Update on Food protein-induced enterocolitis syndrome (FPIES)

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Abstract. Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy (FA) characterized by delayed and severe gastrointestinal symptoms that typically occurs within the first year of life. Many aspects of this pathology are currently unclear. FPIES is classified as a non-IgE immune-mediated FA in which the immune response is thought to act mainly through cell-mediated mechanisms. In patients with FPIES the symptom pattern is determined by the frequency and dose of food allergen in the diet. Diagnosis of FPIES may be difficult, mainly due to the lack of specific biomarkers to confirm or exclude the diagnosis. FPIES is a clinical diagnosis, mainly based on clinical features which, although not specific, are reproducible every time the patient eats the food. Different diagnostic criteria of FPIES were published over time in the literature. The present narrative review aims to analyze the current clinical evidence in epidemiology, pathophysiology, diagnosis, and management of this condition. (www.actabiomedica.it)

Key words: food protein-induced enterocolitis syndrome, FPIES, non-IgE mediated food allergy, diagnosis

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE mediated food allergy (FA) characterized by delayed and severe gastrointestinal symptoms that typically occurs within the first year of life. Usually, the manifestations of FPIES are non-specific with a wide range of severity: repetitive and prolonged vomiting from 1 to 4 hours after the ingestion of the culprit food, pallor, lethargy, followed by diarrhea, and in severe cases, by hypothermia, hypotonia, hypotension and metabolic derangements (1). Many aspects of this pathology are currently unclear. Epidemiological data are limited, but they allow us to affirm that it is a not rare pathology with a cumulative incidence of 0.05% to 0.7% (2,3,4). The pathophysiology of FPIES is still not well defined and requires further investigation. Given the lack of biomarkers, the diagnosis is based on symptoms and clinical responses to elimination diets with the disappearance of symptoms, and on oral food challenge (OFC) with the re-appearance of symptoms following the ingestion of culprit food may be used if the diagnosis is unclear. Treatment of FPIES consists of eliminating the culprit food, medical treatment in case of accidental

exposure, and periodic reassessment by supervised OFC to evaluate the achieved tolerance[1]. The present narrative review aims to analyze the current clinical evidence in epidemiology, pathophysiology, diagnosis, and management of this condition.

Epidemiology

Epidemiological data regarding FPIES are limited, and the true prevalence of this condition is not well known. The variety of the manifestations, the frequent misdiagnosis, the absence of diagnostic markers, the lack of diagnostic criteria until 2017, and a code of the disease until 2015 contribute to the lack of accurate epidemiological data. The FPIES cumulative incidence rates estimated using single-center birth cohorts or through a national survey of physicians are between 0.15-0.75% (2,3,4). The first prospective study of FPIES was published by Katz et al, who reported a cumulative incidence of 0.34% in the Israeli population (2). This study was conducted in a single hospital for milk-induced FPIES for two years. Using a population-based survey of 1400 involved pediatricians using the Australian Pediatric Surveillance Unit network, Mehr et al. reported a prevalence of 15.4/100.000/year (0.015%) in children younger than two years in Australia (4). The first prospective study of FPIES incidence in Europe was performed in Spain by Alonso et al. in 2019. In a cohort of about 1000 infants followed for 18 months from a single hospital (PREVALE study), the prevalence of FPIES was estimated to be 0.7% (3). Previously, Miceli Sopo et al. reported a prevalence of 19%, higher than for the general population, in three Italian pediatric referral centers and highlighted the increasing trend of FPIES from 4 cases in the first four years (2004-2007) to 13-17 in the period 2008-2009 (5). In a retrospective study, Ludman et al. revealed an incidence of 0.36% of FPIES in the United Kingdom (6). A prevalence of 0.47% among patients referred to a Greek pediatric allergic clinic was reported by Xepapadaki et al. (7). The first population survey estimating the lifetime prevalence of FPIES in the USA and the prevalence among adults reported a prevalence of 0.51% in pediatric groups and of 0.22% in adults (8). Ruffner et al. recently published the first study of FPIES in the

USA birth cohort. The authors identified 214 patients with FPIES among 158.510 children born from 2001 to 2018, for a prevalence of 0.14% (9). There are no available data regarding the prevalence of chronic FPIES because its symptoms are difficult to differentiate from those of food protein enteropathies (10). Any food may cause FPIES, but geographical differences must be taken into account. Liquid food-induced FPIES accounts for 65% (11). Cow's milk (CM) is the principal liquid food to cause FPIES worldwide, and it was found to be responsible respectively for 44%, and 67% of the cases of FPIES reported respectively by Caubet et al. and by Ruffner et al. in USA (12,13). Similar data were reported from Italy in a food challenge series (43%) (14) and retrospective reviews (67%). Likewise, in Spain CM was reported to be the most common culprit food in birth cohort studies (50%) and in retrospective cases (36.7%) (3,15). In addition, CM is frequently the cause of more severe forms of FPIES, probably because children take this food early and in high doses (16). Soy is the common food trigger in 36-40% of infants with FPIES in the USA and South Korea (13,17), whereas, in geographic areas different from those mentioned above, it is a less common trigger food in relation to the lower use made in feeding or a tolerance achieved later. Combined CM/soy FPIES occurs in 20-40% in the USA, whereas it does not occur in other geographical areas, including Italy (18). Solid food-induced FPIES occurs in 35% of cases. The majority (between 60% to 80%) of infants with FPIES react to a single food, most often CM, while 35% react to multiple foods (9,12). Different rates of multiple FPIES trigger foods are reported in different countries: 15% in Italy, 16% in Spain, 32% in Australia, and 35-69% in the USA. (4,5,12,13,15,19).

Pathophysiology

FPIES is classified as a non IgE-mediated FA in which the immune response is thought to act mainly through cell-mediated mechanisms. However, the underlying mechanism of action by which the trigger foods in FPIES cause symptoms and disease remains unclear. Time of symptoms occurrence in FPIES (generally 1-4 hours) appears to be intermediate between IgE-mediated reactions (usually < 2 hours) and

cell-mediated food reactions (usually several hours or days). The involvement of either the adaptive arm and/or the innate arm of the immune system has been. Exposure to a food has been hypothesized to induce inflammation in the gut, mainly in the colon, which may increase intestinal permeability, leading to a fluid shift into the gastrointestinal lumen. However, its exact immune mechanism is unknown. Several cellular elements and cytokines are thought to be involved. A T-cell mediated response was suggested because of the in vitro proliferation to food antigen exposure of peripheral blood mononuclear cells in patients with FPIES compared with controls (20,21). This activation would be followed by the release of high levels of proinflammatory cytokine Tumor Necrosis Factor - α (TNF-α) and TH-2 cytokine (IL-10, IL-4) (22,23) . However, more recent studies have not confirmed these observations. Caubet et al. found no difference in proliferation of T cells or Th2 cytokine production when children with CM-FPIES were challenged with casein (24). Similarly, Goswami et al. found no evidence of an abnormal antigen-specific T-cell response (25), even if they claimed that lack of detection of an increased frequency or altered phenotype of allergen-responsive T cells does not necessarily rule out a role of T cells in FPIES. The same authors, however, showed a profound systemic innate immune activation in children with FPIES. In particular, they observed that casein antigen-induced TNF-α and IL-10 production was localized to a CD14+ monocyte population in children with the positive food challenge. The same activation was observed in neutrophils, eosinophils, and CD56 natural killer. In acute FPIES reactions, patients may have elevated peripheral neutrophils counts, and for this reason, an increase in the circulating neutrophils, peaking approximately 6 hours after OFC, is part of the diagnostic criteria for the interpretation of FPIES food challenge results. Stool examination may reveal neutrophils and eosinophils both in acute and chronic FPIES. Colonic biopsies can show severe inflammation with an increased number of eosinophils (1). This systemic innate immune activation may contribute to shock-like symptoms of FPIES, including hypotension and pallor, and explain the immediate onset of symptoms, hardly compatible with a T-cell mediated reaction. Transforming growth factor β (TGF-β) are a group of cytokines that control many biological processes. A reduced expression of the TGF-β type I receptor was found on the epithelial and mononuclear cells in the lamina propria of duodenal biopsies from children with FPIES (26). Since TGF-β has several effects that increase the link between cells and the protein matrix, its reduced activity could favor the barrier-disrupting effect of T-cell cytokines and, increasing the penetration of food antigens, contribute to the pathogenesis of FPIES. More, Konstantinou et al. showed a reduced response of TGF-β in stimulated supernatants from children with milk-FPIES, while latent TGF-β was significantly higher in the milk-FPIES-resolved group, suggesting a possible role in differentiating between children with persistent FPIES to milk and children with resolved FPIES (27). There are conflicting reports about levels of food-specific antibodies in FPIES. Some authors demonstrated an increase of milk protein-specific IgA not associated with elevated IgG1 or IgG4 antibodies, compared with controls (23). According to other authors, milk-specific IgG1, IgG, IgM, and IgA levels were not elevated in children with FPIES compared with controls who had outgrown their allergy (24, 27). Finally, Adel-Patient et al. recently showed that humoral (and cellular) responses to relevant CM components are inadequate in children with CM-FPIES and suggest that this low level of humoral response is a feature of the disease itself (28).

Even if FPIES is a non-IgE mediated food allergy, some association with atopy and IgE mediated food allergy exists. For example, FPIES is associated with an elevated prevalence of atopic comorbidities (9). In addition, over 10% of children with FPIES initially have or develop food-specific IgE. A switch from IgE-mediated food allergy symptoms to non-IgE-mediated FPIES and vice versa has also been described (30,31).

FPIES Clinical features

Acute. In patients with FPIES, the symptom pattern is determined by the frequency and dose of food allergen in the diet. Acute FPIES typically presents between one and 4 hours (typically 2 hours) after the ingestion of the trigger food, with the principal symptom being profuse and repetitive vomiting, and is often accompanied by pallor and lethargy, with or with-

out diarrhea (2,3,4). Acute symptoms develop with intermittent exposure or re-exposure after a period of avoidance. Additional symptoms can include hypotension (reported in up to 15% of reactions), hypothermia, diarrhea, and metabolic acidosis (5,6). Bloody diarrhea is more commonly reported in Japanese cohorts (7) and infants presenting under two months of age with CM or soy FPIES (8). Infants with acute FPIES are well in between the episodes and are growing and developing well. The acute presentation may mimic sepsis, gastroenteritis, necrotizing enterocolitis (especially in preterm newborns), intussusception, other rare surgical abdominal emergencies, and metabolic crisis (9). A classification scheme (based on expert opinion) for differentiating mild, moderate, and severe acute FPIES presentations has been proposed (8).

Table 1. FPIES Epidemiological studies

Authors/Year/Country	Study Population and sample size	Study design	FPIES diagnosis	Food trigger	Prevalence or incidence
Katz et al. 2011 Israel (2)	13.019 (24 mo)	Prospective-based birth cohort single center	44	CM	0.34%
Mehr et al. 2017 Australia (4)	1400 (< 24 mo)	Population Survey	230	Rice 45% CM 33% Egg 12% Oats 9% Chicken 8%	15.4/100.000/y (0.0154%)
Alonso et al. 2019 Spain (3)	1142 (24 mo)	Prospective-longitudinal	8	CM 50% Fish 37.5% Egg 12.5%	0.7%
Sopo et al. 2012 Italy (5)	346	Retrospective	66	CM 65%	19%
Ludman et al. 2014 United Kingdom (6)	14.800 (8 mo median age)	Retrospective	54	CM 46% Fish 15% Egg 13% Soya 11% Wheat 11% Chicken 7% Banana 6% Oat 6% Beef 4% Rice 4% Carrot 4%	0.36%
Xepapadaki et al. 2019 Grece (7)	15.114 (<24 mo)	Retrospective	72	CM 46% Fish 35% Rice 10% Egg 7% Chicken 2.8%	0.47%
Nowak-Wegrizyn et al. 2019 USA (8)	53.575	Cross-sectional population survey	261 <18 year 113 >18 year	Na Na	0.51% 0.22%
Ruffner et al. 2020 USA (9)	158.510	Retrospective	214	CM 29% Grains 22.3% Soy 14.2% Egg 5.5% Vegetables 10.35 Fruit 5% Legumes 4% Meats 4.5%	0.145%

CM= cow 's milk

Chronic. Chronic FPIES appears if the food antigen is being taken regularly, and it has been described in infants fed with CM or soya-based formulas (10). It presents in infants with features almost identical to that of a food protein enteropathy and is characterized by chronic or intermittent vomiting, diarrhea with or without blood, and failure to thrive (10,11,12). This condition can evolve to acidemia and shock. Once elimination of the trigger food has occurred, infants with chronic FPIES should make a complete recovery, and prolonged persistence of symptoms or ongoing failure to thrive should prompt a search for an alternative diagnosis.

During breastfeeding. Infants who are exclusively breastfed are usually asymptomatic, and they appear to be protected against CM and soy FPIES (32,33) with a 5% rate of breastfed infants developing FPIES even though in Japan it has been reported that a 20% rate develops FPIES during breastfeeding (34). Although rarely, symptoms on exposure to food allergens present in breast milk have been reported, in about 5% of infants, with CM being the most frequent triggering food (17). However, other allergens such as soy, wheat, and egg have been anecdotally described as provoking triggers. For this reason, a focus allergy clinical history is crucial for the diagnosis. In the cases of symptoms onset during breastfeeding, maternal avoidance of the trigger food is recommended. Otherwise, in the absence of a history suggestive of reactions via breast milk (e.g., in exclusively breastfed infants presenting with chronic vomiting, diarrhea, or irritability), maternal avoidance of the trigger food is not recommended (8). The mainstay for the diagnosis of non–IgE-mediated food allergies in the breastfed infant remains eliminating foods from the maternal diet for 2-4 weeks with symptom improvement/resolution, followed by reintroduction with symptom re-appearance.

Solid food FPIES. Along with CM, solid foods are among the most common FPIES trigger. Any solid food can trigger FPIES; however, there may be variation depending on geographic area. It is unclear whether different dietary habits, environmental aspects, or genetic factors influence geographic variability. FPIES from solid food generally appear around 5-7 months of age, later than the forms triggered by CM and soya, which typically occur before six months (1). Rice and oats are the major triggers, followed by soy, egg, fish, fruit (apples, pears, banana, peaches) and vegetable (sweet potato, squash, white potato), meats (poultry, beef, pork), legumes (peas, peanut) seafood (fish, shrimp, mollusks) and nuts (35). Fish represents the most common solid food trigger in infantile acute FPIES in Spain (34,2%) and Italy (12%), likely reflecting the local dietary patterns and weaning habits (5,22,36-38). In a retrospective review on fish-triggered FPIES in Italy, it was found that the most common triggers are sole and cod (81%) (39). The age of onset of fish-triggered FPIES is older than for other solid foods, and this may be concerning the later introduction of these foods. Grains, in particular rice, are the most common cause of FPIES in Australia (45%) (23) and in the USA, whereas in Spain and Italy, rice is a much rarer trigger with no case reported in a Spanish birth cohort and 4-10% in Italian retrospective cohort (3,5,14,18,23). Recently, rice was the most common individual food trigger (53%), overcoming CM and soybean, previously reported as the most prevalent FPIES triggers in the USA (19). Infants with rice FPIES may be at increased risk of reaction to oats (40). Hen's eggs are reported as a trigger food in 11% and 13% of cases in the USA and UK, respectively, (6) as well as in 6% in Italy5 and in the Australian cohort (41). A recent retrospective multicenter study confirms that fish is the principal FPIES solid food trigger in Spain along with hen's eggs (42). Several patients showed a reaction to fruit. In fact, fruits and vegetables tended to be associated with FPIES in more than one food group and were involved in 10% and 8% of all food triggers, respectively (4). In a retrospective study, Blackman et al. conducted a study in a cohort of patients from Texas Children's Hospital; they reported that 40% of patients react to fruit, primarily banana (24%) and avocado (16%) (19). Recently Mehr et al. reported a rate of 10% for fruits, 4% for bananas, and 2% for avocado (4). Peanut and tree nuts are common triggers of IgE-mediated reactions but are rarely described to cause FPIES. A retrospective study conducted in a cohort of 462 children from a single institution reported peanut and tree nuts FPIES in 2% and <1% of children, respectively (13). In a prospective population-based study of 230 children, Mehr reported 0,5% of peanut FPIES (4). The average reported age for developing tolerance differs according to the food involved. It is reported 35 months for wheat and 42 months for other solid (35).

Fish-induced FPIES resolution was reported at 5.5 years (6,27,28,37,43,44,45,46).

Atypical FPIES. A subset of patients present an unusual form of FPIES characterized by the presence of positive skin test and /or serum food-specific IgE to their FPIES-trigger food, either at presentation or during follow-up (12). This form of FPIES is classified as atypical and is characterized by a reduced probability of developing tolerance beyond three years of age and a potential progression to typical IgE-mediated hypersensitivity (2,12,47). In addition, some patients can exhibit coexisting IgE-mediated allergies. Therefore, it has been recommended to test for sensitization by skin prick test or specific IgE the patients in the initial and follow-up evaluations before oral OCF given the risk of conversion to the IgE mediated FA (5,12,39). In the presence of positive specific IgE, it is recommended to perform an OFC according to the protocol adopted in the IgE-mediated forms with the possibility of prompt intervention in case of severe reactions such as anaphylaxis. The frequency of atypical FPIES is estimated to range from about 5 to 25%, and sensitization appears to be more common for CM and egg (2-7,12,21,31,39). However, atypical FPIES has rarely been reported following the intake of foods other than CM (12,13,48)

Diagnostic criteria

Diagnosis of FPIES may be difficult, mainly due to the lack of specific biomarkers to confirm or exclude the diagnosis. Delay of diagnosis is common, with some studies reporting a median delay of four to seven months (6). FPIES is a clinical diagnosis, mainly based on clinical features which, although not specific, are reproducible every time the patient takes the food. Different diagnostic criteria (DC) of FPIES were published over time in the literature, but none were systematically validated in prospective studies (Table 2) (1,47,49-53). The more recent diagnostic criteria proposed by the International Consensus on FPIES are presently widely used by physicians (1). According to these criteria, the diagnosis of acute FPIES is satisfied if the major criterion (vomiting 1–4 h after ingestion of culprit food, without IgE-mediate allergic skin or respiratory symptom) and at least three minor criteria are met. A positive

OFC is necessary to confirm the diagnosis, particularly if only one FPIES episode has occurred. No criteria exist for chronic FPIES. The diagnosis is based on the resolution of the symptoms within days after eliminating the trigger food and the occurrence of acute FPIES reaction when food is reintroduced. OFC is mandatory to confirm the diagnosis (1).

Vazquez-Ortiz et al. have compared the performance of different DC sets (1,47,50,51,53) in a cohort of 51 children with high clinical suspicion of acute FPIES from Southern Europe. The proportion of children meeting the various DCs was as follows: 92.2% for Lee criteria; 76.5% for Nowak-Wegrzyn 2017; 64.7% for Powel modified by Sicherer; 43.1% for Sopo; 17.6% Leonard. In particular, 25% of children in Vazquez-Ortiz cohort did not meet the 2017 Consensus DC, and the authors suggest that this might be related to the number of milder FPIES phenotypes not captured by the latest Consensus (54). These results highlight how DC to date cannot identify all patients with a high clinical suspicion of acute FPIES since some DC include a specific age range, being at the same time unable to encompass different phenotypes and variable severity. Recently, Miceli Sopo et al. solicited (55) the need to expand the 2017 Consensus criteria with specific presentations highly likely of acute FPIES diagnosis. These include i) "mild FPIES," i.e., a child with at least three consecutive episodes consisting of only one vomit, without any other manifestations; ii) "multiple FPIES," i.e., where a single typical episode would be sufficient to diagnose FPIES in a child who has already received a diagnosis of FPIES for another food; and iii) "FPIES with IgE-mediated symptoms," in which patients present with typical FPIES features in addition to IgE mediated respiratory or cutaneous. These observations suggest that validation of diagnostic criteria for FPIES is to date mandatory following prospective studies.

Diagnostic tests

Although FPIES is a non IgE-mediated FA, considering the possibility of atypical FPIES characterized by the presence of specific IgE to the incriminated food (5,12,47) and the possible switch to an IgE-mediated allergy (31,56) , skin prick tests and/or specific IgE are

Table 2. Different diagnostic criteria for food protein induced enterocolitis (modified by Barni 2021)

Authors	Powell 1986 (49)	Sicherer 1998 (47)	Leonard 2012 (50)	Miceli Sopo 2013 (51)	Leonard 2015 (52)	Lee 2017 (53)	Nowak-Wegrzyn 2017 (1)
Diagnosis of FPIES is satisfied if in the presenting episode(s)	All the underlyng items are met: - Disappearance of the symptoms of vomiting and diarrhea, and of diagnostic findings in the stool (blood and leukocytes), after all antigens are removed from diet. - No other cause for the colitis is demonstrable. - Symptoms do not recur and weight gain is normal for one month on a low-antigen formula, such as breast milk or casein hydrolysate formula, as the only dietary source. - Challenge with milk or soy formula, or other offending food antigens, reproduces symptoms.	All the underlyng items are met: - Less than 9 months of age at initial presentation [reaction]. - Repeated exposure to the incriminated food elicited diarrhea and/or repetitive vomiting within 24 h without any other cause for the symptoms. - There were no symptoms other than gastrointestinal symptoms elicited by the incriminated food. - Removal of the offending protein from the diet resulted in resolution of the symptoms, and/or a standardized food challenge elicited diarrhea and/or vomiting within 24 h after administration of the food.	All the underlyng items are met: - Less than 9 months of age at initial diagnosis. -Repeated exposure to causative food elicits gastro-intestinal symptoms without alternative cause. - Absence of symptoms that may suggest an IgE-mediated reaction. - Removal of causative food results in resolution of symptoms. - Re-exposure or oral food challenge elicits typical symptoms within 4 h.	All the underlyng items are met: - Less than 2 years of age at first presentation [frequent feature but not mandatory]. -Exposure to the incriminated food elicits repetitive and important vomiting, pallor, hyporeactivity and lethargy within 2-4 h. -Diarrhea may be present, much less frequently and later. The symptoms last a few hours, usually fewer than 6 h. -Absence of symptoms that may suggest an IgE-mediated reaction. -Avoidance of the offending protein from the diet results in resolution of symptoms. -Re-exposure or oral food challenge elicits typical symptoms within 2-4 h. Two typical episodes are needed to deliver the definitive diagnosis.	All the underlyng items are met: Major criteria - Repetitive vomiting or diarrhea within 6 h of food ingestion. - Absence of cutaneous and respiratory symptoms suggestive of an IgE-mediated allergy. - Removal of causative food results in resolution of symptoms. - Re-exposure or a food challenge elicits the typical symptoms. Minor criteria - Hypotension. - Lethargy, pallor, or hypotonia. - Negative skin-prick test and undetectable specific IgE level. - Absence of fever or hypothermia [36°C]	Major criterion and at least 2 minor criteria are met: Major criterion: - repetitive vomiting (0.5-4 hours) after eating a suspect food(s) Minor criteria: - A second (or more) episode of repetitive vomiting (0.5-4 hours) after eating the same suspect food - Repetitive vomiting episode (0.5-4 hours) after eating a different food - Associated floppiness, pallor, and/or diarrhea (within 24 hours) during at least one episode - Need for an emergency room visit and/or intravenous fluid therapy during at least one reaction	Major criterion and at least 3 minor criteria are met: Major criterion - Vomiting in the 1-4 hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms. Minor criteria - A second [or more] episode of repetitive vomiting after eating the same suspect food. - Repetitive vomiting episode 1-4 h after eating a different food. - Extreme lethargy with any suspected reaction. - Marked pallor with any suspected reaction. - Need for emergency room visit with any suspected reaction. - Need for intravenous fluid support with any suspected reaction. - Diarrhea in 24 h [usually 5-10 h]. - Hypotension. - Hypothermia.

suggested before the OFC (1). If positive, the protocol should be adapted to include a more gradual administration of the food, as IgE-mediated FA (57), combined with a prolonged observation for 4 hours, as recommended for FPIES (1). Based on conflicting results of two small studies (58,59), patch tests are not currently recommended for diagnosing FPIES (1). Patients with acute FPIES reactions often develop abnormalities in general hematological and metabolic lab tests. This includes thrombocytosis, eosinophilia and/or an elevated white blood cell count with left shift (12,60,61). Peripheral neutrophil counts become elevated at the onset of an acute reaction, peak at six h after the ingestion, and return to baseline in about 18–24 h (12,62). All these parameters are not specific but might support the diagnosis of FPIES. An increase of PCR was found six hours after acute episodes, with a peak at 12 hours, significantly correlating with the degree of reaction severity (63). In more severe cases, acidosis and methemoglobinemia have been reported in both acute and chronic FPIES (64,65). Hypoalbuminemia, anemia, eosinophilia, and leukocytosis have been observed in patients with chronic FPIES (66,67). Stool testing is not routinely recommended1. However, occult blood, leukocytes, eosinophils, and increased carbohydrate content are often detected in the stool of patients with chronic and acute FPIES (if diarrhea is present), supporting the diagnosis (62,64,68,69). Fecal calprotectin has been as suggested as a valuable marker for non-IgE gastrointestinal FA, including FPIES. However, data are very limited, and the lack of validated normal ranges in infants limits its utility in this condition (70). Radiologic studies are non-specific in FPIES patients. Endoscopy is not routinely performed in FPIES but might be helpful to exclude other aetiologies in case of chronic symptoms with unclear triggers (1).

Oral food challenge (OFC)

In most patients, a clinical history consistent with acute FPIES is sufficient to make the diagnosis and identify trigger foods, especially if the patient has reacted more than once with the same food, and the patient is well once the food is eliminated from the diet (1). OFCs should be considered in the initial diagnostic evaluation for cases in which the history is unclear or atypical, a single nonsevere episode is reported, a food trigger is not identified, if symptoms persist despite removing the suspected trigger food from the diet or in cases of chronic FPIES symptoms being these less specific (1,71). Most frequently, OFC is used to check the acquisition of tolerance to the culprit food, or to verify the tolerance to foods belonging to the same group of the culprit's food for which co-allergy/cross-reactivity was described (1,71) or to safely introduce new foods in FPIES higher-risk patients (history of reacting to multiple foods from different food groups, history of severe reactions to food(s), parental anxiety with home-based dietary expansion) (72). The procedure is usually considered at least 12 to 18 months after the most recent reaction. OFC should be performed in a safe medical environment by a trained team with emergency drugs available. Intravenous access in FPIES patients during OFC is recommended because a large proportion (50%) of patients need intravenous fluid administration and some (15%) develop severe reactions with hypotension (1,73). A baseline complete blood cell count (CBC) might be of value because an increased neutrophil count of >1500 neutrophils above the baseline count represents one of the minor criteria required to define the positivity of OFC (1). Data from a population-based birth cohort (with a different spectrum of severity) suggested that mild reactions could be treated with oral rehydration (2). The ideal OFC should be the one that can evoke the allergic reaction with the least possible severity of symptoms in all FPIES sufferers. For this reason, thinking the higher the doses of food, the more severe the reactions, several authors suggest beginning the OFC with a low dose. However, the approach to OFC differs across studies in amount and number of doses and timing between the administered doses (2,5,12,47,53,58,62,75,79). The 2017 International Consensus Guideline suggested using a challenge dose of 0.3 g of food protein per kilogram of body weight (range, 0.06-0.6 g/kg body weight) with a maximum total 3 g of protein or 10 g of total food (100 ml of liquid), in 3 equal doses over 30 minutes followed by 4-6 hours of observation. When a very low dose of food protein is administered and there is no reaction after 2-3 hours of observation, some experts advocate administering a full age-appropriate serving, followed by an additional 4 hours of observation. Lower starting dose

(0.06 gr protein/kg body weight), longer interval between doses, or both are recommended for those patients with a clinical history of severe FPIES reaction1. In patients with detectable specific IgE to the challenge food, an OFC protocol for IgE-mediated FA with a longer post-challenge observation period (4 hours) is recommended (1). Some recent studies have raised doubts about using the approach suggested by the Guidelines as FPIES symptoms are usually delayed, ranging from 0.5 to 6 hours. Thus, since most reactions occur after 1 hour and the protocols suggest administering 3 equal doses over 30 minutes, it is impossible to attribute with certainty the severity of the reactions to the dose administered. For this reason, other authors recently proposed a different OFC protocol, respect to both starting dose and intervals between the doses. Barni et al. (76) administered 25% of the total dose (0.3 g food protein/kg body weight) followed by a full dose 4 hours later if no reaction was observed. In this study, the authors observed that revealing a quarter of the full dose was sufficient to trigger a reaction in their patient population, with a mean time latency of 136 minutes (range 60-230 minutes). The reactions were mild, moderate, and severe in respectively 21%, 32% and 47% of children. No patients required to be transferred to the intensive care unit. Similar results were obtained by Infante et al. (77) comparing two methodologies used in the OFC for children with FPIES to fish: method 1 consisted of giving several doses over 30 minutes during the same day vs method 2 that consisted of giving 25%, 50%, and 100% of a standard serving size per age in three non-consecutive days. The authors reported that 25% of the serving was sufficient to elicit symptoms in most patients (81.3%) in the second group. In addition, fewer severe reactions were observed in patients receiving only 25% of the dose on day one than in those receiving a full serving during one challenge day. In contrast to which observed in the studies by Barni et al. and Infante et al, Wang et al. recently showed that FPIES OFC involving one-third serving size was sufficient to elicit symptoms only for 57% of patients ultimately deemed to have a positive challenge and the remaining patients did not react until they consumed more significant amounts at home (78). In the light of these observations, in a recent review Bird et al. (72). highlight the need to reconsider the FPIES OFC protocol suggested by the Guidelines. The authors sug-

gest that "a dose of 25% to 33% of the standard serving size is sufficient to trigger a reaction in most patients with FPIES". They also suggest that a more fractionated and with the closest range between doses should be considered only if there is suspicion of IgEs to the food being challenged (72). However, in addition to the previous history, the dose administered (and the interval between doses), other factors may affect the severity of the reaction to OFC. For example, the age of the population studied could also play a role: in the Wang study (78), patients who required intravenous fluids (IVF) were older than patients who did not require IVF during initial challenge or at home (mean, 51.8 months vs 31.9 months). In the Infante's study (77), a statistically significant difference between the ages of the groups was found, but the multinomial logistic regression model showed that the age did not produce any bias in the severity of the symptoms. Finally, the different types of food also may influence the severity of symptoms: in Sicherer's study, solid food-induced FPIES showed a trend toward more severe reactions (hospitalizations, episodes of shock, sepsis evaluations) compared with the control group (47). In all cases, regardless of the type of OFC, IVF were reported in 42.7%, onset of hypotension in 8.1% and hospitalization in intensive care unit or Emergency Department in 5.4% (Table 3). In conclusion, since the different OFC protocols have not been systematically studied, the timing and severity of previous reactions and the amount of food ingested and age of children should be considered when tailoring OFCs to individual patients. Regarding the OFC outcome, OFC is considered positive if the major criterion (vomiting 1-4 hours after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms) along with at least 2 minor criteria (lethargy, pallor, diarrhea 5-10 h after food ingestion hypotension, hypothermia, increased neutrophil count of >1500 neutrophils above the baseline count) are present (1). Consensus guidelines suggest that OFC outcome should be evaluated by considering that the prompt use of ondansetron could prevent the occurrence of repetitive vomiting, pallor, and lethargy, being minor criteria symptoms. Therefore, OFC may be considered positive in the case of major criterion alone (vomiting) following early administration of ondansetron. Moreover, in the case of hospital settings unable to determine neutrophil counts

Table 3. Studies on oral food challenge (OFC) protocol and development of severe symptoms in children with FPIES, according to the food. CMP: cow's milk protein; ICU: intensive care unit; IVF: intravenous fluid.

Authors	Study population (age)	Suspected food	OFC protocol - Dosage	Latency time to symptoms onset	Positive OFC N. (%)	Severe Symptoms
Katz 2011 (2)	Less than 6 months	Cow's milk	Five consecutive doses: 5mL (150 mg of CMP), 20mL (600 mg of CMP), 30 mL (900 mg of CMP), 60 mL (1.8 g of CMP), 120 mL (3.6 g of CMP), and finally a maximum dose of up to 150 mL (4.50 g of CMP) depending on the tolerance of the infant to drink such a volume. After the 60-mL dose and thereafter, the time interval between the doses was 45 minutes	Range time: 60-315 min from the first dose (mean time: 221.2 ± 71.5 SD min) Mean time: 120 ± 55.2 SD min from the last dose	28 (100)	IVF: 0 Steroids: 0 Ondansetron: 0 Hypotension = 0 Admission to ICU = 0 Severe reactions* = -
Infante 2019 (77)	Two different methods: Method 1 group: 36 months (IQR = 25–48), Method 2 group: 60 months (IQR = 29.5–84)	Fish	Method 1 consisted in giving several doses over 30 min during the same day. Initially, a dose equal to 1/8 (12.5%) of the serving size per age was given, then a 1/4 (25%), 1/2 (50%), and finally the remaining of the whole meal Method 2. The first day a unique dose of 25% of the serving size per age was given followed by a 4-h clinical observation. If the children remained asymptomatic for the next 24 h, 48 h later a 50% of the serving size per age was served followed by a 4-h observation, and if they still remained asymptomatic for the next 24 h, we gave them a normal serving size per age on the third non-consecutive day	Method 1, except in two of them, the symptoms started after the complete serving size per age was given Method 2, only in 6 (18.75%) the symptoms appeared after the whole meal was eaten.	43 (57.3)	Method 1: Severe reactions: 17 (39.5%) Admission to ED or hospitalized: 18 (42%) Method 2: Severe reactions: 4 (12.5%) Admission to ED or hospitalized: 8 (25%)
Hwang 2008 (74)	aged 36 days, (SD 14) range 13–58	Cow's milk, soy	A single dose consisting of 0.15 g of CMP/kg body weight (one spoon of formula mixed with 20 ml of water).	The symptoms began not before than 1,1 from the single dose	27 (37.5)	IVF = - Hypotension = 3 (11.1) Admission to ICU: - Cyanosis: 6 (22%) Lethargy: 27 (100) Projectile vomiting 27 (100) Diarrhoea 9 (33) Steroids: - Severe reactions = -
Powell 1978 (62)	5.5 months (average age)	Cow's milk, soy	A single serving dose of cow's or soy milk (100 ml)	Only in one of them onset of symptoms at at 1h, the remaining at least 1,5 h after the single dose	14 (77.8)	IVF = - Vomiting = 10 (71.4) Diarrhoea =14 (100) Hypotension = 0** Admission to ICU = 0 ** Severe reactions* = 0
Sicherer 1998 (47)	median age at diagnosis was 7 weeks (range, 1 week to 7 months).	Cow's milk, soy, corn	0.6 g protein/kg body weight. 0.15-0.3 g protein/kg body weight for patients with history of severe reactions with small ingestion	Positive challenges elicited symptoms 1 to 4 hours after ingestion of the challenge substance.	11 (68.7)	IVF = 7 (43.7) Steroid = 3 (18.7) Hypotension = - Admission to ICU: - Severe reactions* = 7

Table 3. Studies on oral food challenge (OFC) protocol and development of severe symptoms in children with FPIES, according to the food. CMP: cow's milk protein; ICU: intensive care unit; IVF: intravenous fluid.

Study	Age	Food	OFC protocol	Time to reaction	n (%)	Management / outcomes
Caubet 2014 (12)	15 months (median) IQR (9.24)	Cow's milk, soy and solid foods	0.06- 0.6 g of food protein/kg body weight (usually 0.3 g of protein) in 3 equal doses over a 45-minute period and remained under observation for 4 to 8 hours after the ingestion of the challenge food. In the case of grains with low protein content, such as rice and oat, an age-appropriate food portion was served.	From the first-dose: mean 150 min (range 35-370 min) From the last dose: mean 120 min (range: 5- 320 min)	61 (83)	IVF = 70 (96) Hypotension = 14 (19) Admission to ICU = 0 Steroids = 69 (94) Ondansetron = - Admission to ED or ICU or hospitalized = 0 Severe reactions* = -
Miceli Sopo 2012 (5)	1 year and 1 month to 5 years and 5 months	Cow's milk and egg well cooked and mixed with wheat	Three different methods: Rome: 50% serving size for age with 2-h observation and then full serving size for age with 4-h observation. Florence: 25%, 50%, and full serving size for age, each followed by 4-h observation Benevento: 0.4 g protein/kg body weight in 3 equal doses over 3 h with 4-h observation, then full serving size followed by 2-h observation	Median time: 2 h (range, 0.5–4 h) (not specified from which dose)	35 (53)	IVF or steroids = 15 (43) Ondansetron = - Hypotension = - Admission to ICU = - Severe reactions* = -
Lee 2017 (53)	Median age 17 months (IQR 10.8-51.3)	Cow's milk, egg, fish, rice	a single serving size of the food allergen (at least 3 g of food protein, rice at least 1 g), with a 4-hour observation period.	Median time: 2.5 h (2-3 h)	20 (25)	IVF = 6 (20) Steroids = - Ondansetron = 13 (65) Hypotension = 1 (5) Admission to ICU = 0 Severe reactions* = -
Fogg 2006 (58)	15.6 months (range 5-30 months)	Cow's milk, egg, soy, wheat, rice, oat,	0.05–0.15 g protein/kg body weight of the suspected protein in two increasing doses over a 30-min interval	Mean time: 2.8 ± 0.8 h from the last dose	15 (80)	IVF = - Steroids = - Ondansetron = - Hypotension = 0 Admission to ICU = 0 Severe reactions* = -
Vaquez Ortiz 2017 (75)	0-18 years	Cow's milk, egg, rice, corn, fish,	an age-appropriate portion (0.3 g/kg and 3 g as maximal dose) divided into 3 equal doses given at 90-minute intervals, except for cow's milk in which 7 consecutive doses were given at 90-minute intervals.)	After the first dose: 0 After the second dose: 12 pts (36.4%) After the third dose: 17 pts (51%) After the fourth dose: 1 pts (3%) After the fifth dose: 3 pts (9%)	33 (41)	IVF = - Steroids = - Ondansetron = - Hypotension = 0 Admission to ICU = 0 Severe reactiomns* = -
Barni 2019 (76)	12.7 ± 16.4 months (range 1-93 months)	Cow's milk, fish, grain, egg, other	OFC protocol consisted in administering 25% of the full dose, calculated as 0.3 g of food protein/kg body weight, and the remaining dose 4 hours later, followed by another 4 hours of observation. If the patient had a previous history of severe reactions, a lower dose of 0.06 g protein/kg body weight was used.	Mean time latency: 136 min (range 60-230 min; median: 120 min) from the first dose	19 (35.2)	IVF = 11 (57.9) Steroids = 14 (73.7) Ondansetron = 15 (78.9) Hypotension = 0 Admission to ICU = 0 Severe reactions* = 9 (47)

Table 3. Studies on oral food challenge (OFC) protocol and development of severe symptoms in children with FPIES, according to the food. CMP: cow's milk protein; ICU: intensive care unit; IVF: intravenous fluid.

Study	Age	Food	n (%)	OFC protocol	Timing	Reactions/Management
Guenter 2020 (79)	Median age 18.5 months (range 6–118 months, 0.5–9.8 years).	Uncooked milk, soy, rice, lightly cooked eggs, baked egg, cooked, cheese, peanut, and pork	10 (11)	doses ranged from 0.03–0.6g food protein/kg body weight divided in 3 equal doses over 30 minutes	all reactions occurred within 2-3 hours after completion of the initial dose	IVF = 1 (10) Steroids = 0 Ondansetron = 9 (90) Epinephrine = 1 (10) Hypotension = - Admission to ICU = - Severe reactions* = -
Wang 2019 (78)	2.8 years (average age)	19 different foods (most frequently milk, soy, wheat, oat, rice, egg, corn, etc.)	17 (56)	Two different protocols: before July 2016 patients received a 2-dose challenge, receiving a cumulative of one-quarter to one-third serving size for age. After July 2016, food challenges were performed by a 1-dose protocol: administration of one-third of serving size for age. After a 4-hour observation period	Symptoms occurred at least 85 minutes after dosing. In the majority (76%) the symptoms started at least 120 minutes after dosing.	IVF = 14 (82.3) Steroids = - Ondansetron =12 (70.6) Hypotension = 2 (11.7) Admission to Emergency department = 5 (29.4) one of these in ICU = 1 (5.8) Severe reactions* = 5 (29.4)
Total			333			IVF = 124 /290 (42.7) Hypotension = 20 244 (8.1) Admission in ICU o Emergency Department= 13/238 (5.4)

before and during the OFC, the possibility to judge the OFC outcome would be guided only by the clinical manifestations. On the contrary, in research settings, more rigorous criteria should be taken into account to confirm OFC positive outcome (1).

Management

Acute treatment of reactions during OFC relies on fluid rehydration with normal saline bolus (10-20 mL/kg repeated as needed) and possibly administration of ondansetron (0.15 mg/kg, maximum dose 16 mg) intravenously or intramuscularly in patients 6 months or older. Methylprednisolone (1 mg/kg, maximum dose 60 mg intravenously) may be considered in severe reactions, although no controlled studies support this recommendation (1,72). Mild-to-moderate FPIES reactions may resolve with oral rehydration at home. There is a certain variability in the proportion of patients who experience single versus multiple FPIES (4). In general, tolerance to one food from the food group is considered a favorable prognostic indicator for tolerance to other foods from the same group (1). While the International Consensus Guideline reports that infants with CM or soy FPIES appear to be at higher risk of FPIES to other foods1, this has not been reported in a recently published Australian cohort study(4). Most breastfed infants with FPIES appear to tolerate breast milk from an unrestricted maternal diet(33), although some anecdotal cases of reaction to proteins passing through breast milk have been described (80,81). In general, routine avoidance of the allergenic food by the breastfeeding mother is not recommended for infants who did not present symptoms of FPIES while being breast-fed, although the mother was consuming allergenic food. Infants with CM/soy-induced FPIES can be breast-fed unless maternal ingestion of an allergen triggers FPIES symptoms; in the persistence of symptoms in the

infant despite maternal avoidance diet, an extensively hydrolyzed formula can be used (82). When breastfeeding is not possible, Consensus Guideline recommend extensively hydrolyzed infant formula as the first choice in case of FPIES due to CM1, while the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines (83) recommend the use of an amino-acid-based formula, particularly if in association with growth faltering. Noteworthy, 10% to 20% might require an amino acid-based formula to resolve their symptoms and catch up on their growth (2, 32, 81). In infants, goat's milk or other animal milk should not be used because of high homology to CM with a high risk of cross-reactivity (1, 80). There are still many open questions and controversies regarding the management of FPIES due to the lack of evidence. For example, there are currently no conclusive data supporting tolerance to baked milk or egg in patients with FPIES (84,85). It is unclear if the tolerance to heated products should be necessarily tested in a supervised setting or at home, which the clinician made case by case. If the child was already consuming baked milk or egg in the diet without symptoms, he could be reasonably allowed to continue. Similarly, no clear evidence exists regarding the introduction of solid foods to prevent FPIES (86), with an only available empirical recommendation regarding the mode of introducing solids in infants with FPIES (1,87).

In the choice of first weaning foods and introducing different foods, important issues to be taken into account are the differences existing across countries and cultures regarding weaning practice (88). OFC or home introduction can be decided at the discretion of the physician, preferring supervised OFC in infants and children with multiple FPIES. Noteworthy, infants and children with FPIES are at risk of significant dietary restrictions and nutritional deficiencies due to parental anxiety about trying new foods, particularly for infants with multiple FPIES triggers. Thus, nutritional counseling by a dietician for parents of infants with FPIES is recommended.

Conclusion

Recent years have seen an increased awareness of FPIES. As a result, we certainly know more about the epidemiology and the different phenotypes of this form of food allergy typical of the first year of life. Although the publication of guidelines in 2017 was crucial as it guided the diagnosis and the treatment of the disease, many obscure points remain regarding the pathophysiology, the natural history of the disease, and the potential consequences over time, and others (Table 4). Therefore, further future studies are needed to improve the understanding of this pathology.

Table 4. What is known and what is unknown in FPIES

What is known	What is unknown
FPIES typically occurs in infants and children; age of onset depends on theintroduction of food into the diet	Underlying immunologic mechanisms
	Natural history
FPIES mostly occur in non-breast-fed infants; FPIES whilst an infant is breastfed is rare	Potential consequences over time
	Starting Doses of oral food challenge
Repetitive vomiting is the most prominent symptom	Interval between doses during oral food challenge
FPIES can be classified according to onset (early versus late), severity (mild-to-moderate vs severe), and timing (acute versus chronic)	Tolerance to cooked/baked product
	Tolerance to small amount of trigger food
There is no single diagnostic test specific for FPIES, thus diagnosis is aclinical one	Timing of solid foods introduction
	Type of first solid food introduction
OFC should be considered in the initial diagnostic evaluation for cases in which the history is unclear or atypical, a single episode is reported, a food trigger is not identified, if symptoms persist despite removing the suspected trigger food from the diet or in cases of chronic FPIES symptoms being these less specific	
When breastfeeding is not possible, or if there is no improvement of symptoms whist a maternal elimination diet an extensively hydrolysed formula is recommended	
In case of FPIES with growth faltering or failure of eHF an elemental formula is recommended	

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