

What is New in the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome?

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Abstract

Purpose of Review Many aspects of food protein-induced enterocolitis syndrome (FPIES) remain poorly studied, such as its pathophysiology, dietary management, biomarkers for diagnosis and onset of tolerance. Research in the last decade has steadily advanced our knowledge of the condition. We review the recent literature in relation to the diagnosis and management of FPIES.

Recent Findings FPIES is predominantly a paediatric non-IgE-mediated gastrointestinal food allergic disorder. Infants typically present with delayed profuse vomiting, pallor and floppiness 2–4 h after ingesting a newly introduced food. Some cases can be severe, with associated impaired consciousness, hypotension and/or hypothermia. Common triggers include cow's milk, soy, rice and egg. The prognosis of the condition is generally excellent, with most outgrowing the condition by early childhood. Recent studies elucidate epidemiological variations, which have aided the development of upcoming international consensus guidelines on the diagnosis and management of FPIES.

Summary Much remains to be understood about FPIES. Current and upcoming research along with efforts to form consensus-based guidelines will help clinicians in diagnosing acute FPIES from other more common paediatric conditions.

Keywords FPIES · Investigation · Management · Diagnosis

Introduction

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food allergic disorder that typically presents in infancy and outgrown by the majority in early childhood. It is less common than IgE-mediated allergy, with an estimated incidence in Australia of 1 in 10,000 infants <2 years of age [1]. Acute and chronic FPIES are described. Acute FPIES often presents by 4–6 months of age, representing the typical age of formula or solid food introduction. Infants usually present 2–4 h after ingesting a newly introduced food protein with profuse vomiting, pallor and floppiness (reviewed in [2, 3]). Diarrhoea, uncommonly bloody, may be seen within 24 h of trigger ingestion. In more severe cases, hypotension and/or hypothermia can occur. So severe can acute presentations be that some infants undergo septic evaluations by abdominal imaging, electrocardiograms, electroencephalograms and abdominal surgery, since many of the clinical and laboratory features of FPIES mimic septic shock, gastroenteritis and an acute surgical abdomen [4, 5, 6]. Common food triggers of acute FPIES include cow's milk, soy, grains such as rice and oats, and egg, although triggers from all food groups have been reported [4, 5, 7, 8, 9, 10]. Although the most commonly reported food triggers can vary between countries, grains, cow's milk and soy represent the most common triggers of FPIES in almost all studies from the USA, Australia and UK [4, 5, 7, 8, 9, 10]. Acute FPIES is more probably common than chronic FPIES, although there is no universally accepted definition of the chronic form. FPIES was

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originally described in the chronic form in the 1960–1970s [11–13]. This phenotype is now rarely reported in Western literature, but is still described in Japanese cohorts [14, 15] and has been noted in one Taiwanese child [16]. Infants with chronic FPIES tend to present in the first 2 months of life with daily symptoms of vomiting and/or diarrhoea (often bloody) [11–16]. Complications may include failure to thrive and hypoalbuminaemia [13]. This presentation has significant overlap with protein enteropathy and is likely to be diagnosed as such, rather than as chronic FPIES. Continuous exposure to cow's milk or soy formula is the only reported triggers of chronic FPIES [11–16]. Acute on chronic FPIES has been reported, such that avoidance and subsequent ingestion of cow's milk/soy protein then results in the acute FPIES phenotype [13].

Until recently, little research has been conducted on FPIES. An effort to consolidate our collective knowledge of FPIES has improved over the last few years, with current research providing new information about all aspects of the disease, including the diagnosis, pathophysiology and management of the condition. We review recent literature on acute FPIES, with the aim of guiding clinicians on how to distinguish acute FPIES from other more common paediatric conditions and to manage the condition in the short and long term.

Diagnosis

FPIES diagnosis is made clinically. The majority of infants have a history of at least two to three reactions before a diagnosis is made [4, 7], with some experiencing at least six reactions before a diagnosis of FPIES is considered [5, 9]. These delays in diagnosis are due to multiple factors. FPIES is an uncommon entity, not well recognised by physicians and the general community (reviewed in [17]). FPIES can initially be mistaken for other conditions such as sepsis and gastroenteritis, given infants do not present with cutaneous or respiratory features, which are more recognisable as signs of an allergic reaction. The onset of reaction is typically 1–4 h following ingestion, and hence a causal link may not be immediately appreciated. Finally, common food triggers such as rice or oats may be initially perceived by parents and physicians as “low allergenic” and incapable of causing an allergic reaction.

There have been multiple attempts at introducing diagnostic criteria for acute FPIES based on the case series; however to date, no universally accepted definition exists. In early 2015, an international consensus guidelines for the diagnosis and management of FPIES was initiated by a work group assembled by the American Academy of Allergy, Asthma and Immunology [18]. This is a global and multidisciplinary effort, with input from allergists,

gastroenterologists, emergency medicine and intensive care physicians, social workers and community interest groups. These guidelines are yet to be published, but are the first steps in establishing an accepted case definition. An agreed definition of FPIES will help researchers in the area, but may be of less practical use to busy emergency physicians, who are often the first point of contact of those presenting with acute FPIES.

Certain clinical features can aid the busy physician in the diagnosis of acute FPIES. Acute FPIES needs to be considered in any infant presenting with repeated distinct episodes of profuse vomiting, particularly if associated with pallor/floppiness, where the infant remains well in between reactions/episodes and the episodes occur within a few hours (1–4 h) of a newly or recently introduced food(s).

The difficulty facing physicians is that many infants present with profuse vomiting, pallor and lethargy, and such presentations may be caused by a multitude of different pathologies. However, some of the distinguishing clinical features of an acute FPIES reaction include:

- a) The vomiting, pallor and floppiness are transient and usually infants completely self-recover in the emergency department within a few hours of their initial presentation with either no treatment or oral/intravenous rehydration. Diarrhoea may not occur for hours and may last a few days following the acute episode [2]. This rapid and complete rate of recovery is unexpected in sepsis, gastroenteritis or the surgical abdomen and serves as one of the best clinical signs of FPIES.
- b) Fever is uncommon in FPIES, having only been reported in Japanese cohorts [14, 15] to cow's milk/soy. Most cases of acute FPIES present with a normal body temperature, or in more severe cases hypothermia [4].
- c) Rice and oats are a common trigger of FPIES, and if profuse vomiting follows 2–4 h after the initial introduction of these grains, FPIES must always be considered [10].

It is unusual for a child to have FPIES to a food they have tolerated regularly for weeks with most children reacting after the first or second known ingestion [1].

Laboratory Investigations as Aids to FPIES Diagnosis

There is currently no laboratory test that confirms the diagnosis of FPIES. There is an unmet need for a study to identify potential biomarkers of an acute FPIES reaction and markers to assist in tolerance prediction. There are, however, some laboratory investigations that would be

helpful when used in conjunction with the clinical history to support a diagnosis of FPIES.

Full Blood Count

Following an acute FPIES reaction, neutrophilia may be observed in up to 50 % of cases and thrombocytosis in almost two-thirds of emergency department presentations [4•]. There is no alteration in any other cell type on the full blood count reported. The reasons for the increase in neutrophil and platelet counts remain unclear, but are possibly related to elevations in interleukin-6, interleukin-8 and tumour necrosis factor- α , all of which have been implicated in reactive neutrophilia [19] and thrombocytosis [20]. Elevations of these cytokines have been documented in some cases of acute FPIES (reviewed in [21•]). The presence of neutrophilia is another feature FPIES shares with sepsis; hence, its occurrence should not warrant exclusion of the diagnosis of FPIES. How rapidly the neutrophilia resolves or the differences in the magnitude of rise in FPIES compared to sepsis are yet to be investigated.

C-Reactive Protein

Recently, Kimura et al. [14] reported elevations in C-reactive protein (CRP) in a series of 18 infants with cow's milk FPIES undergoing an oral food challenge (OFC). The elevations in CRP occurred in 11 infants, but the overall rise in CRP was marginal (from <0.1 mg/dL at baseline to 0.22–4.84 mg/dL in positive cases) and was more apparent in those who developed fever at OFC.

Serum Electrolytes and Blood Gasses

Despite the presence of protracted vomiting during acute FPIES, there have been no published reports that serum electrolytes are impaired. Hyponatraemia has been reported in those with chronic FPIES [12, 13]. Electrolyte abnormalities are probably more likely in chronic FPIES, where intestinal inflammation is persistent and thus diarrhoea more chronic. Metabolic acidosis and in severe cases transient methemoglobinaemia have been reported in cases of acute FPIES [22].

Stool Analysis

Stool analysis is generally not indicated in those with FPIES, unless performed to exclude other conditions, such as infective gastroenteritis. In acute FPIES, blood and leucocytes can be isolated from stool samples (reviewed in [23]). Recently, Wada et al. [24] studied changes in faecal samples in infants during the acute phase of an FPIES reaction. They observed elevated eosinophil-derived

neurotoxin in stool samples in a small cohort of patients 1–2 days after a challenge-induced acute FPIES reaction. A modest increase in faecal calprotectin was also noted. Further studies are required to determine the accuracy of serial faecal sampling for eosinophil-derived neurotoxin as a potential diagnostic biomarker for FPIES.

Serum-Specific IgE Levels or Skin Prick Test to the Triggering Food

FPIES is a non-IgE-mediated disorder and hence one would assume there would be little value in performing serum-specific IgE (ssIgE) or skin prick testing (SPT). However, there are roles for performing such IgE-based tests in those with non-IgE-mediated FPIES, particularly in cases of cow's milk FPIES. ssIgE/SPT testing in FPIES is useful in the following situations.

To provide prognostic information. Sicherer et al. [25] initially reported longer than expected delays in tolerance in a small cohort of FPIES children sensitised to the food trigger. More recently, Caubet et al. [26•] found that the presence of detectable cow's milk IgE was a risk factor for the persistence of cow's milk FPIES beyond 3 years of age. Sensitisation in these cases was usually of low level and more likely to be detected by ssIgE testing than an SPT. It remains unclear whether sensitisation to other common FPIES food triggers, such as rice (where sensitisation rarely occurs) and egg (where sensitisation is more likely [27]), are also risk factors for delayed tolerance.

To ensure that IgE-mediated transformation to cow's milk has not occurred. Transformation of cow's milk FPIES from a delayed non-IgE mediated reaction to an IgE-mediated reaction was noted in 7 out of 17 subjects (44 %) in the study of Caubet et al. [26•] and in 8 out of the 44 children (18 %) in the study of Katz et al. [28•]. To date, there have been no reports of the IgE-mediated transformation of other food triggers. The fact that this can occur is important, as it means any child undergoing an FPIES challenge to cow's milk should have an ssIgE/SPT before the challenge is commenced, since much larger volumes are initially administered during an FPIES OFC.

Determine the presence of co-existent IgE-mediated allergies. Approximately, 10 % of children with FPIES have a concomitant IgE-mediated allergy to another food [4•]. We do not recommend screening all children with FPIES with ssIgE/SPT to common food allergens (e.g. cow's milk, soy, egg, nuts, seafood, wheat) that are yet to be introduced. However, clinicians should perform an ssIgE/SPT in FPIES cases who have had a concomitant IgE-mediated reaction to another food, or some clinicians may choose to perform ssIgE/SPT tests to common allergenic foods (e.g. peanut, egg, cow's milk) not yet introduced in infants with concomitant severe eczema.

Patch Testing to the Triggering Food

Only two studies have examined the utility of patch testing in ascertaining tolerance at OFC. Fogg et al. [29] reported a negative patch test to the food trigger to have a negative predictive value of 100 % at OFC. However, Jarvinen et al. [30] found the patch test to be poorly predictive of tolerance at OFC, with a negative predictive value of only 55 %. Given the lack of standardisation of patch testing, with different methods and allergen concentrations used, combined with current conflicting results, patch testing is not recommended to predict the likelihood of tolerance. Further research is required to assess the accuracy of peripheral blood mononuclear cell stimulation by food antigens (the laboratory “equivalent” of patch testing) to predict the challenge outcomes [31, 32].

Endoscopy

Endoscopic evaluation in infants and children with acute FPIES is not required or helpful for making a clinical diagnosis. Biopsies in patients with chronic FPIES have advanced what little understanding we have in the immune mechanism and pathophysiology of FPIES. A recent review by Berin [21•] summarised reports of intestinal biopsy and immunohistochemistry. Findings included elevations in CD4+ T lymphocytes, eosinophils, IgA and IgM producing plasma cells and tumour necrosis factor- α . In addition, there is evidence of changes in the cytoarchitecture of the gastrointestinal epithelium, with lowered expression of transforming growth factor- β 1 and villous blunting [33]. Ishige et al. [34] also recently described the presence of mast cells in the rectum in an 8-week-old Japanese infant girl presenting with chronic cow’s milk FPIES.

The Oral Food Challenge

OFC remains the gold standard for the diagnosis of FPIES. A diagnostic OFC may not be required when infants present with a convincing history, especially if they have had two or more reactions to the food or reactions to at least two different foods.

A diagnostic OFC is suggested if the food trigger remains unclear or the reaction was unusual (e.g. reaction occurred >12 h after exposure, persistence of profuse vomiting for >24 h, fever at the time of presentation, other members of the family were unwell with gastroenteritis at the same time). It is recommended that all diagnostic OFC be performed under medical observation given it is not possible to predict a reaction, nor its severity. In one cohort, 96 % of positive FPIES challenges required intravenous fluid resuscitation [26•].

Some centres perform an OFC to another food that carries a higher risk of cross-reaction, but is yet to be introduced into the child’s diet. Although most children

react on initial exposure to a newly introduced food, a limitation with this practice is that children can react on subsequent exposures [4•]. Nevertheless, it is uncommon to react after the infant has tolerated the food three or more times [4•]. At our institution, those with rice FPIES are challenged to oats under medical observation (~20 % of rice FPIES appear to react also to oats [35]), and those with cow’s milk FPIES are challenged to soy under observation (since 20–45 % of cow’s milk FPIES react to soy [5, 10•, 25, 26•]). Little remains known about fish FPIES, and recently Sopo et al. [7] reported on 70 cases of fish FPIES and found that most had FPIES to a single species. However in 60 % of these individuals with single fish FPIES, no other fish had actually been trialled. Of the 15 individuals that tolerated another fish, four had tolerated tinned tuna, three of whom had reacted to sole tolerated cod, and five who reacted to cod tolerated sole. Only 4 out of the 70 individuals with fish FPIES had eaten shellfish and none had reacted. Until further evidence is available, we suggest anyone with a fish FPIES have another fish introduced under medical observation. Tinned fish and cod for those with sole FPIES and vice versa may be a safe initial alternative, although common cross-reactive species are likely to vary depending on the region and the predominant fish allergen. Until further data are available, it would be safer to introduce shellfish under observation in those individuals with fish FPIES.

One of the main roles of OFC in FPIES is to ascertain tolerance, which will be discussed in the management of FPIES. Various protocols used for FPIES OFC exist [23]. Double-blind placebo control challenges for FPIES are unnecessary, given a positive challenge outcome is based on objective clinical symptoms. Many experts recommend securing an intravenous line (IV) prior to the challenge, or at minimum IV access readily available. Intravenous fluid resuscitation with 20 mL/kg of normal saline remains the first line of treatment. No randomised controlled trials have been performed with any therapy used to manage FPIES reactions, including intravenous/oral fluids, ondansetron or corticosteroids. Recently, the use of ondansetron to manage acute reactions has been investigated in two small non-controlled studies [36, 37]. Ondansetron use appeared to shorten the duration of vomiting without any adverse reactions. Randomised control trial evidence is currently required to be able to guide the best practice for the management of acute FPIES.

Management

The Initial FPIES Reaction

Management of acute FPIES in the emergency department revolves around fluid resuscitation, either oral or in more

severe cases intravenous fluid administration. If the diagnosis of FPIES is certain (e.g. the child is known to have FPIES and accidentally ingested the same food, or another newly introduced food has caused a similar reaction), treatments to consider include IV fluids, ondansetron and in severe cases corticosteroids [2]. Once a diagnosis is suspected, referral to a paediatrician or allergist is recommended for discussion of dietary modification, action plans, and the performance of OFC to ascertain tolerance at a future time. Provision of adrenaline auto-injectors for individual FPIES alone is not warranted, as adrenaline does not play a role in the acute management of non-IgE-mediated food allergy.

Dietary Modification

Allergen Avoidance

Definitive management of FPIES generally involves the strict dietary elimination of the causative trigger food. However, Sopo et al. [38] reported seven cases of FPIES (four to cow's milk, two to egg and one to soy), where four children tolerated the baked form of the allergen (three with cow's milk and one with egg). The same group reported four cases of fish FPIES tolerating tinned tuna [7]. These cases suggest that even in non-IgE-mediated food allergy, tolerance to a heat modified protein allergen is possible. The risk/benefit of this strategy in the management of FPIES is currently unclear.

Parents of infants with FPIES, having witnessed their child become limp/floppy with profuse vomiting, are likely to be anxious to introduce new foods [17]. This is compounded by the lack of tests to determine whether other foods are likely to trigger a similar reaction. Greenhawt et al. [39] recently assessed health-related quality of life of caregivers of FPIES patients. Compared to paediatric patients with IgE-mediated food allergy, parents of patients with FPIES often reported lower quality of life scores. Thus, it is important to communicate to parents that most infants with FPIES react to a single trigger [40]. Additional reassurance should be provided by discussing the lack of fatalities, the need to ingest a large dose in most cases [26] and the excellent long-term outcome in the majority of children with most children outgrowing the condition by 3–4 years of age [4, 10].

Breastfeeding

Avoidance of the food trigger in the maternal diet is generally not required, since only rarely have FPIES reactions been reported to occur due to food allergens in breast milk [41, 42]. Presumably, FPIES triggered by breast milk is

uncommon as the amount of allergen in human milk is insufficient to cause an FPIES reaction in most infants.

Formula Feeding

Infants who present with cow's milk FPIES and require a formula are usually recommended an extensively hydrolysed formula instead of soy formulas, due to the higher risk of concomitant cow's milk and soy FPIES (reviewed in [23]). Soy-based formulas can still be chosen, but in these circumstances a soy OFC is suggested. Amino acid formulas are generally recommended in those who react to extensively hydrolysed formulas.

Introduction of New Foods

Advice on new food introduction following an initial FPIES reaction is based on expert opinion. Some experts suggest introduction of yellow fruits/vegetables at 6 months instead of grains in those presenting with any FPIES reaction [23]. Other advice includes avoiding grains, legumes and chicken in the first year of life, and cow's milk/soy to be introduced after 12 months in those presenting with FPIES [23]. However, no randomised control trials have been performed to determine whether such dietary manipulation is necessary. Such empiric advice is often based on US cohorts, where children present with multiple food FPIES reactions to specialised allergy centres [5, 10, 25], and thus are likely to represent a referral bias of more complex cases. Based on the data currently available, dietary advice for FPIES at our institution includes the following:

- Cow's milk FPIES: can have soy formula under 12 months via an OFC.
- Rice FPIES: can have wheat and corn introduced at home, whilst oats should be introduced under medical observation.
- Fish FPIES: other fish/shellfish could be introduced via an OFC.
- Chicken FPIES: avoid all poultry.
- Dietary restriction of other foods is unnecessary unless the child presents with reactions to two or more different foods. In these cases, discussion with an allergist is required to determine whether other foods, not yet introduced, should be delayed in the infant's diet.

Action Plans

Child-care workers, teachers and other carers may need to look after infants and children with FPIES. Given the

Fig. 1 Action plan for FPIES for preschools/schools/carers



Name: _____

Date of birth: _____

Confirmed triggers: _____

Family/emergency contact name(s): _____

Work Ph: _____

Home Ph: _____

Mobile Ph: _____

Plan prepared by: _____

Dr: _____

Signed: _____

Date: _____

ACTION PLAN FOR FPIES (FOOD PROTEIN INDUCED ENTEROCOLITIS SYNDROME)

FPIES is a delayed gut allergic reaction, which presents with repetitive, profuse vomiting that may not start for a few hours after a triggering food(s) is eaten. Some individuals with FPIES may develop diarrhoea, lethargy, become pale, floppy and/or feel cold.

Adrenaline autoinjectors and antihistamines do not play a role in the management of FPIES

MILD TO MODERATE SYMPTOMS

- Vomiting
- Diarrhoea

ACTION FOR MILD TO MODERATE SYMPTOMS

- Notify parent/guardians
- Observe for progression

SEVERE SYMPTOMS - Any one of the following in addition to vomiting

- Pale and floppy
- Cold to touch

ACTION FOR SEVERE SYMPTOMS

- 1 Phone ambulance: 000 (AU) or 111 (NZ)**
- 2 Phone family/emergency contact**

Some individuals with FPIES may also have a food allergy and be at risk of anaphylaxis to other foods. They will have a separate ASCIA Action Plan for Anaphylaxis for this food allergy.

Additional instructions: _____

© ASCIA 2015. This plan was developed as a medical document that can only be completed and signed by the patient's treating medical doctor and cannot be altered without their permission.

lack of community awareness of the condition, carers may be unsure of how to manage children with FPIES. Action plans for IgE-mediated food allergy exist, but these plans are inappropriate for those with FPIES. Unlike IgE-mediated food allergy where cutaneous exposure may result in contact hives/angioedema, or inhalation of the food (e.g. fish fumes [43]) can result in a reaction, in FPIES cutaneous/airborne allergen exposure has not been reported to cause a reaction. Ingestion of the allergen appears to be the only means of inducing an FPIES reaction.

The Australasian Society of Clinical Allergy and Immunology (ASCIA) recently devised two documents to be completed by the treating doctor and given to parents. One is an action plan aimed at carers (e.g. parents, child-care workers, teachers) (Fig. 1; this can be downloaded for free at http://www.allergy.org.au/images/pcc/ASCIA_Action_Plan_FPIES_2015.pdf). The other is a letter to be provided by the parent to a physician/nurse in case the child has an accidental reaction and requires emergency care (Fig. 2; a template of this letter is currently only available to ASCIA members).

Fig. 2 Explanatory FPIES letter that can be presented by parents at times of an acute reaction to an emergency physician/nurse

Dear Doctor,

Diagnosis

The patient named on the attached ASCIA Action Plan has a food allergy called Food Protein Induced Enterocolitis Syndrome (FPIES). This information is being provided so that FPIES is considered in the differential diagnosis for this patient in the event of symptoms, principally if the individual has eaten one of the foods he/she is allergic to.

What is FPIES?

FPIES is a delayed gut allergic reaction, which presents with repetitive, profuse vomiting that may not start for a few hours after a triggering food is eaten. It is most common in young children although occasionally adults may be affected. The most common foods in children are cow's milk, soy and rice. Some may develop diarrhoea, lethargy, and become pale, floppy and develop hypothermia. FPIES does *not* cause typical IgE mediated allergic symptoms such as urticaria, angioedema or bronchospasm. Usually the individual recovers within a few hours of the reaction. No death from FPIES has been reported. Further information about FPIES, including a Dietary Guide, is available on the ASCIA website: www.allergy.org.au/patients/food-other-adverse-reactions

Investigations

The WCC and platelet counts may be raised following an FPIES reaction.

Treatment

The treatment for FPIES is symptomatic and includes:

- Hydration (oral or IV depending on severity)
- Ondanestron (wafer, intramuscular or intravenous)

NOTE: Adrenaline autoinjectors and antihistamines do not play a role in the management of FPIES.

Differential diagnosis

This advice does not preclude the possibility of other illnesses (e.g. infection, toxin ingestion) that may manifest in a similar way. Thus the treating physician is encouraged to pursue any other treatments deemed necessary.

Yours sincerely,

Follow-Up OFC to Ascertain Tolerance

The main role of OFC in FPIES is to ascertain tolerance, given in most cases diagnosis is apparent on clinical history, and thus a diagnostic OFC is often unnecessary. OFCs to ascertain tolerance should be conducted under medical observation. One of the recent changes to practice has been the earlier age at which OFCs are conducted to ascertain tolerance. The standard practice had been to perform an OFC to the triggering food at 3–4 years of age. However some centres now suggest challenges to be performed 12 months following the infant's last reaction, and hence more infants are being challenged at 18–24 months of age [5]. Still, little is known about the rates of tolerance and factors that influence its acquisition, particularly to solid foods. Although cow's milk tolerance is the best described, there is significant variation in rates of tolerance to cow's milk among studies. Some report high rates of tolerance. Hwang et al. [44•] found 100 % of children tolerated cow's milk by 20 months of age, while Katz et al. [28•] reported 94 % cases by 30 months of age. In contrast, most US

studies report a much lower rate of cow's milk tolerance (16–60 % by 3 years of age [5, 25]). Some of this discrepancy may be related to the higher proportion of US cases with IgE sensitisation to cow's milk, which appears to delay tolerance acquisition. However, IgE-mediated sensitisation to rice is rare, and marked discrepancy in the rates of tolerance still occurs between studies, suggesting that other factors modify tolerance acquisition. Recently, our group examined the rates of tolerance in those with FPIES to rice, cow's milk, egg and fish, and found that those with rice and cow's milk had a much higher rate of tolerance at a younger age than those with egg and fish FPIES [45•]. Poor prognosis of fish FPIES in terms of time to tolerance has been reported by others [7, 8]. Although only prospective studies performing challenges at regular intervals will be better able to reveal the natural history of FPIES, based on current available data we suggest that challenges to egg and fish FPIES be delayed until the child is 5 years of age or older, whilst those with rice and cow's milk FPIES may be challenged by at least 18–24 months of age.

Conclusions

Much remains to be studied about FPIES. The persisting lack of understanding of the immunopathophysiology is reflected in the current way we diagnose and manage the disease. However, over the last few years, FPIES has become an area of interest to a number of research groups. Most promisingly, the collective effort to produce international consensus guidelines for diagnosis and management of FPIES will provide the opportunity for studies to be conducted with more consistent methods. This will establish what we currently need for FPIES research, a strong foundation of evidence-based knowledge to better comprehend the disease and implement this in clinical practice to benefit patients.

Compliance with Ethics Guidelines

Disclosure The authors certify that there are no affiliations with any organisation with financial or personal interests in the subject matter discussed within this manuscript.

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