPIES or to evaluate for resolution of FPIES. There is debate as to when follow-up challenges are appropriate. One conservative approach recommends follow-up challenges every 18 to 24 months in patients without recent reactions.[2] In a study of 27 Korean infants with cow's milk FPIES, 64% tolerated cow's milk at 10 months and 92% tolerated soy at 10 months.[24] The investigators recommended follow-up challenge be undertaken sooner: after age 12 months for cow's milk and between ages 6 and 8 months for soy. Indeed, resolution of cow's milk FPIES appears to require more time than soy. In the Israeli birth cohort, 34 of 36 patients with cow's milk FPIES recovered by the age of 30 months.[3] Of the last 2 patients who were not tolerating cow's milk, one had a positive challenge result at 42 months of age and the other refused a challenge and continued to avoid cow's milk.

The protocol for conducting OFCs for FPIES is outlined in Table 2. An FPIES OFC is considered a high-risk procedure and should be conducted in a setting where intravenous access can be secured and rapid fluid resuscitation given if a reaction occurs. Although an inpatient setting is the most appropriate for FPIES OFCs, outpatient settings equipped with resuscitation capabilities with access to a laboratory (for neutrophil counts and stool analysis) can be used. Unless there is a history of near fatality, which is rare, performing FPIES OFCs in an intensive care unit is unnecessary.[13] For the first serving, doses are administered in 3 portions during 45–60 minutes for a total of 0.06 to 0.6 g/kg of food protein, starting at a lower dose in patients with a history of severe reactions.[6,21] The total amount does not generally exceed 3 to 6 g or 10 to 20 g of total food weight (100 mL of total liquid). If the patient is asymptomatic after 2 to 3 hours, then an age-appropriate serving is usually given as a second serving and the patient is observed for several more hours. First-line therapy in the event of a positive challenge result is rapid intravenous hydration of normal saline given in 20-mL/kg

Table 2. Food Protein–Induced Enterocolitis Syndrome Oral Food Challenge Protocol

- Basic requirements: physician supervision, secure intravenous (IV) access, immediate availability of fluid resuscitation
- Baseline vital signs and peripheral neutrophil count
- Gradual (during 1 hour) administration of food protein 0.06–0.6 g/kg body weight in 3 equal doses, generally not to exceed total 3 g of protein or 10 g of total food (100 mL of liquid) for an initial feeding
- If no reaction in 2–3 hours, administer an age-appropriate serving of the food followed by several hours of observation
- Fluid resuscitation: 20-mL/kg IV boluses of normal saline
- Steroids: methylprednisolone, 1 mg/kg IV (maximum, 60–80 mg)
- Most patients (>50%) with positive challenge results require treatment with intravenous fluids and steroids

Table 3. Positive Food Protein–Induced Enterocolitis Syndrome Challenge Results

Symptoms
   Emesis (onset, 1–3 hours)
   Diarrhea (onset, 2–10 hours; mean, 5 hours)
   Lethargy (onset, 1–3 hours)
Laboratory
   Elevated neutrophil count (>3500/µL, peaks at 6 hours)
   Fecal leukocytes, red blood cells, and/or eosinophils
   Gastric juice leukocytosis (>10 leukocytes per high-power field, at 3 hours)[a]

[a] Requires further study.[25]

boluses. Intravenous corticosteroids (methylprednisolone 1 mg/kg intravenously once, maximum of 60–80 mg) may also be used in severe reactions (repetitive emesis, profuse diarrhea, lethargy, hypotension, and/or hypothermia) to help reduce the presumed cell-mediated intestinal inflammation.[2] Epinephrine should be available for potential hypotension and shock; however, in our experience, epinephrine does not improve symptoms of emesis and lethargy. In the small proportion that develop positive skin test results and/or detectable food specific IgE levels, determination of when a follow-up OFC will be performed should also take into consideration the possibility of more acute IgE-mediated reactions, and appropriate medications such as epinephrine and antihistamine should be readily available in these cases.

Challenge results are considered positive if typical symptoms and laboratory findings are present (Table 3). Symptoms include emesis (onset, 1–3 hours), lethargy (onset, 1–3 hours), and diarrhea (onset, 2–10 hours; mean, 5 hours).[6,8,25] Laboratory values include elevated neutrophil count (>3,500/µL) and fecal leukocytes, frank or occult blood, and/or eosinophils.[6,8,16,25] A complete blood count with differential should be measured prior to challenge, and approximately 6 hours after challenge if there are symptoms. If diarrhea is present, stool guaiac tests may be performed and stool samples tested for fecal leukocytes, red blood cells, and eosinophils.

For equivocal OFC results, gastric juice analysis showing more than 10 leukocytes per high-power field has been proposed as a confirmatory test.[25] Because of symptoms such as severe vomiting and bloody diarrhea, as well as results of intestinal biopsies that indicate the presence of gastrointestinal inflammation, gastric juice analysis was performed in 1 study of infants with suspected cow's milk FPIES to look for early signs of inflammation occurring with OFC.[25] A neonatal orogastric feeding tube was inserted, and 1 to 3 mL of gastric juice was aspirated and analyzed at baseline and 3 hours after the OFC. Elevated gastric juice leukocyte counts of more than 10 leukocytes per high-power field were seen in 15 of 16 patients with positive challenge results after 3 hours, including 2 infants without early symptoms of emesis or lethargy. Gastric juice leukocyte counts were not elevated in 8 control infants with negative challenge results. This potential laboratory test needs further validation in larger groups of patients and may not be practical in every setting or with older patients.

MANAGEMENT

Management of FPIES consists of removing the offending food from the diet. For infants, exclusively breastfeeding can be protective. If this is not possible or the infant is exclusively formula-fed, casein hydrolysate–based formula is recommended due to frequent concomitant cow's milk and soy FPIES. Rarely, amino acid formula or, in severe cases, intravenous fluids are needed. An example of a typical cow's milk and soy FPIES case is presented in Table 4.

Because approximately one-third of infants with cow's milk or soy FPIES develop solid food FPIES and reactions to rice and other grains represent the most common types of solid food FPIES, introduction of yellow fruits and vegeta-

Table 4. Clinical Case of Cow's Milk and Soy Food Protein–Induced Enterocolitis Syndrome

An 8-month-old girl was initially breastfed and supplemented with a cow's milk–based formula. From birth she had issues with increased gas and appeared uncomfortable. She also had recurrent vomiting, which typically would occur soon after eating, and intermittent bloody streaks in her stool, which were green in color and often very loose. Her symptoms did not improve when a short trial of soy formula was given at 2 weeks of age. At 3 weeks of age she was prescribed ranitidine and formula was changed to a casein hydrolysate–based formula with resolution of vomiting and improvement in her symptoms. At 4 months of age she was given soy formula and within 1 hour developed repetitive vomiting, became lethargic and pale, and her parents described her as nonresponsive. Emergency services were called, and she was brought to the emergency department, where she was treated with oral rehydration. Her brother had had diarrhea around the same time, and it was thought that the infant's symptoms could be secondary to viral gastroenteritis. She was seen by an allergist, and food allergy testing was performed. The results of skin testing to milk, soy, and egg were negative at the time, and specific IgE was undetectable to milk, soy, egg, wheat, and peanut. Because of negative test results, an attempt was made to slowly reintroduce soy into her diet at home. She was given a bottle with 1 oz of soy formula and 7 oz of casein hydrolysate–based formula and did not complete the bottle. Within 2 hours, she developed repetitive vomiting but was not pale or lethargic and she recovered within 1 hour. She did not have any shortness of breath, rash, or angioedema with any of these reactions. Her diet currently includes hydrolyzed casein formula, grains (rice, wheat and oat), several fruits and vegetables, and chicken. She has dry patches of skin on her legs at times but has never been diagnosed as having eczema. She has no history of asthma or wheezing. There is a strong family of history of allergy, including cousins with food allergy and eczema, as well as her father with a history of allergic rhinitis. This infant's history is consistent with milk and soy food protein–induced enterocolitis. A plan was made to continue with a casein hydrolysate–based formula and avoid soy and milk. A follow-up in 1 year was recommended to consider performing a physician-supervised food challenge to milk or soy at approximately 2 years of age. This challenge would be done with intravenous access in place and rapid hydration available.

bles instead of cereal has been suggested at age 6 months in these patients.[2,5] Because of the high rate of reactions to multiple foods, it may benefit infants with solid food FPIES to avoid grains, legumes, and poultry in the first year of life.[2] Introduction of cow's milk and soy in infants with solid food FPIES may be attempted after 1 year of age (preferably under physician supervision) if there is no prior history of reactivity to these foods. Tolerance to 1 food from each high-risk group, for example, soy from legumes, chicken from poultry, or oat from grains, increases the likelihood of tolerance to other foods in the same group.[2]

NATURAL HISTORY

Resolution of FPIES appears to be population dependent, particularly for cow's milk and soy. Although in our experience based on a referral allergy population, cow's milk FPIES resolves in approximately 60% by 3 years of age, the Korean cohort showed more than 60% resolution by 10 months of age and the Israeli birth cohort showed 90% resolution by 3 years of age.[3,5,21,24] More striking, in our population we have seen that only 25% of soy FPIES resolves by 3 years of age, whereas in the Korean cohort, more than 90% of children showed resolution of soy FPIES by 10 months of age.[5,24] This difference may be explained by the higher proportion of subjects with detectable food-specific IgE levels and atopic dermatitis who were referred to a major allergy center in our population compared with the Israeli and Korean populations. There are not as many data for resolution of solid food FPIES. In our studies on solid food FPIES, resolution by 3 years of age occurred in 67% for vegetables, 66% for oat, and 40% for rice. Atypical FPIES (associated with food-specific IgE) may be more severe and/or protracted. Because patients initially presenting with or later developing food-specific IgE antibodies are at risk for persistent FPIES, including skin prick testing and/or measurement of serum food-specific IgE levels in the initial and follow-up evaluations is useful.

CONCLUSIONS

FPIES is a non–IgE-mediated food allergy that most commonly affects infants. FPIES may be more prevalent than previously appreciated; a recent study from an Israeli birth cohort reported that milk FPIES affected 0.34% of infants, whereas IgE-mediated milk allergy affected 0.5% of infants in the first year of life. Early recognition of symptoms of FPIES and removal of the offending food are imperative to prevent misdiagnosis and mismanagement of symptoms that may mimic viral illness or sepsis and lead to failure to thrive. Close follow-up is required to determine when foods may be added back into the diet. Although cow's milk and soy FPIES resolve in most patients by 3 years of age, patients with solid food FPIES and/or detectable food specific IgE levels may have more protracted courses. Physician-supervised OFC remains the criterion standard for diagnosis of FPIES. Further studies are needed to determine the pathophysiology and biomarkers of FPIES, as well as the features of natural history that are unique among specific foods.

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CME Examination

1–7, Leonard SA. 2011;107:95–101.

CME Test Questions

1 Symptoms of food protein-induced enterocolitis syndrome (FPIES) include which of the following?
   a. Urticaria
   b. Angioedema
   c. Emesis
   d. Wheezing
   e. Reflux

2. What is the most common solid food trigger for FPIES?
   a. Egg
   b. Rice
   c. Peanut
   d. Wheat
   e. Sesame

3. What laboratory findings may be seen in FPIES?
   a. Elevated neutrophil count
   b. Thrombocytosis
   c. Anemia
   d. Methemoglobinemia
   e. All of the above

4. What is the first-line treatment in an acute FPIES reaction?
   a. Corticosteroids
   b. Epinephrine
   c. Antihistamine
   d. Intravenous hydration
   e. Ondansetron

5. Which of the following components carries a higher risk of persistent FPIES?
   a. Detectable food-specific IgE to the offending food
   b. FPIES to more than one food
   c. Food allergies to other foods
   d. Failure to thrive
   e. Early onset of symptoms

6. FPIES is often originally misdiagnosed as which of the following condition?
   a. Sepsis
   b. Viral illness
   c. Necrotizing enterocolitis
   d. Immunoglobulin-E-mediated food allergy
   e. All of the above

7. What is the recommended management of milk-FPIES in infants?
   a. Soy formula
   b. Total parental nutrition
   c. Lactose-free formula
   d. Intravenous fluids
   e. Casein hydrolysate-based formula