

Management of Food Protein-Induced Enterocolitis Syndrome (FPIES): Current Approach and Future Needs

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Abbreviations *FPIES* Food protein-induced enterocolitis syndrome · *IgE* Immunoglobulin E · *OFC* Oral food challenge

Opinion Statement

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE, cell-mediated food allergic gastrointestinal disorder triggered by ingestion of food proteins (cow milk, soy, rice, oat, egg, and others). The acute FPIES begins approximately 1–4 h after food ingestion with profuse, repetitive emesis that is accompanied by lethargy and pallor and may be followed later by diarrhea; 15% will require hospitalization because of hypotension and hemodynamic instability due to severe dehydration. A chronic FPIES is less frequent and develops from few days to 4 weeks after the offending food has been introduced and fed daily. Chronic FPIES presents with intermittent emesis, bloody diarrhea, dehydration, weight loss, and failure to thrive and has been only reported in young infants fed with cow's milk and soy-based formulas. Acute FPIES to seafood has been reported in older children and in adults. The majority of patients react to a single food; however, FPIES can be triggered by more than one food, especially between cow milk/soy and rice/oats.

Diagnosis of FPIES is based on the recognition of clinical manifestations, exclusion of

alternative etiologies, and a physician-supervised oral food challenge (OFC). OFC is the gold standard; however, most patients do not need to undergo confirmatory OFC, especially if they have a history of severe reactions and become asymptomatic following elimination of the suspected food from diet until tolerance through OCF is proven. Management of FPIES is based on elimination of the trigger food in the diet, medical treatment of acute reactions due accidental exposure (intravenous hydration, methylprednisolone, ondansetron), nutritional counseling regarding avoidance of trigger foods, and introduction of the complementary foods and periodic oral food challenges to evaluate for resolution. The first international consensus guidelines on diagnosis and management of FPIES published in 2017 provide practical support for the providers caring for patients with FPIES.

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE, cell-mediated food allergic gastrointestinal disorder [1••]. As initially described by Gryboski and Powell, FPIES may manifest with acute or chronic symptoms, depending on the frequency and the dose of the offending food allergen in the diet [2, 3].

Acute FPIES develops within days of food introduction into the diet (usually following several feedings) and occurs with intermittent feedings, e.g., every several days or following a more prolonged period of food avoidance, e.g., weeks to years [4]. Acute FPIES reaction begins approximately 1–4 h after food ingestion (typically 2 h) and manifests with profuse, repetitive emesis that is accompanied by lethargy and pallor; diarrhea may follow in 6–10 h in a subset of patients [5]. There is typically a significant elevation of the white blood cell count with the neutrophil predominance [6]. During acute FPIES reactions, about 15% will require hospitalization because of hypotension and hemodynamic instability due to fluid third spacing and severe dehydration [7]. Acute FPIES is most commonly triggered by cow's milk (CM) and soy, rice, and oat in infants and begins usually within the first year of life [5, 8, 9•]. Acute FPIES can be triggered by a variety of other foods, including egg, fish, wheat, peanut, beef, fruits, and vegetables, similar to IgE-mediated food allergy [5, 8, 10]. In a study from Australia, early onset of FPIES (median age, 5 months), especially to fruits and vegetables, is a risk factor for reactions to multiple foods [11•]. FPIES to seafood has been reported in older children and in adults [12, 13]. The majority (60–75%) of patients react to a single food; however, FPIES can be triggered by more than one food, especially both cow milk/soy and rice/oats [5]. Fish-FPIES does not carry a high risk of

adverse reactions to other common FPIES triggering foods [14]. In the fish-FPIES case series reports, shellfish-FPIES was rare, less than 10% [15, 16].

Chronic FPIES is less frequent, usually develops from 1 to 4 weeks after the offending food has been introduced and fed daily [17•]. Chronic FPIES presents with intermittent but progressive emesis, watery diarrhea (occasionally with blood or mucous), dehydration, weight loss, and/or failure to thrive. If feedings with the offending food are continued, chronic FPIES symptoms worsen progressively and may lead to hypovolemic shock and metabolic acidosis requiring hospitalization and emergency management [18]. Chronic FPIES has been only reported in young infants fed with CM and soy-based formulas [19, 20]. It is unclear whether lower doses of the problem food (e.g., solid foods or food allergens in breast milk) may lead to intermittent vomiting, and/or diarrhea, without dehydration or metabolic acidosis.

Foods triggering FPIES vary by country, likely reflecting differences in the regional diets. Globally, the most common food is CM followed by rice, oats, and soy; egg, other grains and legumes, vegetables, and poultry are also being frequently reported [5, 8–10, 11•]. In Italy and Spain, fish and shellfish are the most frequent solid food triggers for acute FPIES [14–16]. In Australia, rice is the single most common trigger of acute FPIES [11•, 21, 22].

The prevalence of CM-FPIES has been estimated as 0.34% [8] in a population-based Israeli birth cohort from a single hospital [9•]. In Australia, another prospective population-based study conducted by reporting cases of acute FPIES by pediatricians through the national Australian Pediatric Surveillance Unit over the period

2012–2014 showed a prevalence of 15.3 per 100,000 in children younger than 2 years old [11•]. This estimate is higher than the estimated prevalence of pediatric eosinophilic esophagitis (8.9/100,000/year) and Crohn's disease under the age 2 years (2.01/100,000/year) in Australia, suggesting that FPIES is a more common disorder than previously appreciated. Regarding the allergy departments, the FPIES diagnosis represented 19% of the total diagnosis of food allergy in children in a 7-year period of time in an Italian multicenter study [23]. This figure likely overestimates the prevalence of FPIES because it reflects the patients with more severe phenotype referred to specialized pediatric allergy centers.

Natural history of FPIES varies by the triggering food, population, and age of initial reaction [24]. In Israel, Australia, and Japan, the resolution of CM and rice-FPIES occurs in approximately 90% of children by age 30–36 months [21, 23, 25–27]. In contrast, the studies from the USA reported the median age of cow milk-FPIES resolution of about 5 years [5, 8]. Older age at FPIES onset and specific food-IgE positivity (detected by serologic or skin prick tests and referred to as atypical FPIES) are associated with delayed FPIES resolution [5, 28–30]. Egg- and fish-FPIES tend to be more persistent, resolving in about 25% by age 5 years [5, 8, 24, 30].

The diagnosis of FPIES relies on clinical history of typical symptoms and exclusion of other etiologies [1••, 7]. Although physician-supervised OFC is the gold standard, most patients do not need to undergo confirmatory OFC, especially if they have a history of severe or repeated reactions to the same triggering food and become asymptomatic following the elimination of the suspected food from diet. Recently, an international

consensus was reached and guidelines for diagnosis have been published including major and minor criteria for FPIES diagnosis [1••]. Briefly, major criterion for acute FPIES is vomiting in the 1–4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms. Minor criteria include (1) a second (or more) episode of repetitive vomiting after eating the same suspect food, (2) repetitive vomiting episode 1–4 h after eating a different food, (3) extreme lethargy with any suspected reaction, (4) marked pallor with any suspected reaction; (5) need for emergency room visit with any suspected reaction, (6) need for intravenous fluid support with any suspected reaction, (7) diarrhea in 24 h (usually 5–10 h), (8) hypotension, and (9) hypothermia. The diagnosis of FPIES requires that a patient meet the major criterion and at least three minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group.

For chronic FPIES, general criteria are provided, but given the paucity of published reports of chronic FPIES, specific major and minor criteria could not be established. Severe chronic FPIES: when the offending food is ingested on a regular basis (e.g., infant formula) intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis.

Milder chronic FPIES: lower doses of the problem food (e.g., solid foods or food allergens in breast milk) lead to intermittent vomiting, and/or diarrhea, usually with poor weight gain/failure to thrive, but without dehydration or metabolic acidosis.

Long-term management of acute and chronic FPIES

There are no therapies available to accelerate resolution of FPIES. The primary long-term management of FPIES is the avoidance of the offending food, nutritional counseling to avoid nutritional deficits, counseling regarding solid food introduction, provision of an emergency treatment plan in case of accidental ingestions, and periodic re-evaluation for resolution with OFC [1••].

Elimination of the food trigger

The elimination of the food trigger should be strict, including baked foods. There is no conclusive evidence that extensively heated milk or egg in the form of the baked foods can be tolerated in FPIES, although few reports suggest that a subset of patients might be able to ingest such foods without a reaction, likely

Table 1. Empiric guidelines for selecting weaning foods in infants with FPIES (reprinted from reference no. 1)

Ages and stages	Lower risk foods ^a	Moderate risk foods ^a	Higher risk foods ^a
4–6 months (as per AAP, CoN) If developmentally appropriate and safe and nutritious foods are available. >Begin with smooth, thin purees and progress to thicker purees. >Choose foods that are high in iron. >Add vegetables and fruits.	Broccoli, cauliflower, parsnip, turnip, pumpkin	Vegetables Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
6 months (as per WHO) Complementary feeding should begin no later than 6 months of age. >In the breast-fed infant, high iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age. >Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated.	Blueberries, strawberries, plum, watermelon, peach, avocado Lamb, fortified quinoa cereal, millet	Fruits Apple, pear, orange High iron foods Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Banana
8 months of age or when developmentally appropriate. >Offer soft-cooked and bite-and-dissolve textures from around 8 months of age or as tolerated by infant. 12 months of age or when developmentally appropriate. >Offer modified tolerated foods from the family table—chopped meats, soft-cooked vegetables, grains, and fruits.	Tree nuts and seed butters ^a (sesame, sunflower, etc.) ^a Thinned with water or infant puree for appropriate infant texture and to prevent choking	Other Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish
This table should be considered in the context of the following notes: (a) exclusive breastfeeding until 4–6 months of age and continuing breastfeeding through the first year of life or longer as long as mutually desired by both mother and child and (b) if an infant tolerates a variety of early foods, subsequent introduction may be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered as a favorable prognostic indicator for tolerance of other foods from the same group (legumes) AAP American Academy of Pediatrics, CoN Committee on Nutrition, WHO World Health Organization ^a Risk assessment is based on the clinical experience and the published reports of FPIES triggers			

reflecting a milder phenotype of FPIES [1•, 31]. It is recommended that tolerance to the baked forms of FPIES triggers is initially evaluated during a supervised OFC. However, if the patient has been regularly ingesting baked foods, they can be continued without a restriction. Infants with FPIES may continue breastfeeding, and mother should not be routinely advised to avoid food triggering FPIES from her diet, unless the infant exhibits acute or chronic FPIES symptoms or is failing to thrive [1•, 32, 33]. In Australia, less than 5% of infants experience acute FPIES during breastfeeding [11•]. For such cases, hypoallergenic extensively hydrolyzed formulas are recommended as the first choice; in a small subset, amino acid formula may be required [1•, 5, 28]. Soy

formula may be an acceptable alternative, especially in infants older than 6 months; however, cautious introduction is warranted due to the potential for co-reactivity between soy and CM-FPIES [5, 34].

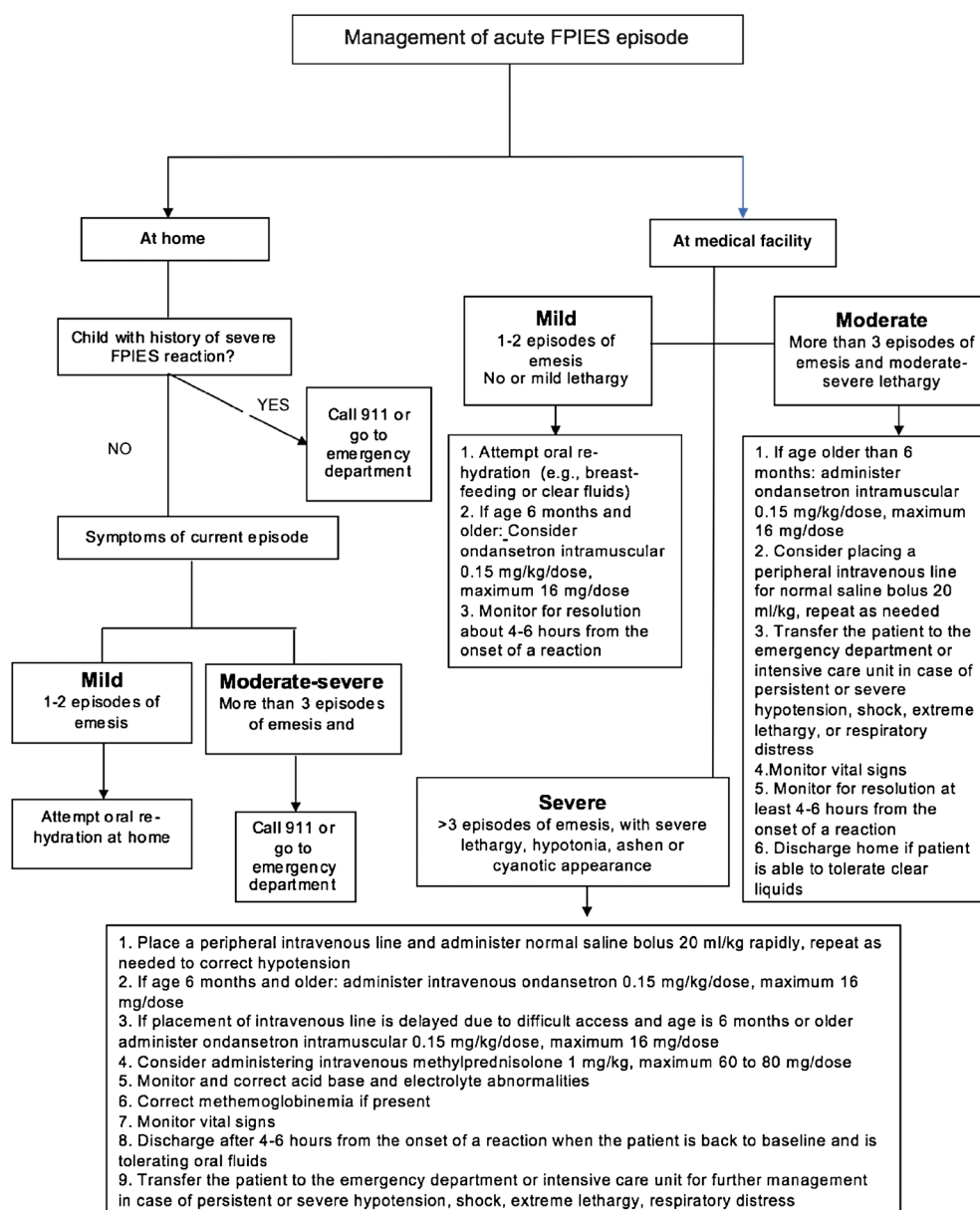
No systematic studies have explored the threshold doses for acute FPIES. However, in the Israeli cohort, among 28 children undergoing diagnostic CM-OFC, 82% tolerated 50 ml of milk before developing symptoms of acute FPIES [9•]. During fish-OFC, 45.4% (5/11) of children developed a reaction after eating a half (9%) or a whole (36.4%) age-appropriate serving size of the trigger fish [15]. It is unknown if small and frequently ingested amounts of a trigger food can cause chronic (or subclinical) FPIES. Severe reactions due to very low thresholds—even by trivial oral mucosal contact and a progressive reduction of threshold doses in the event of a repeated episode of contact/ingestion of the trigger food—have been rarely reported [35]. Considering that such extreme low thresholds are very uncommon, avoidance of commercial food products with precautionary statements is not routinely recommended in FPIES [1••].

Nutritional counseling to avoid nutritional deficits

FPIES guidelines recommend a consultation with a dietician to avoid nutritional deficiencies and to facilitate weaning, especially in the breast-fed infants and those with FPIES to multiple foods [1••]. However, even single food elimination (especially cow milk) can be associated with significant nutritional deficiency, if the major nutrients are not properly replaced. Food allergic children are at risk for deficiency of energy, protein, vitamins A and D, calcium, iron, and zinc as well as thiamine, riboflavin, and niacin. NIAID Guidelines for the Diagnosis and Management of Food Allergies recommend close growth monitoring of all children with food allergy [36]. Growth (weight, length/height, head circumference) should be assessed at regular intervals, based on the national standards.

Counseling regarding timely introduction of solid foods to enhance feeding skills

Delayed introduction of solid foods beyond 10 months of age is associated with an increased risk of food refusal [37]. Timely introduction of various flavors and textures has beneficial effect on the development of food acceptance, feeding skills, and eating behaviors [37–43]. Avoidance of a greater number of foods increases the risk of food refusal and aversions and makes finding appropriate flavors and textures difficult [43]. However, various textures may be provided even if only one food is tolerated. A fruit or vegetable may be prepared into a thin or thick puree, served with lumps, soft cooked for finger foods, or freeze dried or fried/oven baked in refined oil for a crispy, crunchy texture. The selection of foods for introduction in infants with FPIES is affected by the potential risk of co-reactivity with known FPIES triggers. The practical approach to introducing solids based on an estimated risk is presented in Table 1; this approach needs to be modified based on an individual patient's known trigger foods. In general, tolerance of one food is thought to indicate likely tolerance of other foods from the same food group [1••]. Parents may need support especially if they have previously not prepared many foods at home or have limited experience with introducing new foods. It is commonly recommended that caregivers introduce a new food as a single ingredient and with high-risk trigger foods, waiting at least 4 days before introducing another food as



Strong consideration should be lent in performing food challenges in children with history of severe FPIES in the hospital or other monitored setting with immediate availability of intravenous resuscitation.

Oral challenges in the physician's office can be considered in patients with no history of a severe FPIES reaction, although caution should be urged as there are no data that can predict future severity of FPIES reactions.

Fig. 1. Strong consideration should be lent in performing food challenges in children with history of severe FPIES in the hospital or other monitored setting with immediate availability of intravenous resuscitation. Oral challenges in the physician's office can be considered in patients with no history of a severe FPIES reaction, although caution should be urged as there are no data that can predict future severity of FPIES reactions.

sometimes, it may take that long for a reaction to develop. In some cases of anxious caregivers, office-based physician-supervised introductions of few solid food are helpful to empower them for future diet expansion at home [1●●].

Clinical pearl-counseling caregivers about natural history

Caregivers of infants with FPIES report significant negative impact of child's food allergic disorder on their quality of life [44]. In addition to the obvious stressors, such as the need for food elimination, anxiety about potential reactions with food introduction at home, and increased financial costs due to the hypoallergenic diets and special child care arrangements, there might also be uncertainty about the diagnosis (lack of a biomarker) and worry about potential future complications [45]. It is helpful to explain to the caregivers that FPIES has a very favorable natural history and that it is not associated with any known long-term consequences. It is important to provide very specific instructions regarding food introductions at different stages and to follow up patients periodically, usually more frequently at young ages and with multiple food avoidances. Some caregivers might benefit from formal counseling to help them cope with the stress of child's FPIES diagnosis.

Emergency treatment plan in case of accidental ingestions

FPIES is frequently underdiagnosed and mismanaged in an emergency setting due to atypical nature of the symptoms, including delayed onset, lack of allergic cutaneous (pruritus, urticaria, angioedema) and respiratory (wheezing, cough) manifestations, dehydration, and hypotension. Therefore, an emergency treatment plan in a form of a letter describing the FPIES diagnosis and management (intravenous hydration, ondansetron, a single dose of steroid in case of severe reaction) is recommended for all patients [46]. A template of such letter can be found at www.fpies.org. Epinephrine autoinjectors are not routinely prescribed for FPIES patients because they have no role as a first-line treatment, unless the patients has known risk factors for anaphylaxis, e.g., high levels of food-sIgE, IgE-mediated allergy to other foods [1●●].

Management of FPIES emergencies at home

Figure 1 illustrates a practical approach to managing FPIES reactions at home based on the severity of the current symptoms as well as the severity of the past FPIES episodes. When the symptoms are mild, emesis is infrequent (1–2 episodes), and lethargy is absent, and the patient does not have prior severe hypotensive FPIES episodes, it may be possible to attempt oral rehydration at home, via breastfeeding or by feeding small amounts of clear liquids. With the more severe manifestations or past history of severe symptoms, it is recommended to activate emergency response system and seek evaluation and management at the medical facility. Oral antihistamines or epinephrine autoinjectors have no role in managing FPIES reactions and no effect on emesis and hypotension, unless IgE-mediated component is suspected [12].

Considering the efficacy of ondansetron for FPIES in the OFC setting as well as extensive experience with ondansetron use in emergency departments for managing vomiting due to a variety of etiologies (e.g., viral gastroenteritis, otitis media), a prescription for oral ondansetron (0.15 mg/kg/dose, max dose 4 mg) may be provided for immediate use at home (as a first-line treatment, single

dose 5–10 min after the most recent emesis episode) followed promptly by evaluation and appropriate management in the emergency department [47, 48]. This approach is based on ANW's unpublished personal experience and is not officially recommended by the FPIES guidelines.

Management of FPIES emergencies in the medical facility

The severe acute FPIES reaction in the medical setting is treated as an emergency with a rapid restoration of hemodynamics through aggressive rehydration preferably through intravenous access with isotonic fluids, normal saline 10–20-ml/kg bolus (Fig. 1). Intravenous or intramuscular ondansetron (dose 0.15 mg/kg, max dose 16 mg, approved in the USA for ages 6 months and older) can be used to stop vomiting. Intravenous or intramuscular methylprednisolone 1 mg/kg as a single dose (max 60–80 mg) may be used empirically based on the inflammatory pathophysiology [1••] [6, 27, 49, 50]. The intravenous access is crucial for severe FPIES reaction in which hypovolemic and metabolic derangements might require bicarbonate for acidemia (usual dose 2–5 mEq/kg IV infusion over 4–8 h; higher doses required for cardiac arrest) and methylene blue for methemoglobinemia (1–2 mg/kg, up to a total of 50 mg as a 1% solution in IV saline over 3–5 min; methylene blue is contraindicated in patients with G6PD deficiency). In extreme cases, vasopressors, intubation, and mechanical ventilation may be required. Hospitalization should be considered based on the case-by-case basis and other gastrointestinal diseases that have a similar presentation must be ruled out [8]. In milder cases, oral rehydration may be possible [9•].

Periodic re-evaluation for resolution

Considering favorable natural history of FPIES in childhood, periodic reassessments for resolution are recommended, usually every 12–24 months, but could be done more or less frequently, at the physician discretion and the patient/family preference [1••, 5, 9•, 24, 34]. FPIES guidelines recommend evaluating for cow milk-specific IgE by skin prick or serologic testing before OFC, considering the risk of conversion to the IgE-mediated cow milk allergy. Some studies identified CM-IgE positivity (atypical FPIES) as a risk factor for delayed resolution of CM-FPIES that may influence decision regarding the timing of CM-OFC [5, 8, 28, 51].

OFC for FPIES

Foods that have caused FPIES reactions in the past should generally be reintroduced under physician supervision during a formal oral food challenge (OFC) [1••]. Placement of a secure peripheral venous access prior to the onset of the OFC is warranted in the patients with past severe reactions requiring an emergency room visit or hospitalization. Securing a peripheral intravenous line prior to the challenge is also prudent in infants and older patients with anticipated difficult intravenous access [23, 28]. In milder reactions, oral rehydration may be sufficient, Fig. 1 [9•]. The timing of the FPIES food trigger reintroduction is variable, ranging from 6 months to 12–24 months or longer from the most recent FPIES reaction, depending on the nutritional and or social importance of the food, family preference, and physician experience [1••].

Oral food challenge protocol in FPIES

Oral food challenge could be considered for confirm diagnosis when clinical history is not sufficient to confirm a food as trigger of FPIES, when only one episode has occurred or to assess a resolution of FPIES.

There is no consensus regarding oral food challenge protocol [1••, 52]. In one approach, the total dose of the challenge food is calculated as 0.06–0.6 g food protein per kilogram body mass, not to exceed 3 g of food protein, 10 g of whole food, or 3 oz. (90 ml) of liquid food. This total amount is divided into three equal portions and given over 30 min, followed by observation [5,6,29]. In patients with history of severe reactions, e.g., hypotension hospitalization, or reactions to trace amounts of food, the lowest dose 0.06 g of food protein per kilogram body mass should be administered initially followed by a full serving of food if no symptoms appeared within 2 h.

Interpretation of the oral food challenge outcome in FPIES

The FPIES guidelines have defined vomiting in the 1–4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms as the major criterion for challenge positivity [1••]. Minor criteria include (1) lethargy, (2) pallor, (3) diarrhea in 5–10 h after food ingestion, (4) hypotension, (5) hypothermia, and (6) increased neutrophil count of at least 1500 neutrophils above the baseline count. The OFC is considered positive if the major criterion is met with at least two minor criteria. This interpretation should be modified if ondansetron is used immediately at the onset of symptoms, because it may avert repetitive vomiting, pallor, and lethargy. In addition, not all facilities performing challenges have the ability to obtain neutrophil counts before and after the challenge in a timely manner. Therefore, the treating physician may consider a challenge to be diagnostic even if only the major criterion was met. However, in challenges performed for research purposes, stringent criteria for challenge positivity should be adhered to.

Post-challenge observation

Recommended duration of the post-challenge observation in FPIES is minimum 4 h in a negative challenge [1••, 7, 52]. In case of a positive (symptomatic challenge), the patient should be observed until symptoms have resolved and the patient is able to tolerate at least clear liquids by mouth and is not dehydrated. This usually takes about 6 h from the beginning of the OFC.

OFC in atypical FPIES

In patients with detectable food-specific IgE to the food being challenged (atypical FPIES), the procedure should be adjusted to the standard incremental protocols for IgE-mediated food allergy, because up to 30% of such patients may evolve into IgE-mediated reactions [5, 8, 11•]. The observation post challenge should be at least 4 h to account for the possible FPIES reactions.

Conclusions

FPIES is not rare and the providers need to recognize FPIES manifestations, diagnostic criteria, and management principles. Management of FPIES focuses on the elimination of the food trigger and treatment of emergencies. There are no therapies that accelerate the resolution of FPIES, and there is an unmet need to define the pathophysiology of FPIES and to develop immunomodulatory strategies to accelerate resolution. The first international FPIES consensus guidelines (available as an open access) provide a very practical advice regarding dietary avoidance of FPIES triggers, managing acute reactions, introducing complementary foods, and reintroducing foods that have caused FPIES reactions.

Compliance with Ethical Standards

Conflict of Interest

Dr. Elżbieta Jarocka-Cyrta declares that she has no conflict of interest. Dr. Marcela Valverde-Monge declares that she has no conflict of interest. Dr. Anna Nowak-Węgrzyn declares speaking for and receiving a research grant for wheat OIT molecular diagnosis from Thermo Fisher Scientific.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of major importance

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