REVIEW

Food protein-induced enterocolitis syndrome – a review of the literature with focus on clinical management

Marine Michelet[1,*]
Dominique Schluckebier[2,*]
Laetitia-Marie Petit[2]
Jean-Christoph Caubet[3]

[1]Children Hospital, Pediatric Allergology Unit CHU Toulouse, Toulouse, France; [2]Geneva University Hospitals, Pediatric Gastroenterology Unit, [3]Geneva University Hospitals, Pediatric Allergology Unit, Geneva, Switzerland

*These authors contributed equally to this work

Abstract: Food protein-induced enterocolitis syndrome (FPIES) is a potentially severe presentation of non-IgE-mediated gastrointestinal food allergy (non-IgE-GI-FA) with heterogeneous clinical manifestations. Acute FPIES is typically characterized by profuse vomiting and lethargy, occurring classically 1–4 hours after ingestion of the offending food. When continuously exposed to the incriminated food, a chronic form has been described with persistent vomiting, diarrhea, and/or failure to thrive. Although affecting mainly infants, FPIES has also been described in adults. Although FPIES is actually one of the most actively studied non-IgE-GI-FAs, epidemiologic data are lacking, and estimation of the prevalence is based on a limited number of prospective studies. The exact pathomechanisms of FPIES remain not well defined, but recent data suggest involvement of neutrophils and mast cells, in addition to T cells. There is a wide range of food allergens that can cause FPIES with some geographical variations. The most frequently incriminated foods are cow milk, soy, and grains in Europe and USA. Furthermore, FPIES can be induced by foods usually considered as hypoallergenic, such as chicken, potatoes or rice. The diagnosis relies currently on typical clinical manifestations, resolving after the elimination of the offending food from the infant's/child's diet and/or an oral food challenge (OFC). The prognosis is usually favorable, with the vast majority of the case resolving before 5 years of age. Usually, assessment of tolerance acquisition by OFC is proposed every 12–18 months. Of note, a switch to an IgE-mediated FA is possible and has been suggested to be associated with a more severe phenotype. Avoiding the offending food requires education of the family of the affected child. A multidisciplinary approach including ideally allergists, gastroenterologists, dieticians, specialized nurses, and caregivers is often useful to optimize the management of these patients, that might be difficult.

Keywords: FPIES, FPIES management, FPIES diagnosis, non-IgE-mediated gastrointestinal food allergy, cow milk

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a severe presentation of non-IgE-mediated food allergy affecting the gastrointestinal (GI) tract mainly in infants and young children.[1,2] This syndrome is typically characterized by profuse vomiting and lethargy, occurring classically 1–4 hours after ingestion of the offending food.[3] Diagnosis of FPIES is difficult, and misdiagnosis is common.[4,5] There are a number of differential diagnosis that should be ruled out. Thus, FPIES is often confounded with sepsis, metabolic diseases, severe gastroenteritis, or even abdominal surgical

Correspondence: Jean-Christoph Caubet
Geneva University Hospitals, Pediatric Allergology Unit, 6 Rue Willy Donzé, 1205 Geneva, Switzerland
Email jean-christoph.caubet@hcuge.ch

emergencies before reaching a final diagnosis.[6] Recent studies have suggested that FPIES is not as rare as previously believed.[4,6–8] But despite increased interest, our understanding of its pathomechanism remains limited, and many management aspects are still highly debated, including emerging recommendations regarding the introduction of new foods in FPIES patients and follow-up.

In this review we will discuss the epidemiology, clinical characteristics, incriminated foods, pathomechanisms, diagnosis, and differential diagnosis of FPIES, with a particular focus on management aspects.

Epidemiology

Although FPIES was initially described in the 1940s, a limited number of studies have been published until the recent surge in interest.[9] Currently, FPIES is one of the most actively studied non-IgE-mediated GI food allergies (non-IgE-GI-FAs).[10] Epidemiologic data are lacking, and estimation of the prevalence is based on a limited number of prospective studies.[7,11] Thus, a prospective birth cohort study conducted over 2 years in Israel reports a 0.34% prevalence of FPIES to cow's milk (CM) and 0.5% IgE-mediated FA to CM in the same study cohort.[7] These results were quite surprising, as the prevalence of FPIES was believed to be much lower than the one of IgE-mediated allergy. Another prospective study cohort conducted through a national register in Australia showed an incidence of 1/10,000 cases per year including all different food triggers.[11] However, this lower incidence is likely to be underestimated due to methodological issues.[5]

FPIES can present at all ages, with a slight male predominance.[5] In contrast to eosinophilic esophagitis, there is no strong familial association in both parents and siblings.[12,13] However, association with atopic diseases is commonly reported, particularly atopic dermatitis (up to 57%).[14,15] Other atopic diseases such as allergic rhinitis, asthma, IgE-mediated FA, and eosinophilic esophagitis or gastroenteritis might also be infrequently associated.[4,12,16] Katz et al, observed that infants with CM-FPIES were more often delivered by c-section, suggesting a role for intestinal microbiota in the development of FPIES.[7] However, these data have not been confirmed afterwards.

Further epidemiologic data are needed in the future, not only to have an accurate estimate of the prevalence in different countries, but also to identify risk factors to develop FPIES.

Clinical manifestations

FPIES is classical described as chronic or acute.[17,18] In the chronic form, as initially described by Powell, patients typically present with chronic intermittent emesis, diarrhea with blood or mucus, abdominal distension, and/or lethargy. In the most severe cases patients progress to dehydration, metabolic abnormalities, nutritional deficiencies, and failure to thrive (FTT). In some cases, even older children can present with chronic FPIES in case of frequent repetitive solid food ingestion.[19] However, chronic FPIES remains not well defined and due to its aspecific clinical symptoms, the diagnosis is often difficult, particularly as symptoms may overlap with other non-IgE-GI-FAs mediated allergy (food protein-induced enteropathy [FPE] and food protein-induced allergic proctocolitis [FPIAP]). In addition, the literature regarding this disorder is poor and most of the currently published studies did not include a confirmatory oral food challenge (OFC). Moreover, some authors have been speculated that chronic FPIES might be a separate disease entirely, not just a different presentation.[20]

Acute FPIES is typically characterized by repetitive profuse vomiting (90%–100%), pallor (14%–67%), and/or lethargy (3%–85%), typically occurring 1–4 hours after ingestion of the offending food.[2,10] Diarrhea may follow 5–10 hours later, in up to 50% of infants and in only 30% of children older than 1 year of age.[2,4,7,10] Hypotension in FPIES has been reported in up to 15% of patients in some series.[7,10,12,16] Of note, acute FPIES can be the initial presentation or may occur after a period of exclusion in patients with chronic FPIES after reintroduction of the offending food (acute-on-chronic form). In the vast majority of cases, the first reaction appears after the first or second ingestion of the causative food.[4] Although chronic form of FPIES may occur in breastfed infants, the acute form has been rarely described in exclusively breastfed infants.[5,6]

The age at presentation for the acute form is variable and may depend on the offending food. Thus, it has been shown that FPIES to solids typically appears later than FPIES to CM or soy, probably owing to the timing of solid foods introduction into the diet.[2,12] But other factors (i.e., environmental and genetic) probably influence the development of FPIES. Adult onset FPIES to fish and/or shellfish is an example of FPIES, probably unrelated to delayed food introduction.[12,21]

Pathophysiology

FPIES is typically classified as a non-IgE-GI-FA, but its exact pathomechanisms remain not well defined.

Several studies have suggested a key role for T cells in FPIES patients, particularly by founding positive patch test or positive lymphocyte transformation test to the specific

food allergen.[22–28] It has been suggested that secretion of proinflammatory cytokines TNF-α and IFN-γ, in combination with a relative lack of expression of TGF-β-receptors (known as a protector of the intestinal wall) may contribute to local inflammation and increased intestinal permeability.[16,29–31] Nevertheless, it has been shown that neither peripheral blood mononuclear cell proliferation nor patch tests can be used as a diagnostic tool at an individual level, questioning the role of T cell in FPIES patients.[22–26,29] The role of these cells has been further challenged by recent data showing similar CD4+ T cell-proliferative responses after casein stimulation in CM FPIES patients to those with IgE-mediated CM allergy and those tolerating CM.[32]

The mechanism of tolerance acquisition in FPIES remains unclear. CD4+CD25+ regulatory T cells might be implicated, as they have been increasingly identified in infants/children who acquired tolerance to the incriminated food.[33] It is hypothesized that they exert a suppressive action via cell to cell contact and by the production of TGF-β and IL-10.[26,33] Recently, data support the suggested key role of IL-10 in acquisition of tolerance in patients with CM FPIES.[32]

The role of neutrophils has also been discussed, as they typically increase after ingestion of the incriminated food, peaking at 6 hours.[18] In addition, neutrophils have been found in gastric aspirate and stool mucus in patients with FPIES, as well as in biopsies from FPIES patients. An increase of serum IL-8 levels after positive OFC also suggested a key role of these cells.[32] However, their role in the pathomechanism of FPIES has not been clearly demonstrated; the rise in peripheral neutrophil count could simply reflect unspecific stress response or the side effect of steroid administration as treatment.[1,4,17,18,34] From another point of view, eosinophils have been found in biopsies from FPIES patients, suggesting a potential involvement of these cells.[35,36] Recently, a potential role of mast cells has been suggested, but these data need to be confirmed by further studies.[32]

Although FPIES is typically categorized as a non-IgE mediated allergic disorder, some FPIES patients may have positive specific IgE to the causal protein either at onset or during follow-up; this is referred to as "atypical FPIES".[12,19,37] Of note, a switch from the non-IgE to an IgE phenotype, or the opposite is possible, and the relation between non-IgE-GI-FA and IgE-mediated FA required further investigation.[2,33,37]

The observed increase of specific IgA and IgG antibodies in patients with FPIES has raised the question of a humoral response in this disorder.[24,34,38] However, recent study suggests that their role is probably limited.[32]

Further studies are needed to better understand the pathomechanism of this disease. Recent pathological findings are summarized in Table 1.

Offending foods

There is a wide range of food allergens that can cause FPIES. In Europe and USA, the most frequently incriminated foods are CM, soy, and grains.[5–8,15,16,20,39–41] Furthermore, FPIES can be induced by foods usually considered as hypoallergenic, such as meat, white and sweet potatoes, chicken, mushrooms, fruits and vegetables.[2–4,6,15,16,19,20,39–47] There are some geographical variations regarding the frequency of incriminated foods in FPIES that are summarized in Table 2. These differences may be related to country-specific food habits, in particular differences in the timing of food-introduction in infancy.[2,20,48] Thus, FPIES to CM and soy commonly appear in the first 3 months of life. It has been recently suggested that early introduction of CM or soy formula is a risk factor for the development of CM or soy FPIES, respectively.[2] American infants have a lower rate of breastfeeding and are earlier exposed to formula CM than Australian infants.[5] In Australia and Europe soy formula is rarely used in the first 24 months of life, whereas soy formula is frequently used in the USA even before 6 months of life.[11,49] This might explain, at least partially, the relatively high prevalence of FPIES to soy in USA compared to other countries. In Australia chicken is one of the first solid foods introduced in the child's diet,

Table 1 Summary of our current understanding of the pathophysiology of FPIES

- A central role of T cells in the local intestinal inflammation has been suggested, but still need to be confirmed
- A deficit in TGF-β1 response and overzealous TNF-α response may be important factors in FPIES
- IL-10 might play a key role in acquisition of tolerance in patients with FPIES
- Increased serum IL-8 levels in patients with active FPIES suggest neutrophils involvement
- A potential role of IL-9 in the pathogenesis of FPIES has been recently suggested, potentially through its influence on intestinal permeability
- Elevated baseline serum tryptase levels have been found in patients with active FPIES suggest low-grade intestinal
- Mast cell activation or increased mast cell load
- Paucity of humoral response in FPIES has been suggested in several studies

Although several immune changes have been shown in FPIES patients, the pathophysiology of the disease remains not well defined and requires further characterization

Abbreviation: FPIES, food protein-induced enterocolitis syndrome.

Table 2 Distribution of offending food for FPIES in different countries

Year	Country	Total no of cases	Cow milk	Soy	Grains	Fish	Poultry	Vegetables	Fruits	Other	Comment	References
1998	USA	16	11	11	0	0	1				7 patients to both	1
2003	USA	14	5	8	9 O, 10 R, 2 B	0	1			3	11 (78%) > 1 food 9 (64%) also soy + CM	12
2003	Israel	6	3	2	0	0	4			2		39
2005	Spain	14				14					1 patient with IgE	40
2009	Korea	23	11	12	1 R	1	0			1		8
2009	Australia	31	7	10	14 R, 1 O	1	1			1	36% avec R-FPIES reaction to other foods	15
2011	Israel	44	44									7
2012	Italy	66	44	3	3 R 1 C	8	2			5	56 (85%) react to only 1 food	6
2013	USA	462	309	189	88 R, 74 O, 46 W, 18 B, 37 C	4	21	50	45	81	70% react to 1–2 foods	14
2013	Australia	4			Egg	None						41

Abbreviations: B, barley; C, corn; CM, cow milk; FPIES, food protein-induced enterocolitis syndrome; O, oat; R, rice; W, wheat.

which might explain why FPIES to chicken appears earlier in Australia compared to USA where only 28% of the children under 6 months have tried chicken.[11,50]

Most children react to a single food (i.e., 65%–80%).[10] Nevertheless, FPIES to multiple foods is not uncommon and the prevalence seems to vary geographically.[4,6,7] Thus, it has been shown that a significant proportion of infants with FPIES to CM or soy (i.e., 37%–50%) will also react to soy or CM respectively, as well as to other foods (19%).[8,20,23,51] However, these associations have not been found in other studies.[4,6,7] FPIES to multiple solid foods has also been particularly described in infants with FPIES to grains.[2,14] Indeed, infants with FPIES to grains such as rice, oat, or barley are particularly at risk of developing FPIES to other grains.[2,20] In American studies, it has been shown that concomitant FPIES to oat and rice can occur in up to 35–44% of patients with FPIES to oat or rice.[2,14] However, the proportion of FPIES to multiple solid foods was significantly lower in studies outside USA. Higher proportion of patients reacting to multiple foods in USA might also be explained by inclusion of more severe cases recruited in tertiary centers, compared to studies from Israel, Italy or Australia. In addition, the pathophysiology, heritability and molecular mechanisms of co-allergies remain unclear and furthers studies are needed. FPIES to fish is mainly described in older children and adults, and is relatively common in Italy and Spain.[40,52] Of note, in most of the cases (65%) children react to one single fish.[52]

Diagnosis

Diagnosis of FPIES may be difficult, particularly due to the lack of specific biomarkers to confirm or exclude the diagnosis. Indeed, FPIES is a clinical diagnosis, mainly based on typical clinical manifestations, after exclusion of other causes. Currently, there are no fully validated diagnostic criteria for FPIES. The different proposed diagnostic criteria are detailed in Table 3. The more recent diagnostic criteria have been adapted from the initial criteria proposed in 1978 by Powell, to include the acute phenotype of FPIES.[18] Basically, the infant/child should present with typical digestive symptoms that resolve after avoidance of the incriminated food. The reexposition to the incriminated should lead to reappearance of clinical signs. Symptoms must be limited to the digestive tract and IgE-mediated symptoms should be excluded.[53]

A positive OFC has been part of diagnostic criteria for a long time. However, in clinical practice a confirmatory OFC is not performed in children with several clear FPIES reactions. In fact, at the present time, common practice is to diagnose FPIES without confirmatory OFC in patients experiencing 2 or more typical episodes.[6] When OFC is performed, the interpretation is usually based on Powell's diagnostic criteria.[54] A revision of these criteria has also been proposed, which focus on clinical aspects (especially vomiting) and blood testing (leukocytosis) over stool analysis.[55] Indeed, diarrhea is present only in a small proportion of patients, and stool analyses are not routinely performed in most reference centers.

Of note, an OFC should always be performed in an appropriate setting, particularly with a trained team and emergency drugs available.[55,56] A peripheral intravenous (PIV) line is historically recommended, but its utility remains debated, particularly in patients with mild initial reaction.[7,57,58] Although

Table 3 Diagnostic criteria FPIES

Powell[18]	Powell[54]	Leonard and Nowak-Wegrzyn[53]	Miceli Sopo et al[74]
Onset of symptoms at <2 months of age Infants <9 months of age at study time	Disappearance of symptoms (vomiting and diarrhea) and of diagnostic findings in the stool (blood and leukocytes) after all Ag are removed from the diet	Less than 9 months of age at initial diagnosis	Less than 2 years of age at first presentation (frequent feature but not mandatory)
While receiving the offending food (formula) the infant has watery stools with mucus, blood and leukocytes, and a peripheral PNL	No other cause for colitis detectable	Repeated exposure to causative food elicits gastrointestinal symptoms without alternative cause	Exposure to the incriminated food elicits repetitive and projectile vomiting, pallor, lethargy within 2–4 hours. Diarrhea may be present, much less frequently and later. The symptoms last a few hours, usually resolve within 6 hours
Diarrhea ceases and normal growth resumes when the offending food Ag is eliminated	Symptoms do not recur and weight gain is normal for 1 month on a low Ag formula as the only dietary source	Absence of symptoms that may suggest an IgE-mediated reaction	Absence of symptoms that may suggest an IgE-mediated reaction
The response to challenge meets the criteria of OFC	Challenge with CM or soy formula or other offending food Ag reproduces symptoms of vomiting within 1–3 hours and or diarrhea within 4–10 hours	Removal of causative food results in resolution of symptoms	Avoidance of the offending protein from the diet results in resolution of symptoms
		Reexposure or OFC elicits typical symptoms within 4 hours	Reexposure or OFC elicits typical symptoms within 2–4 hours Two typical episodes are needed to establish the diagnosis without the need to perform OFC

Note: Reproduced from Serafini S, Bergmann MM, Nowak-Węgrzyn A, Eigenmann PA, Caubet JC. A case of food protein–induced enterocolitis syndrome to mushrooms challenging currently used diagnostic criteria. *J Allergy Clin Immunol Pract.* 2015;3(1):135–137.[75]
Abbreviations: Ag, antigen; CM, cow milk; FPIES; food protein-induced enterocolitis syndrome; PNL, polymorphonuclear leukocytosis; OFC, oral food challenge.

it has been found that up to 15% of patients developed hypotension,[10] the majority of studies were performed in tertiary allergic medical centers, treating potentially more complex and severe cases. In comparison, Katz et al, treated successfully 28 reactions during OFC with simple oral rehydration, without any case of hypotension reported.[7,57] The need for PIV access should be therefore carefully evaluated and let to the physician evaluation.

To date, there is no consensus on the optimal protocols for OFC in FPIES patients. Recommendations vary between the administration of one (full) single dose up to 3 increasing portions (0.06–0.6 g/kg).[20] A lower dose should be considered in patients who presented with a severe initial reaction. Skin prick and/or specific IgE measurement are recommended before performing OFC because of the potential risk of an IgE-mediated allergy.[48] In case of IgE mediated FA, the OFC protocol should be adapted to an IgE-mediated allergy protocol.[1,48]

Some authors have found positive patch tests to the specific food antigen.[21–27,31] Nevertheless, others have shown that patch tests have a poor predictive value (75%) and could be falsely negative in up to 45% in patients with FPIES. Thus, they are not routinely recommended.[11,22–29] Similarly,

measurements of IgG and IgG4 antibodies in blood are not recommended. It is important to note that because diagnostic criteria focus on systemic impairment, local intestinal evaluation via endoscopy, and histological findings in FPIES remains poorly characterized. Although not recommended for routine diagnosis, endoscopy might be helpful in cases of unclear diagnosis to help rule out other conditions. In addition for research purposes, studies assessing macroscopic or histological changes in FPIES would be very useful.[59]

Differential diagnosis
As clinical features of FPIES are rather nonspecific, the differential diagnosis is extensive as shown in Table 4. Mehr et al, reported that a diagnosis is established in only 11% of patients presenting with an isolated acute episode, whereas the rest received no diagnosis or a misdiagnosis, such as viral infection or sepsis.[5,56]

Acute FPIES symptoms are very similar to infectious disease.[4,54] Viral gastroenteritis is often suspected during the first episode. Hypotension and lethargy in infant can falsely lead to a diagnosis of sepsis.[60] In the presence of hypotension, anaphylaxis is more often suspected than FPIES. In severe cases, FPIES can mimic an acute surgical abdomen.[61] Of note,

Table 4 Clinical features of FPIES and its differential diagnosis

Clinical features	Differential diagnosis
Signs and symptoms	**Infections**
Repetitive vomiting every 10 to 15 minutes, onset 1–3 hours after ingestion (>90%)	Viral gastroenteritis Sepsis
Diarrhea, onset 5 hours after ingestion (<50%)	Bacterial enteritis (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*)
Lethargy (70%)	Parasites
Pallor (70%)	
Dehydration	**Allergic disorders**
Hypotension (15%)	Other gastrointestinal non-IgE mediated food allergy disorders (food protein-induced enteropathy and eosinophilic gastrointestinal disorders)
Hypothermia (25%)	
Abdominal distension	Acute IgE mediated allergy (anaphylaxis)
Laboratory findings	**Gastrointestinal disorders**
Elevated neutrophil count	Gastroesophageal reflux disease
Thrombocytosis	Hirschsprung disease
Metabolic acidosis	Intussusception
Methemoglobinemia	Volvulus
Fecal leukocytes and eosinophils	Pyloric stenosis
Frank or occult fecal blood	Celiac disease
Increased carbohydrate content in stool	
Elevated gastric juice leukocytes	**Other**
Negative IgE test to the trigger food in most cases	Neurologic disorders (i.e., seizure, encephalopathy, or bleeding)
	Heart defects (i.e., congenital heart disease, cardiomyopathy, or arrhythmia)
Radiologic features	Necrotizing enterocolitis
Intramural gas	Congenital methemoglobinemia
Air-fluid levels	Intoxication
	Metabolic disorders, that is, hypoglycemia, MCAD deficit, biotinidase deficit or anomalies of urea cycle

Note: Reproduced from Barasche J, Stollar F, Bergmann MM, Caubet JC. Severely altered-consciousness status and profuse vomiting in infants: Food Protein-Induced Enterocolitis Syndrome (FPIES) a challenging diagnosis. *Pediatr Emerg Care*. Epub 2016 Oct 6.[76] http://journals.lww.com/pec-online/pages/default.aspx. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact healthpermissions@wolterskluwer.com for further information.
Abbreviations: FPIES, food protein-induced enterocolitis syndrome; MCAD, medium-chain-Acyl-CoA-dehydrogenase.

although specific blood tests are not necessary for FPIES diagnosis, they might be needed to eliminate sepsis, a metabolic disorder or a congenital methemoglobinemia for example.

Regarding the chronic form of FPIES, congenital mucosa abnormalities or necrotizing enteropathy could present with similar symptoms, and need to be ruled out in neonates and especially in preterm children. The chronic form of FPIES is clinically close to other food allergies such as celiac disease, FP or FPIAP.[10] FPIAP appears often in exclusively breastfed and well-being infants in the first month of life, with isolated bloody stools. In this case, anemia can be the characteristic laboratory finding. FPE is characterized by inflammation localized in the small bowel causing malabsorption, leading to diarrhea, intermittent emesis and/or FTT. In most cases, FPIAP and FPE occur after ingestion of CM or soy formula.[62] Moreover, primary eosinophilic GI disorders (EGIDs) may present with a phenotypic overlap. In addition, histological findings in EGIDs are also characterized by eosinophilic and mast cell infiltration. Thus, distinction between these disorders might be difficult in clinical practice, and from a physiopathological point of view, it is not clear if they are distinct disorders and if they are part of continuum.

Natural history

FPIES appears most frequently in the first months of life but can manifest at any age.[2,42] FPIES to CM or soy begins in early infancy from several days to 4 weeks after the introduction of infant formula. In an Israeli population-based birth cohort the median onset of CM-induced FPIES onset was 30 days and all patients presented before 6 months.[20] In breastfed infants the delay of onset seems to be longer. FPIES to solid-food usually begins in older infants because of later introduction into the diet, in general after 4 months of age.[2,14]

FPIES resolves at different ages according to the food involved and the population.[6] Thus, in an American study CM-FPIES resolved in 20% of cases by 3 years of age, while a Korean cohort showed >60% resolution by 10 months of age, and an Israeli birth cohort showed 90% resolution by the age of 30 months.[2,7,8] Similar rates were found for soy FPIES in the American cohort with 20% of resolution by

3 years of age, and again 90% of the Korean children showing resolution by 10 months of age.[8] Those differences are probably explained by inclusion of different phenotype in the different studies, that is, more severe cases in American studies based on tertiary center. The natural history of FPIES to solid foods is less known and data are sparse. It has been found that 65.5% of children reactive to grains resolved their FPIES by 5 years of age, whereas those children who reacted to meat and fish/shellfish took more time: 50% and 0% at 5 years of age, respectively.[2] FPIES to seafood seems to last longer than for other solids.[12,50,63] Of note, it has been suggested that patients with atypical FPIES (i.e., with positive food-specific IgE to the incriminated food) appear to have a more protracted course.[2,12]

Management

The management of FPIES is still controversial in many aspects and mostly empiric, but the international guidelines are due out soon (Nowak-Wegrzyn et al, JACI, in press). In general, management of these patients has to include acute phase treatment as well as maintenance therapy in order to avoid recurrence of acute relapse, but also prevention of nutritional deficiencies.[3,12,29]

Acute management
Supportive therapy
Fluid repletion is the first line and the cornerstone of management. As acute FPIES mostly occurs at home, acute management starts there via oral hydration. Medical management is essential either in an outpatient clinic or in hospital to discuss intravenous volume repletion with normal saline bolus (20 mL/kg, that should be repeated if needed). Amines supportive therapy will be rarely needed, as the evolution is in most case quickly favorable after rehydration. Of note, although the use of epinephrine may be indicated to treat hypotension, it has no effect on preventing emesis.[10,42]

Steroids therapy
As local inflammation is suggested to be part of the pathophysiology of FPIES, a single dose of intravenous (IV) methylprednisone Solumedrol® (1–2 mg/kg up to 60–80 mg) in case of severe reactions may be considered.[10] It can also play a role in the volume supportive therapy. But the utility of corticosteroids in FPIES has not been clearly demonstrated.

Ondansetron
Based on small case series reporting effectiveness of ondansetron injection during acute FPIES, its administration may be considered.[64–66] Ondansetron, a 5-HT$_3$ receptor antagonist has antiserotoninergic effect, that may play a role in gut secretion and motility via the afferent nerves.[62,65,66] Ondansetron seems not only to reduce or prohibit nausea and vomiting, but also the development of diarrhea.[62,65,66] The recommended dose ranges from 0.1 to 0.15 mg/kg administered IV or intramuscular (maximum single dose 16 mg) and is generally well tolerated. Sublingual administration can also be discussed. Nevertheless, contraindications (i.e., prolonged QT-interval and arrhythmia) exist[10] and further large prospective and multicentric studies confirming its efficacy and safety are needed.

Maintenance therapy
After review of the acute episode, an emergency treatment letter including teaching of clinical features and management of acute FPIES episode should be provided to the parents/patient and can be shown in case of emergency to the physician. Indeed, formal education of the parents and, if appropriate, the child or adolescent is very important in order to avoid misdiagnosis of future episodes.

Maintenance therapy should include discussion of the following key points:

Elimination of the offending food protein
The diet until reintroduction under medical supervision is the rule. Avoidance of products with precautionary labeling (e.g., "can contain traces of", "run the same line") is usually not necessary.[67] The success of the avoidance diet will also depend on whether they have seen a dietitian with experience in dealing with FPIES or not, as well as commercial availability of food, parental resources, cooking skills in the family, the number of allergens to avoid and/or the period of avoidance required.[3] Indeed, these infants/children may benefit from nutritional evaluation and guidance, but also from laboratory assessment of iron, calcium, and vitamin D status. Supplementation may be then indicated and prescribed to these patients. Future studies should systematically evaluate the prevalence of feeding difficulties, poor weight gain, and growth and nutrient deficiencies for preventive intervention in this at-risk population. Of note, growth monitoring of those patients is particularly important.

Breastfeeding
The majority of infants with FPIES tolerate the incriminated allergen through breastfeeding without the need for a maternal eviction diet.[20,68] Therefore, breastfeeding should be encouraged and routine avoidance of allergenic food is not recommended in breastfeeding mothers.[3] Regarding patients

with persistent symptoms, particularly FTT, empiric eviction of allergens by the mother might be indicated.[69] The ideal length of the eviction trial is not known, probably several days up to 4 weeks appear sufficient.[70]

The choice of formula

The recommendations about formula in young infants with FPIES to CM who cannot be breastfed vary. While the guidelines from the World Allergy Organization recommend the use of an extensively hydrolyzed formula (EHF), the European society of pediatric gastroenterology, hepatology, and nutrition advise amino acid-based formula (AAF) for infants with FPIES, especially those with FTT, as AAF may confer advantages for catch up growth.[3,70,71] Of note, it has been shown that ~10%–20% of FPIES patients will require an AAF.[2,20] A reasonable approach would be to initiate treatment with EHF, and in those patients who do not display satisfactory symptom relief or catch up growth within 2 weeks, it would be necessary to switch to AAF.[2,20] For patients with severe FPIES an AAF might be the optimal initial choice. As the palatability of the EHF formula is different, infants and children may decrease their daily volume of intakes and can be at risk for deficiency of calcium and other minerals and vitamins. This requires follow-up and supplementation in case of deficiency.[72]

Heated or baked food proteins

Current recommendations suggest avoiding all forms of the offending allergen, including baked and processed food. Indeed, there is only one report suggesting tolerance of small amount of the cooked offending food.[72] But the introduction of baked foods under medical observation might be discussed if the family is interested, particularly baked egg or milk in patients with FPIES to egg or milk, respectively.

Timing and setting of reintroduction of the offending food

The actual recommendation based on US and Western Europe approach is an OFC 12–18 months after the last reaction. However, as previously discussed, the natural history of FPIES varies according the food incriminated, the population studied and probably the severity of the initial reaction. Thus, the decision to attempt reintroduction in order to assess tolerance acquisition should take all these factors into account. Shorter intervals might be adequate for patients with milder forms and those reacting to CM or soy, while longer intervals may be needed for patients with more severe form and those reacting to solids. However, further well-designed

studies are needed to determine the optimal timing of OFC to assess tolerance acquisition.

General nutritional recommendations for infants and children with different types of FPIES are described in the following sections.[73]

In infants with CM FPIES

Avoidance of soy formula is usually recommended during the first months of life because of possible co-allergies with varying frequency in different countries.[2,10,14,74] A reasonable approach would be to propose an OFC after 6 months to assess tolerance of soymilk formula in those patients. In patients with CM FPIES, the risk to develop FPIES to solids exists, and it is usually recommend to start between 6 and 12 months of age with yellow fruits or vegetables unlikely to cause FPIES, followed by meats and cereal grains.[10] As there is a risk of successive FPIES on solid food, the introduction of solids known to cause solid FPIES such as grains, rice, and fish should be initiated with caution. It can be performed in a medical facility (particularly for severe CM FPIES) or at home at the discretion of the treating physician and with the supervision of a dietician who can support the whole weaning process and avoid unnecessary restriction. We recommend the introduction of one food per week. Introduction of any other animal milk, especially goat or sheep milk, is not recommended due to a higher risk of cross reactivity proteins.[30,77]

Infants with soy FPIES

Like infants with CM FPIES, infants with soy FPIES are at risk to react to CM formula as well as to solid foods, known to cause FPIES. Therefore, the recommendations are similar to those for infants with CM FPIES.

Solid FPIES

Infants/children with grains FPIES: Children with FPIES to rice, oat, barley or wheat are at risk to present symptoms after the ingestion of other grains.[2,20] Because of their vulnerability, these patients might benefit from delayed introduction of grains beyond the first year of life. Introduction should be conducted under medical observation. CM and soy, if not already part of the child's diet, should be introduced after 6 months of age and under medical observation as co-allergies have been reported. The ingestion of all food already introduced and not responsive of the symptoms should be continued.

Infants/children with fish and/or shellfish FPIES: FPIES to fish follows the same guidelines than others solid food

FPIES but with some specificities. It is a common solid-food FPIES in Italy and Spain.[52] Similarly to IgE-mediated fish or shellfish allergy, as there are potential co-reactions with other fishes or shellfish, respectively, an OFC should be performed to assess tolerance. Of note, there is little data on resolution of FPIES to fish and seafood in older children and adults, and reintroduction should be considered in these patients, with a longer delay than for patients with FPIES to CM or soy.

Conclusion

FPIES is a non-IgE-GI-FA with heterogeneous features and is not a rarity in infants and children. It can potentially present with severe reactions requiring cautious management in short and long term. Diagnosis relies on medical history and typical symptoms like vomiting, pallor, lethargy, and diarrhea resolving after the elimination of the offending food from the infant's/child's diet and might relapse after OFC. The natural history is usually good in the vast majority of the case, supporting the reevaluation by OFC every 12–18 months. But the possible switch to IgE-FA seems to predispose to a more prolonged phenotype.

Avoiding the offending food requires education of the family for the exposed patient. Because of the possible prolonged evolution before and after diagnosis, a multidisciplinary approach is required between allergists, gastroenterologists and dieticians, specialized nurses, and caregivers. Although some new recommendations have emerged those past years, new international guidelines are currently needed to improve the management of those patients.[73]

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Disclosure

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