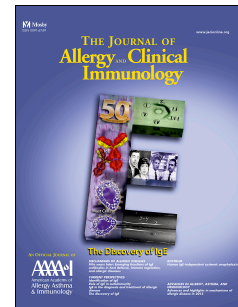


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International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome

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Workgroup Report of the Adverse Reactions to Foods Committee, American Academy
of Allergy, Asthma, and Immunology

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Introduction

Food protein-induced enterocolitis (FPIES) is a non-IgE, cell-mediated food allergic disorder that can be severe and lead to shock.¹ In spite of the potential seriousness of reactions, awareness of FPIES is low, high-quality studies providing insight into the pathophysiology, diagnosis, and management are lacking, and clinical outcomes are poorly established. Unmet needs in the field include identification of the non-invasive biomarkers, clear understanding of the disease mechanisms, data regarding prevalence, and having uniform approaches to diagnosis and management. This document is the first international consensus based on the available evidence and aims to assist practitioners in their care for the patients with FPIES.

Methods

An international workgroup was convened through the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the International FPIES Association advocacy group. The work group included allergists, gastroenterologists, a general pediatrician, a pediatric intensive medicine physician, a pediatric emergency medicine physician, nurses, dietitians, and representatives from lay patient organizations from the USA, UK, Australia, Italy, Switzerland, Japan, Korea, and Greece to provide broad stakeholder input. The workgroup members held face-to-face meetings on March 2, 2014 in San Diego, California, USA, and on February 20, 2015 in Houston, Texas, USA as well as multiple periodic conference calls.

A comprehensive literature review was performed with the assistance of a research librarian, with searches run in PubMed/Medline, Web of Science, and Embase using combinations/permutations of the following terms: vomiting, protracted vomiting, diarrhea, bloody diarrhea, lethargy, hypovolemic shock, shock, food hypersensitivity, food allergy, prevention, diagnosis, enterocolitis, enteritis, proctitis, proctocolitis, gastrointestinal hypersensitivity, allergic gastroenteritis, allergic colitis, allergic proctocolitis, protein enteropathy, protein enterocolitis, immune mediated enteropathy, immune mediated hypersensitivity, food protein induced enterocolitis, FPIES, preschool child, infant. A total of 879 citations were identified through February 2014. Three authors (ANW, TBW, MG) rigorously reviewed all citations for applicability for inclusion, yielding 110 final citations that were mutually agreed upon. Per decision of the authorship group, abstracts were excluded. Non-English language articles were translated to English for review prior to inclusion where appropriate. (Supplemental figure 1)

Individual sections of the document were written by sub-group teams, then critiqued and revised based upon the feedback from all authors in an iterative process until consensus was achieved. Evidence was graded according to the previously established grading system for clinical practice guidelines used by the Joint Task Force on Allergy Practice Parameters. (Box 1) Final evidence grading and recommendation strength was then agreed upon in a similar fashion by the section chairs and the senior authors (ANW and MG), as depicted in Table I.²

SECTION I: Definition and Clinical Manifestations

SUMMARY STATEMENT 1: Manage FPIES as a potential medical emergency, which presents as delayed onset of protracted emesis and/or watery/bloody diarrhea, which culminate in hemodynamic instability and hypotension in at least 15% of reactions.

[Strength of Recommendation: Strong; Evidence strength IIa/IIb; Evidence grade B]

FPIES is a non-IgE-mediated food allergy that typically presents in infancy and is characterized by repetitive, protracted vomiting that begins approximately 1-4 hours following ingestion of a causal food. The vomiting is often accompanied by decreased activity or lethargy and pallor, and potentially later followed by diarrhea. Delayed onset and absence of cutaneous and respiratory symptoms suggest a systemic reaction distinctly different from anaphylaxis.^{1 3} Severe cases may progress to hypothermia, methemoglobinemia, acidemia, and hypotension resulting from hypovolemic shock, as noted in Table II.^{3 4 5} Laboratory findings in the setting of an acute reaction typically reveal leukocytosis with neutrophilia and/or thrombocytosis.⁶ The presentation can mimic sepsis. Internationally, FPIES is most commonly triggered by cow milk (CM).^{5,7-10} In the US, soy is the second most common trigger, though soy-FPIES is less-frequently reported in other countries.^{6,11 12} Rice and oat are the most reported solid food triggers, followed by egg, other grains, vegetables, poultry, fish, and other solid foods. The relative prevalence of specific triggers varies by country and regional diet, however.^{13 6 12} New onset of FPIES to CM, soy, rice or oat has been rarely reported in children older than 12 months. New onset of FPIES may occur in adults, with a few cases attributable to fish and shellfish.^{14 4} The clinical phenotype of FPIES is varied

and influenced by age of onset, severity of symptoms, diet, nationality, the timing and duration of symptoms, and associated IgE-mediated food allergy, as detailed in Table II.

SUMMARY STATEMENT 2: Recognize that the symptom phenotype in FPIES is determined by the frequency of food ingestion. [Strength of Recommendation: Strong; Evidence strength IIa; Evidence grade B]

The manifestations and severity of an FPIES episode may vary depending on the frequency and quantity of exposure to the offending food, as well as the phenotype of an individual patient, with additional variability possible within particular patient over time.^{6,8,10,15} Table III details mild-to-moderate and severe symptoms of acute FPIES. The distinct pattern of emesis occurring within 1-4 hours following food ingestion (acute FPIES) has been observed when the food is ingested intermittently or following a longer period of avoidance. Watery diarrhea (occasionally with blood and mucous) typically develops in some cases within 5-10 hours of ingestion and may be present for up to 24 hours after exposure. Diarrhea may be more common in infants and young children, and more commonly reported in Japan/Korea compared to the US, UK, Australia, and Italy.^{6,11,16-18} Symptoms of acute FPIES reactions usually resolve within 24 hours following the food ingestion. In most children with acute FPIES, longitudinal growth is normal.

Chronic FPIES is poorly characterized compared to acute FPIES, and only reported in infants younger than 4 months of age. This chronic form develops upon regular/repeated ingestion of known triggers or low doses of a trigger, presenting as

chronic/intermittent emesis, watery diarrhea, and failure to thrive. In severe cases, chronic FPIES may lead to dehydration and shock.^{7 8} Features of chronic FPIES are detailed in Table II. Hypoalbuminemia and poor weight gain (<10 g/day) have been identified as independent predictors of chronic CM-FPIES in young infants with chronic gastrointestinal symptoms.¹⁶ With elimination of the chronic FPIES food trigger(s), symptoms resolve and subsequent feeding (oral food challenge, OFC) induces an acute FPIES reaction within 1-4 hours of food ingestion, as highlighted in Table III. The acute symptomatology following food avoidance distinguishes chronic FPIES from other disorders, such as food protein-induced enteropathy, eosinophilic gastroenteritis, or celiac disease. Chronic FPIES has been reported in response to CM and soy and is more commonly reported in Asian countries, primarily Japan and Korea compared to the US.^{16,18,19}

Summary and assessment of future needs

FPIES is classified as a non IgE-mediated food allergy, which manifests acutely or chronically, depending on the dose and frequency of food allergen ingestion and the individual patient. While acute FPIES has been well-studied, a better characterization of the chronic FPIES is necessary.

SECTION II: Epidemiology

There is limited, wide-scale epidemiologic information available regarding FPIES.²⁰ FPIES was only recognized and formally defined in the mid-1970's.⁸ In the 10th revision of the International Statistical Classification of Diseases and Related Health

Problems (ICD-10) code for FPIES (K52.2) was implemented in October 2015. Prior to this, no uniform ICD code existed.

Powell outlined initial diagnostic criteria in the 1970's, describing neonates/infants reactive to CM or soy protein with symptom onset within the first 2 months of life, and features of poor growth, leukocytosis, and diarrhea (+/- bloody stools) and emphasizing repeat challenge to confirm diagnosis.⁸ Sicherer et al. introduced broadened criteria of FPIES that included older infants, solid food triggers, and children with IgE sensitization to the causative food (e.g. atypical FPIES).¹⁵ The Sicherer criteria and subsequent proposed modifications by Leonard et al. better define infants with the more commonly recognized acute phenotype.^{15,21} These modifications have further de-emphasized hematologic findings and included more liberalized symptom presentations (e.g. vomiting 1-6 hours after food ingestion as a sole symptom).^{5,6,10,12,13,15}

Consequently, multiple definitions of disease exist, and the heterogeneity in FPIES definition further complicates accurately assessing its epidemiology. Data quality has been variable with high reliance on case reports or case series, involving small numbers of patients from single centers, which limits their applicability and generalizability. However, several larger (>100 patient) case series have been published recently.^{4,5,11,18}

FPIES prevalence estimates vary greatly. Katz et al is the only published FPIES prospective birth cohort, noting a cumulative incidence of CM-FPIES infants of 3 per 1000 newborns born at a single hospital over 2 years (0.34%)¹¹ A Japanese retrospective survey of the prevalence of "neonatal milk allergy" in a neonatal intensive

care unit noted a rate of 0.21% among 69,796 neonates hospitalized in a one-year period.^{22,23}

Prevalence estimates for FPIES likely underestimate true rates, given unknown/unmeasured community rates of disease compared to those from academic referral centers. Providers must have awareness that some cases may never present to an allergy specialist or for hospital intervention, contributing to potential underestimation. Potential cases may be misdiagnosed as more common pediatric illness, such as gastroenteritis or sepsis.²⁴ It is also likely some patients never seek medical attention, representing possible ascertainment bias.

SUMMARY STATEMENT 3: Recognize that onset of FPIES to milk/soy may occur at younger ages compared to FPIES to solid foods, but also may occur in adults with prior tolerance to the trigger. Patients may have a single trigger or multiple triggers. [Strength of Recommendation: Strong; Evidence level IIb-III; Grade C]

FPIES typically occurs once CM or soy-based formulas and/or solid foods are introduced into the infant's diet.²⁰ Most FPIES occurs in infants aged 2-7 months, corresponding to the most common time period formulas and/or solids are introduced into an infant's diet.^{4,6,11,12,15,24}

Table IV compares age of onset of FPIES to different triggers. Infants with CM and soy-FPIES typically present at a younger age (<6 months) compared to those with solid food FPIES (6-12 months) because these items are generally introduced into the diet earlier. The median age of onset of solid food-FPIES is similar between most series (5-7 months).^{4-6,13,15} FPIES to grains (particularly rice/oats) occurs at an earlier age than FPIES to fish, egg and poultry, which also likely reflects a natural hierarchy in the timing of complimentary food introduction and cultural practices.²⁰

The early studies on CM/soy-FPIES and reports from Japan and Korea (who used the Powell diagnostic criteria) have reported a neonatal onset (<28 days). In contrast, most other reports detail onset between 1-2 months of age or older. In combined analysis of these data, infants developing FPIES to CM/soy at under 2 months of age were significantly more likely to present with diarrhea, bloody diarrhea/blood in the stools, and failure to thrive compared to those presenting at older than 2 months of age ($p < 0.05$ for all comparisons).^{10,12,17,18,25-28} Older infants were more likely to present with vomiting alone ($p < 0.05$).²⁹ An acute on chronic phenotype also exists, where neonates initially present with the chronic FPIES, but upon accidental "on off" exposure, present with the acute FPIES phenotype.^{7,8}

FPIES in adults has been described to fish/shellfish in small case series or isolated reports. The most prominent features in these patients were delayed onset vomiting, persistence of the diagnosis, and a history of previous tolerance to the trigger.¹⁴ Egg has also been described as an adult FPIES trigger.³⁰

As detailed in Table V, the most commonly reported triggers of FPIES are CM, soy and grains. There are limited data regarding other causes of FPIES besides CM or soy occurring in Israel, Japan, and Korea.^{11,17,31} Soy-FPIES and combined soy/CM-FPIES are common in the US (~25-50% in reported case series), but uncommon in series from Australia, Italy and Israel. Most reported solid food-FPIES is attributable to grains, particularly rice and oat. Rice is the most commonly reported grain trigger in all series; in Australia, rice is also the most common FPIES trigger.⁶ Combined rice/oat FPIES has been reported in almost a third of cases of rice-FPIES in both the US and Australia.⁴⁻⁶ In contrast, fish is a common cause of solid food-FPIES in Italy and Spain, but a less common trigger elsewhere.^{12,32} Rice appears to be a rare trigger in Italy.¹² In a prospective birth cohort, Katz et al noted no development of soy-FPIES among those developing milk-FPIES.¹¹ Multiple factors may be involved to explain this geographic variation, including differences in the populations studied in the case series, presence of atopic disease, intestinal microbiota, breastfeeding and dietary practices, and yet-to-be-discovered genetic factors. Limited data on solid food-FPIES exist for Japan, Korea, and Israel.^{11,17,31,33}

Cases of multiple-food triggered FPIES (>1 trigger) have been noted in several countries, with higher rates often reported in series from the US, compared to elsewhere. More work is needed to understand multiple food FPIES phenotypes.

SUMMARY STATEMENT 4: Consider specific IgE testing of children with FPIES to their trigger food, as co-morbid IgE-mediated sensitization to triggers such as CM may infer greater chance of persistent disease. [Strength of Recommendation: Moderate; Evidence level IIb-III; Grade C]

FPIES is immunologically distinct from IgE-mediated disease, but many children with FPIES have co-morbid atopy including eczema and food sensitization. Studies from the US and Australia report frequent atopic co-association, especially eczema (Table V; 31-57% of cases), though this association is rare in Korea, Israel and Italy (0-9%). In Italy, Sopo et al. reported a mean onset of FPIES at 5 months, but reported eczema in only 9%, suggesting geography may influence atopic predisposition in those with FPIES.¹²

Children with FPIES may also have co-existing IgE-mediated food allergy at presentation or upon follow-up assessment, reported in 2-12% of patients with FPIES. Mehr et al reported 4 cases (11%), Sopo et al 1 case (2%) and Caubet et al 19 (12%) cases of co-existent IgE mediated food allergy.^{4,6,12} Sicherer et al has described co-morbid IgE-sensitization to the triggering food and called it “atypical” FPIES.¹⁵ Caubet et al reported that children with CM-FPIES and IgE sensitization to CM were more likely to have persistence of CM-FPIES after 3 years of age compared to those without sensitization.⁴ Sensitization to other food proteins did not appear to delay tolerance acquisition.

SUMMARY STATEMENT 5: Do not recommend any specific pre-natal or post-natal food introduction/avoidance, health behaviors, or advise patients regarding any specific genetic factors known to moderate the risk of an individual developing FPIES. [Strength of Recommendation: weak; Evidence level IIb-III; Grade C]

No firm data support an association between pre-natal or peri-natal maternal/paternal risk factors or moderating health behaviors and the development of FPIES. In the Israeli birth cohort study, no association was noted between the development of FPIES and gestational age, maternal age, number of siblings, maternal dairy consumption, or age of introduction of CM, though an association was noted with spontaneous vaginal delivery (smaller proportion developed FPIES) and Jewish religion (greater proportion developed FPIES).¹¹ In Japan, birth weight <1kg was associated with a higher rate of neonatal milk allergy (though FPIES was not isolated in this series), and Nomura et al noted an association with lower birth weight and a less severe FPIES symptom cluster.^{22,31} US, Italian, and Australian case series have not assessed pre-natal or post-natal risk factors.^{5,6,12,13,15} The use of antibiotics during pregnancy, delivery, breastfeeding, or during the first months of life have not been studied as a potential risk factor as well. There are no studies that have explored genetic associations or loci of interest associated with the development of FPIES. It is unclear if this relates to a lack of such studies being performed, or the potential low prevalence/recognition of disease.²⁰ There appears to be slight predominance of affected males noted across several different cultural and geographically distinct FPIES populations but no data

regarding FPIES familial recurrence risk. Although a family history of atopy appears common among those with FPIES (20-77%), to date there has been only three published cases of siblings with FPIES. All three cases were twins, one identical and two fraternal twins.^{13 34}

SUMMARY STATEMENT 6: Consider FPIES as a heterogeneous disorder associated with a number of geographic variations in the features of disease, representing a spectrum of “syndromes” as opposed to a uniform “syndrome”. [Strength of Recommendation: Strong; Evidence level IIb-III; Grade B]

The majority of the reports in the literature are from Western countries and predominantly of White race.²⁰ Japanese data suggest that different FPIES phenotypes may exist based on diet, race or ethnicity.¹⁹ In a group of 46 Japanese infants with early onset of vomiting and or bloody stools, who underwent a diagnostic OFC to cow's milk, 30 developed symptoms consistent with FPIES.¹⁸ Among these 30 patients, vomiting was observed in all, bloody stools in 47%, and fever in 13% at the initial presentation. Forty-seven percent had detectable serum CM-specific IgE antibodies and 10% percent reported symptoms during breastfeeding.¹⁹ This phenotype appears distinct to Japan, in contrast to the vomiting-predominant presentation without bloody stools in slightly older infants more commonly reported in most other countries.²⁰ Further studies in other populations using the cluster analysis technique employed by Nomura et al may help to elucidate other phenotypic subtleties.²⁰

Summary and assessment of future needs

FPIES is a syndrome with heterogeneous features with multiple evolving diagnostic criteria. FPIES appears to be associated with co-morbid atopic disorders, notably atopic dermatitis and other IgE mediated food allergy. Co-morbid IgE sensitization to CM may be indicative of a more prolonged FPIES phenotype. The age of onset of FPIES is variable by country and trigger type. Cultural feeding practices likely influence these rates. Risk factors and genetic associations for developing FPIES remain poorly identified. Further population based prospective studies and studies using advanced multivariate analytic techniques, such as the cluster analysis employed in Japan, may prove useful in other cohorts to determine if disease phenotypes exist. Current epidemiology is limited by heavy reliance on small, single-centered studies limited by clustering effects and selection bias that define the bulk of FPIES knowledge. These are all rather urgent needs to be met in the next 5 years as more FPIES research is performed.

SECTION III: Diagnosis of FPIES

Summary Statement 7: Diagnose FPIES primarily upon a clinical history of typical characteristic signs and symptoms, with improvement following withdrawal of the suspected causal food. Exclude other potential etiologies and use oral food challenge to help confirm the diagnosis if the history is unclear and there is a favorable risk to benefit ratio. [Strength of Recommendation: Strong; Evidence Level IIb-III; Grade B]

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550 A careful history is by far the most important diagnostic tool in the evaluation of
551 suspected FPIES.^{3,35} (Table VII) Acute FPIES typically presents with a constellation of
552 unique and sometimes dramatic signs and symptoms. Therefore, the clinician must
553 obtain a detailed history regarding all possible reactions, including specific symptoms,
554 the timing of symptoms in relation to food intake, all foods suspected of causing
555 reactions, and the reproducibility of reactions with repeated exposures to the suspect
556 food(s). In the vast majority of cases of acute FPIES, the history alone is generally
557 sufficient to make a diagnosis and identify casual foods.

558 If the diagnosis is unclear after taking a careful history, OFC should be used to confirm
559 the diagnosis. There is no laboratory or other diagnostic procedure specific for
560 diagnosing FPIES although there are a variety of other laboratory tests to help support
561 the diagnosis, and more importantly to rule out other conditions, discussed in Table VI.

562 Though OFC is the gold standard to diagnosis of FPIES, infants presenting with a
563 convincing history of FPIES likely do not require challenges to confirm their initial
564 diagnosis. The revised diagnostic criteria for acute and chronic FPIES are presented in
565 Table VII. In fact, in the face of a clear history with repeated reactions to the same
566 food(s), the risk of an OFC may outweigh its benefits. OFC is best reserved in the initial
567 diagnostic evaluation for cases in which the history is unclear, a specific food trigger has
568 not been identified, the time course of symptoms is atypical, or if symptoms persist
569 despite removing the suspected culprit food(s) from the diet. OFC is highly useful to
570 determine if a trigger has been outgrown, as well.

In patients with symptoms suggestive of chronic FPIES, the diagnosis may be unclear based on the history alone. In one study of infants diagnosed with chronic FPIES, hypoalbuminemia and poor weight gain were identified as independent predictors of CM FPIES.¹⁶ Given the less specific nature of chronic FPIES symptoms, a trial of food elimination followed by supervised OFC to potential culprit items may be necessary for a conclusive diagnosis. In select cases, endoscopy and biopsy may be warranted to exclude other etiologies.

Summary Statement 8: Conduct OFCs in patients with suspected FPIES in medically supervised settings where access to rapid fluid resuscitation is available, and prolonged observation can be provided if necessary. [Strength of Recommendation: Strong; Evidence Level IIb; Grade B]

OFCs in patients with suspected FPIES should be conducted with considerable caution, as up to 50% of positive challenges may require treatment with intravenous fluids.³⁵ Home challenge of foods suspected of provoking FPIES is not recommended given the potential for severe adverse reactions. Although one recent study reported successful management of OFC reactions with oral rehydration and anecdotally many reactions are managed with oral rehydration,¹¹ it is advisable to have intravenous hydration readily available in case of severe reactions.

A variety of protocols for FPIES OFCs have been published.^{3,8,35-37} The protocols mainly vary in dosing regimens, laboratory assessment, and treatment. All OFCs require close supervision with immediately available access to intravenous (IV) fluids. Some experts

recommend that IV access be secured prior to the initiation of the challenge. A baseline complete blood count (CBC) with differential may be of value, especially in the research setting (as a comparator with a post-challenge CBC) but should be considered optional in challenges performed for clinical indications. Although some challenge protocols provide the entire dose in a single serving size portion, the current consensus is to administer the challenge food at a dose of 0.06 to 0.6 grams, usually 0.3 grams of the food protein per kilogram of body weight in three equal doses over 30 minutes, generally not to exceed a total of 3 grams of protein or 10 grams of total food (100 mL of liquid) for an initial feeding (which aims to approximate a serving size), and observe the patient for 4-6 hours.³⁷ Lower starting dose and/or longer observation period between doses should be considered in patients with a history of severe reactions.³⁵ When a very low dose of food protein is administered and there is no reaction after two to three hours of observation, some experts advocate that the patient should ingest a full age appropriate serving of the food followed by four hours of observation.^{2,37} In patients with detectable food-specific IgE to the challenge item, a more gradual administration of the challenge food according to the protocols for IgE-mediated food allergy is recommended, with a longer post-challenge observation period typical for FPIES, to account for possible delayed FPIES reaction.³⁷ The total dose and the dosing regimen for FPIES OFC have not been systematically studied, so practices may vary internationally, and it is ultimately left to the discretion of the treating physician to potentially modify the regimen as per the individual patient circumstances.

With a positive (e.g. failed) challenge, typical FPIES symptoms which include emesis (usually protracted, repetitive emesis), pallor, and lethargy begin within one to three

hours after ingestion. Diarrhea may also occur but is usually more delayed with an onset in about 5-10 hours. Challenge outcomes are usually very clear based on the clinical symptoms but some clinicians also obtain laboratory tests to help confirm the clinical impression. This most often includes a CBC before and after challenge, which in a positive OFC typically reveals a rise in the neutrophil count (>1500 cells / ml) peaking 6 hours after food ingestion.^{4,7,8} In addition, in patients who develop diarrhea, a stool sample can be assessed for the presence of occult blood, leukocytes, or red blood cells. Revised criteria for interpretation of OFC results are presented in Table VIII.

First line treatment for a positive challenge is fluid resuscitation with 20 mL/kg IV boluses of normal saline. Two small case series suggest that ondansetron 0.1 to 0.15 mg/kg IV or intramuscular (IM) (maximum single dose 16 mg) may be effective in shortening the duration of emesis.^{38,39} Glucocorticoids (e.g., methylprednisolone 1 mg/kg IV) are also commonly recommended but have not been systematically studied for efficacy.⁴⁰

Summary Statement 9: Do not routinely perform testing for food specific IgE by either prick skin testing or serologic assessment in the diagnosis of food triggers for FPIES, as FPIES is not an IgE-mediated process. However, since some patients with FPIES may exhibit co-existing IgE-mediated allergies, testing may be considered in patients with certain comorbid conditions. Assessment of chemistry or blood count can help rule-out other causes of symptoms if obtained in the acute setting. [Strength of Recommendation: Moderate; Evidence Level III; Grade C]

639

640 The majority (over 90%) of patients with FPIES have negative skin prick tests and
641 undetectable serum food-specific IgE to the suspect food at the time of their initial
642 diagnosis.^{4,11-13,15} However, IgE testing is still an option to consider in patients with
643 FPIES at follow-up visits, dictated by interval history since 4%-20% may eventually test
644 positive to the suspect FPIES food(s), and 20-40% will test positive to other common
645 food allergens.^{4,12,15} There are some children who demonstrate sIgE to their trigger
646 food who do have slower resolution of their FPIES, and these children are important to
647 potentially identify.^{15,41} Therefore periodic testing e.g., prior to an OFC) for food specific
648 IgE can be considered in patients with comorbid conditions, such as IgE-mediated food
649 allergy to other foods and atopic dermatitis felt to be influenced by a food allergen, but is
650 not recommended at the initial evaluation for an FPIES trigger. In CM-FPIES, CM-
651 specific IgE should be tested before performing a food challenge, considering the risk of
652 conversion to the IgE-mediated CM allergy. Atopy patch testing (APT) has also been
653 evaluated in two small studies as a possible means of identifying specific food
654 sensitivities in patients with FPIES. However, these studies had conflicting results as to
655 its diagnostic value in predicting challenge outcome, and no recommendation regarding
656 the utility of APT can be made.^{42,43}

657

658 In terms of other laboratory testing, patients with chronic FPIES may demonstrate
659 varying degrees of anemia, hypoalbuminemia, an elevated white blood cell count with a
660 left shift and eosinophilia.¹⁶ In acute FPIES reactions, patients may have elevated
661 peripheral blood neutrophil counts and CSF neutrophils. This frequently leads to a

complete sepsis evaluation in the emergency department.¹³ Thrombocytosis was reported in one acute FPIES series in 65% of patients.⁶ Metabolic acidosis and methemoglobinemia have also been reported in both acute and chronic FPIES due to hemodynamic shifts.⁴⁴

Stool analyses may also be abnormal in both acute and chronic FPIES. In acute reactions with diarrhea, frank or occult blood, mucus, leukocytes, and increased carbohydrate content may all occur.⁸ In infants with chronic FPIES with diarrhea, stool examination may reveal occult blood, neutrophils, eosinophils, Charcot-Leyden crystals, and/or reducing substances.¹⁶ Finally, gastric aspirates were assessed in one series before and 3 hours after undergoing an OFC, revealing >10 leukocytes/hpf in 15/16 patients in a single case series with positive OFC to FPIES and 0/8 negative OFC.⁴⁵ It is not felt that any of these evaluations have clinical utility for routine use, and even the acute leukocytosis seen in positive challenges rarely adds to the overall interpretation of the challenge outcome.

Summary Statement 10: Do not obtain radiographic testing in the routine diagnostic work-up of suspected FPIES. [Strength of Recommendation: Strong; Evidence Level III; Grade C]

There is no radiographic finding that is specific to FPIES, which assists in ruling in a diagnosis. Radiologic studies were performed in some older studies involving infants with possible FPIES symptoms including chronic diarrhea, rectal bleeding, and/or failure to thrive. Abdominal radiographs showed air fluid levels, nonspecific narrowing and

thumb printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid.⁴⁶ Intramural gas has also been documented, potentially leading to a misdiagnosis of necrotizing enterocolitis (NEC).⁶

Summary Statement 11: Consider a broad differential for a patient presenting with acute vomiting in making a diagnosis of FPIES. [Strength of Recommendation: Moderate; Evidence Level III/IV; Grade C]

An infant may present with a history of multiple reactions before the diagnosis of FPIES is eventually considered, often leading to extensive diagnostic evaluations. This is especially common when FPIES is caused by solid foods.^{6,13} Delay in diagnosis is most likely due to a combination of nonspecific symptoms, the absence of definitive diagnostic tests, and an overall lack of familiarity with this condition. Delayed diagnosis of solid food FPIES may also be due to the fact, that foods such as rice, oat and vegetables, are uncommon causes of typical, IgE-mediated food allergy.

The differential diagnosis of FPIES is extensive and includes infectious diseases, other food allergic disorders, intestinal obstruction, as well as neurologic and metabolic diseases (Table VI). Often, the initial episodes may be misdiagnosed as acute viral gastroenteritis or be evaluated for sepsis, especially if they present with profound lethargy, hypotension, and have an elevated white cell count with a left shift.^{8 6}

A variety of other conditions may also be considered in the differential diagnosis, especially in infants with repeated episodes of severe or protracted vomiting. Metabolic disorders frequently present with episodic vomiting, dehydration and lethargy, as well as metabolic acidosis but are not associated with specific food intake and there are other associated features such as hyperammonemia, hypoglycemia, hyperpnea, hematologic abnormalities, elevated liver enzymes, renal disease, or developmental delay not seen in adverse food reactions.

Other types of food allergy may also be confused with FPIES. Acute IgE-mediated food reactions may frequently present with vomiting, but the vomiting usually occurs very soon after the food exposure and is not delayed or protracted. Other food allergic disorders that may be confused with FPIES (especially chronic FPIES) include eosinophilic gastrointestinal disorders and food protein-induced enteropathy, a syndrome of small bowel injury causing malabsorption, intermittent vomiting, diarrhea, and failure to thrive.

Finally, other gastrointestinal disorders as discussed in Table VI could be confused with acute or chronic FPIES.

Summary Statement 12: Use distinct criteria to diagnose FPIES in the outpatient/community setting, compared to the monitored setting where OFC is

**being used to rule in the diagnosis. [Strength of Recommendation: Weak;
Evidence Level III/IV; Grade D]**

Revised diagnostic criteria for patients presenting with possible acute and chronic FPIES are detailed in the Table VII. These criteria differ from the criteria proposed by Powell and by Sicherer in that they eliminate an age limit for onset of FPIES and emphasize repetitive vomiting as a cardinal feature of acute FPIES, based on more recent literature.^{5,6,8,11,12,14,15,17,47} Specific major and minor criteria for acute FPIES are provided, based on the collective published evidence.

Major criterion for acute-FPIES is 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 include:

1. A second (or more) episode of repetitive vomiting after eating the same suspect food
2. Repetitive vomiting episode 1-4 hours after eating a different food
3. Extreme lethargy with any suspected reaction
4. Marked pallor with any suspected reaction
5. Need for emergency room visit with any suspected reaction
6. Need for intravenous fluid support with any suspected reaction
7. Diarrhea in 24 hours (usually 5-10 hours)
8. Hypotension
9. Hypothermia

The diagnosis of FPIES requires that a patient meet the major criterion and at least 3 minor criteria. If only a single episode has occurred, a diagnostic oral food challenge

should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group.

For chronic-FPIES general criteria are provided, but given the paucity of published reports of chronic-FPIES, specific major and minor criteria could not be established at this time. Severe chronic-FPIES: when the offending food is ingested in on a regular basis [e.g., infant formula]: Intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis. Milder chronic-FPIES: lower doses of the problem food (e.g. solid foods or food allergens in breast milk) lead to intermittent vomiting, and/or diarrhea, usually with poor weight gain/ failure to thrive, but without dehydration or metabolic acidosis.

However it is important to recognize two distinct hallmarks of chronic FPIES: patients are asymptomatic and maintain normal growth when the offending food is eliminated from the diet, and reintroduction of the offending food induces acute FPIES symptoms. The diagnostic criteria for the interpretation of OFCs in patients with a history of possible or confirmed FPIES are presented in Table VIII. These criteria also differ in the degree of neutrophilia, and remove the stool laboratory findings. These changes reflect recent literature noting a possible phenotype shift represented by a lower frequency of diarrhea and smaller magnitude of neutrophil count elevation during OFCs.^{4,11,17}

Summary and assessment of future needs

Diagnosis of FPIES relies heavily on clinical history of typical symptoms that resolve upon elimination of the trigger food from the diet, and recur during an OFC. Validation of the proposed criteria for a positive challenge is needed in prospective multicenter

studies utilizing a standardized food challenge protocol. Non-invasive diagnostic biomarkers are highly desirable. The optimal treatment protocol for acute FPIES reaction should be developed through multicenter studies.

SECTION IV: Pathophysiology of FPIES

FPIES likely involves antigen-specific T cells, antibodies and cytokines as a cause of the inflammation found in the colon, and with variable degrees the ileus, by endoscopy, colonoscopy and biopsy.^{45,48-54} This inflammation is believed to result in an increased intestinal permeability leading to a fluid shift into the gastrointestinal lumen. However, it has been shown that baseline antigen absorption is normal and does not predispose to FPIES.⁵⁵

The mechanisms of the development of tolerance in FPIES patients are also poorly understood. A higher frequency of antigen-specific CD4⁺CD25⁺ regulatory T cells have been found in children outgrowing non IgE-mediated hypersensitivity to CM protein, and their suppressive action may be exerted by the production of TGF- β and IL-10, which have been shown to increase significantly following development of tolerance.^{56,57} The ultimate proof of T cell involvement in FPIES pathophysiology requires longitudinal studies to determine how the immune response to specific antigens changes as children do or do not develop clinical tolerance to triggering antigens.

Neutrophilia has been noted in patients with acute FPIES, peaking approximately 6

hours after trigger food ingestion and returning to baseline within 24 hours, as has leukocytosis.⁶⁻¹⁰ Neutrophils have been found in the gastric juice aspirate and in stool mucous of FPIES patients in one study.¹⁷ These findings may result from the secretion of different cytokines, particularly TNF-, and chemokines by the local inflammatory cells.⁵⁸ Thrombocytosis is also found in some FPIES patients both during the acute and chronic phase,⁶ as an acute phase reactant (e.g., due to stress induced demargination of platelets from the spleen into the circulation).⁵⁹ The potential active contribution of neutrophils and platelets in FPIES pathophysiology requires further investigations.

7,18,60,61

Peripheral eosinophilia, clusters of eosinophils in intestinal biopsies as well as eosinophils and Charcot-Leyden crystals in stool samples have been non-specifically noted in a subset of infants with FPIES.^{54,62} Gastrointestinal eosinophil accumulation may overlap with other disorders such as eosinophilic gastroenteropathies, food-induced proctocolitis, IgE-mediated food allergy, inflammatory bowel diseases, and gastroesophageal reflux.⁶²

Since acute FPIES is rarely seen in exclusively breastfed children, it has been hypothesized that breast milk IgA may have a protective role, though this has been poorly studied.^{28,63,64} Jejunal biopsies of FPIES patients revealed increased numbers of IgM- and IgA-containing plasma cells.^{50,54} Some authors have noted a trend toward higher levels of food-specific IgA antibodies in patients with a positive OFC compared to patients with a negative OFC, though no difference in milk or casein-specific serum IgA

antibody levels between children with milk-FPIES and milk-tolerant children with FPIES to other foods..^{28,64, 64} These patients also produced lower amounts of specific IgG₄, which may be involved in the pathogenesis of this disorder.^{65,72}

SUMMARY STATEMENT 13: Classify FPIES as a non-IgE mediated food allergy, but be aware that the postulated T-cell mediated mechanism of FPIES requires further validation. [Recommendation: Strong; Evidence Strength IIb/III; Evidence Grade C].

FPIES is classified as a non-IgE mediated disorder.^{13,15,66,67} However, some FPIES patients may have IgE to the causal food protein which may be associated with a more protracted course, in particular casein in CM-FPIES.^{13,35, 4} Phenotypic shifting from IgE-mediated CM allergy to pure non-IgE-mediated FPIES has been reported.⁶⁸ Local intestinal mucosal IgE antibodies could facilitate antigen uptake and lead to the intestinal inflammation. T_H2 responses similar to those occurring in patients with IgE-mediated allergy have been found in FPIES patients.^{56, 69} This corroborates the aforementioned observation of high rates of atopy in FPIES patients.^{3,4} The relationship between IgE and non-IgE mechanisms in FPIES requires further investigations. Reported successful use of ondansetron to treat vomiting, abdominal pain and lethargy in FPIES challenges raises issues of impaired neuroimmune mechanisms as well.^{38,70} Ondansetron reduces activity of the vagus nerve both peripherally and centrally. However, use of ondansetron in FPIES warrants further investigation.

A key role of T cells has been suggested in FPIES patients based on findings of

peripheral blood mononuclear cells (PBMC) proliferation after stimulation by the causal antigen, and positive patch tests with the specific allergen though this remains controversial.^{42,57,60,61,64,71-73} Release of pro-inflammatory cytokines (TNF- α , IFN- γ) by activated PBMC has been suggested to induce local intestinal inflammation.^{56,71} High levels of TNF- α released by antigen-specific T cells could act synergistically with IFN- γ to increase intestinal permeability and then increase the amount of antigen flux into the submucosa with further activation of antigen-specific T cells.⁷¹ Similarly, increased TNF- α and decreased expression of TGF- β receptors, known to protect the intestinal barrier from the penetration of foreign antigen, have been found in the intestinal mucosa of FPIES patients.^{26,54,61,74} TNF- α , IL-6, and T_H2 cytokines (IL-3, IL-5, and IL-13 but not IFN- γ or IL-17) were increased in the supernatant from milk protein-stimulated peripheral blood mononuclear cell cultures from patients with FPIES, compared to non-allergic controls.⁶⁹ The delayed onset of symptoms during acute FPIES is rather atypical for a T cell-mediated process, suggesting these cells are unlikely effector cells in acute FPIES. In chronic FPIES, with ongoing gastrointestinal symptoms, T cell contribution seems more plausible.

Summary and assessment of future needs

The mechanisms underlying FPIES remain poorly characterized and further studies are needed for a better understanding of this disease. The pathophysiology of FPIES needs

to be systematically evaluated in order to develop diagnostic biomarkers and treatment strategies.

SECTION IV: GI Manifestations of FPIES

SUMMARY STATEMENT 14: Do not routinely obtain endoscopic evaluation in the evaluation of FPIES. [Strength of Recommendation: Weak; Evidence strength IV; Grade D]

To date, there are no large case series fulfilling the diagnostic criteria in which gastrointestinal macroscopic and/or microscopic evaluations were performed. In FPIES patients with a chronic presentation including emesis and failure to thrive, upper endoscopy may reveal gastric edema, erythema, and mucosal friability, with gastric antral erosions.⁵² Colonoscopy can be normal in the absence of rectal bleeding or diarrhea.⁷⁵ Gastrointestinal histological features of FPIES during acute FPIES are non-specific, and cannot be used to confirm the diagnosis. In the event of frank rectal bleeding, changes of variable severity in the rectal mucosa seen by proctoscopy have been described within 24 hours of ingestion of the trigger food.^{48,49,76} However it remains controversial as to whether these patients have a co-existent allergen-induced proctocolitis or whether this presentation is part of the FPIES spectrum.

In those patients with rectal bleeding, notable histological features ranging from loss of vascular pattern, spontaneous and induced friability (e.g. easy bleeding upon swabbing), and variable degrees of ulceration with spontaneous bleeding have been

seen. Rectal biopsy histology ranges from slight infiltrate of lymphocytes and plasma cells in the lamina propria to polymorphonuclear leukocytic infiltration of the lamina propria or glands, with occasional crypt abscesses and depletion of mucus from rectal glands. Destruction of the surface epithelium can also be seen. Colonic macroscopic appearance is similar to that of the rectum, with red, fragile, hemorrhagic mucosa seen within a few hours of ingesting the offending food.⁷⁵ Colonic biopsies show severe inflammation with an increased number of eosinophils.⁷⁵ In some infants with FPIES, evidence of small intestinal damage has been described, with variable degrees of villous atrophy,²⁶ although again whether this constitutes a co-existent non-IgE enteropathy or is truly part of the FPIES spectrum remains controversial. Clinically, allergen-induced enteropathy may cause carbohydrate malabsorption, and infants presenting with watery stools that are positive for reducing substances.^{8,76} Gross and histological abnormalities can rapidly revert to normal as soon as two days following removal of the trigger food.⁴⁸

SUMMARY STATEMENT 15: Do not use stool tests to make the diagnosis of FPIES. [Strength of Recommendation: Weak; Evidence strength III; Grade D]

Stool leukocytes may be found in the stools of infants with FPIES consisting of eosinophils, detected using Hansel's stain, along with eosinophilic debris.⁷⁶ Stool cultures and/or evaluation of the stool for pathogenic organisms including parasites should be negative to exclude this from differential diagnosis in cases of possible FPIES associated with chronic diarrhea. Stool leukocytes noted upon trigger food challenge

are a feature of the diagnostic criteria of FPIES described by Powell though this specific feature is rarely considered essential in light of Sicherer's modification to the acute FPIES criteria.⁷⁶ In addition, patients with FPIES can have occult blood in their stools in the chronic phase, or frank blood in the acute phase following elimination and then re-introduction of the trigger food to their diet.^{11,31,76}

SUMMARY STATEMENT 16: Consider a work-up to rule other gastrointestinal diseases result in symptoms that overlap with FPIES. [Strength of Recommendation: Moderate; Evidence strength III; Evidence grade D]

A broad differential must be considered given many infantile gastrointestinal disorders cause symptoms, some of which overlap with those of FPIES, especially in the chronic phase of the disease. Gastroesophageal reflux disease can cause chronic emesis and failure to thrive. Multiple disorders can cause chronic diarrhea. These include infectious disorders, immune-mediated disorders (primary immunodeficiency, autoimmune disorders, inflammatory bowel disease), allergic enteropathies, and surgical disorders such as Hirschsprung's disease related enterocolitis, and necrotizing enterocolitis.⁷⁷ Table VI summarizes several disorders that can present with symptoms that overlap with some of those in FPIES.

Gastroesophageal reflux disease in infancy can cause chronic emesis in infants, which can mimic the vomiting-predominant presentation of FPIES, but mild GERD is mostly seen without failure to thrive, responds to anti-reflux measures, and is not likely to be

temporally related to the particular trigger ingestion. Overlap with IgE-mediated CM was discussed earlier.^{78,79} While a vomiting-predominant symptom phenotype in eosinophilic esophagitis could be confusing to discern from FPIES, acute rapid symptoms with trigger re-exposure do not necessarily immediately occur in EoE (except for possible dysphagia/impaction). Emesis following feeds in infants due to an anatomical obstruction (Table VI) can also mimic FPIES, and can be ruled out by appropriate radiological studies in the proper clinical context.

Food protein-induced enteropathy (FPE) can also cause diarrhea and failure to thrive, and must be differentiated from chronic FPIES. However, FPE lacks features of rapid onset of symptoms +/- shock that occurs in FPIES following elimination and then re-exposure of the offending food. Conditions with diarrhea and stools are positive for occult blood and leukocytes include chronic post-infectious diarrhea with villous atrophy on intestinal biopsies, and Hirschsprung's disease with resultant enterocolitis-induced diarrhea. Hirschsprung's disease is typically diagnosed by history of delay in passage of meconium during the first day of life, or if constipation preceded the diarrhea, and the diagnosis is confirmed by rectal suction biopsy.⁸⁰

In addition, intussusception should be considered in the older infant with colicky pain and irritability.⁸¹ Infectious causes of bloody diarrhea need to be considered here as well, emphasizing the usefulness of stool cultures when the diagnosis of FPIES is unclear.⁸¹ Inflammatory bowel disease is very rare in infancy, but can present with emesis, failure to thrive, and diarrhea with variable degrees of bleeding.

Summary and assessment of future needs

Endoscopic and histological findings in FPIES remain poorly characterized, since the diagnosis typically has been made based on clinical criteria, hence obviating the need for endoscopic evaluation, unless the diagnosis is unclear. These studies are then performed to rule-out other conditions with known histology. Studies are needed to evaluate the gastrointestinal histology in FPIES for better understanding of disease pathophysiology and mechanisms.⁸²

SECTION VI: Management of Acute FPIES

SUMMARY STATEMENT 17: Treat acute FPIES as a medical emergency, and be prepared to provide aggressive fluid resuscitation as nearly 15% of patients may develop hypovolemic shock. [Strength of Recommendation: Strong; Evidence Strength: IIa; Grade: B]

SUMMARY STATEMENT 18: Manage an acute FPIES reaction individually according to severity, and review treatment strategies with the caregivers of each patient. [Strength of Recommendation: Moderate; Evidence Strength: IIb/III; Grade: C]

The priority in acute management of symptomatic FPIES is restoration of stable hemodynamics through aggressive isotonic fluid resuscitation (e.g., 10-20ml/kg boluses of normal saline), repeated as needed, and dextrose saline as a continuous maintenance infusion. (Table IX) Acute FPIES can readily result in hypovolemic shock

and should be managed appropriately as such. A single dose of intravenous methylprednisolone (dosed at 1 mg/kg, with a maximum of 60 to 80 mg), may decrease presumed cell-mediated inflammation, although no studies support this recommendation.³⁶ In severe reactions, patients may require supplemental oxygen, mechanical ventilation or non-invasive positive pressure ventilation for respiratory insufficiency or failure, vasopressors for hypotension, bicarbonate for acidemia, and methylene blue for methemoglobinemia.^{3,35,44 83 39,84 14} Epinephrine autoinjectors are not routinely recommended/prescribed for FPIES, although those with concomitant IgE-mediated allergy should be prescribed an epinephrine auto-injector at the discretion of the treating physician if the patient is deemed at risk for food-induced anaphylaxis.^{1,67} Mild-moderate acute FPIES may resolve with oral rehydration, including breastfeeding, at home, Table X.

SUMMARY STATEMENT 19: Consider ondansetron as an adjunctive management of emesis in acute FPIES. [Strength of Recommendation: weak; Evidence Strength: IV; Grade: D]

Ondansetron is a serotonin 5-HT₃ receptor antagonist used to treat nausea and vomiting, often following chemotherapy but also in viral gastroenteritis. It reduces activity of the vagus nerve both peripherally and centrally. Ondansetron is usually well tolerated and does not cause excessive drowsiness or extrapyramidal reactions. Special caution may be warranted in children with underlying heart disease, due to the potential to prolong QT interval.⁸⁵ Two small case series have reported intravenous ondansetron was helpful in stopping emesis induced during FPIES OFC.^{38 39 70} Double blind and placebo-controlled trials are needed to determine the role of ondansetron in

the management of acute episode of FPIES and better define its efficacy. This intervention is potentially promising, but its use is poorly studied at present.

SUMMARY STATEMENT 20: Utilize dietary elimination of the offending food(s) for the primary management of FPIES, and educate caregivers and other care providers regarding avoidance strategies. [Strength of Recommendation: Strong; Evidence Strength: IIb/IIIIV; Grade: C]

Management of FPIES involves elimination of the culprit food(s), plans for dietary advancement (as applicable), treatment of symptoms at presentation or upon re-exposure (including emergency treatment planning), and a plan for supervised OFC to address FPIES resolution. Nutritional consultation should be strongly considered for any patient, irrespective of the number of food avoidances recommended. However, this is particularly crucial in patients with multiple food FPIES to assure adherence to dietary avoidance and adequate nutrition within the constraints of the limited diet.

Infants with suspected FPIES to CM or soy protein are generally advised to avoid all forms of the inciting food, including baked and processed foods, unless they are already tolerating baked foods.^{67 3,86} There are no conclusive studies to date evaluating tolerance to the extensively heated milk and egg proteins in baked products in children with FPIES, although small case series reported tolerance of baked milk and egg in some with FPIES. New introduction of baked milk and egg should be done under

physician supervision and with a follow-up, as there are unclear long-term outcomes associated with this practice.^{87-91 92}

Infants with milk/soy-FPIES may be breastfed or use a hypoallergenic formula approved for infants with milk allergy, such as extensively hydrolyzed casein-based formula (eHFc). Whenever possible, breastfeeding should be encouraged to be continued, as is consistent with current AAP recommendations for infant feeding.⁹³ A small but significant number of children may not tolerate eHFc; 10 to 20% may require an amino acid-based formula.^{13 4} In infants with CM-FPIES, introduction of soy formula should be considered under physician supervision, and vice versa.

The estimated risk of co-reactivity to both CM and soy appears to be primarily a US problem--in observational case series this is reported in approximately 20-40% of US patients, but is noticeably absent in similar reports from Australia, Israel, and Italy.^{6,11,12} No explicit odds ratio for the development of CM/soy co-FPIES has been calculated. It is unknown whether children with CM-FPIES can tolerate goat or sheep milk; based on high homology of the protein sequences in these animal milks, goat and sheep milk are not recommended in CM-FPIES.⁸⁶ However, it is possible (though not firmly established) that milk from donkey and/ or camel might be tolerated in milk FPIES, as they are usually well tolerated in IgE-mediated CM allergy. Infants with chronic FPIES usually return to their usual state of health within 3 to 10 days of switching to a

hypoallergenic formula, although in severe cases, temporary bowel rest and intravenous fluids may be necessary.^{7,8}

SUMMARY STATEMENT 21: Do not recommend routine maternal dietary elimination of offending triggers while breastfeeding if the infant is thriving and remains asymptomatic. [Strength of Recommendation: Moderate; Evidence Strength: III-IV; Grade C]

Though a handful of case reports describe allergen transmission and acute or chronic FPIES reactions attributed to breast milk, this is thought to be an exceptionally rare occurrence, and the manipulation of the maternal diet while breastfeeding an infant with FPIES remains highly controversial.^{1,67 63 94}

In the case of symptomatic FPIES occurring in an exclusively breastfed infant, the breastfeeding mother should eliminate the suspected trigger food(s) from her diet if the reactions occur after breastfeeding or the infant is failing to thrive, and the mother should seek immediate consultation with allergy specialist for evaluation.^{63 94 19}

Nutritional consultation should be considered to assist the elimination diet in the breastfeeding mother. If resolution of symptoms is not accomplished with maternal dietary elimination diet, discontinuation of breastfeeding and introduction of feeding with a hypoallergenic formula should be considered. In the case of symptomatic FPIES in a breastfed infant (e.g., presenting with chronic vomiting, diarrhea, irritability), the breastfeeding mother should eliminate the suspected trigger food(s) from her diet if the reactions occur after breastfeeding or the infant is failing to thrive, and seek immediate

consultation with a board-certified allergist for evaluation.^{63 94 19} Nutritional consultation may be needed to assist the elimination diet in the breastfeeding mother.

Infants are usually asymptomatic during exclusive breastfeeding without maternal dietary restrictions.^{13 18,19} It is not clear how exclusive breastfeeding moderates the onset of FPIES, but it has been hypothesized that breast milk IgA, either alone or as a complex with secreted antigens, may play a protective role.⁹⁵ No studies support that breastfeeding does more than delay the timing of the outright development of this syndrome.²⁰ Breastfeeding does not appear to be protective of the risk of developing FPIES.^{5,6,11-13,15} Ruffner et al noted no difference in time of onset of FPIES between breastfed and bottle-fed babies, but Nowak-Wegrzyn et al noted that infants developing solid-food FPIES were breast-fed for a longer duration of time than those developing milk/soy FPIES.^{5,13} Caubet et al noted that infants with solid food FPIES were breast fed for significantly longer period than infants with milk/soy FPIES.⁴ In a small Canadian cohort, Beauchamp et al noted that breastfeeding offered no protection against the development of GI symptoms upon introduction of solid foods in children with pre-existing CM-FPIES.⁹⁶

SUMMARY STATEMENT 22: Reintroduce the foods causing FPIES under physician supervision. [Strength of Recommendation: Strong; Evidence Strength IIa/IIb; Grade: B]

Foods that have caused FPIES reactions in the past should generally be reintroduced under physician supervision during a formal OFC or supervised feeding. The timing of

when to approach such an intervention is variable, ranging from 6 months to 12-24 months or longer from the most recent FPIES reaction, depending on the dietary and or social importance of the food, family preference and physician experience. Placement of a secure peripheral venous access prior to the onset of the OFC may be warranted in those patients with past severe reactions requiring an emergency room visit or hospitalization. Securing a peripheral intravenous line prior to the challenge may be advisable in infants and older patients with anticipated difficult intravenous access. In the several published case series, between 45-95% of the reactions during the challenge were treated with intravenous fluids and or steroids.^{12,15} In milder reactions, oral rehydration may be sufficient.¹¹ (Table IX) While some providers may elect to allow families to trial certain foods at home, this should be a shared decision between care provider and parent, accounting for access and distance to local emergency departments, caregiver comfort, the nature of the trigger food, and the severity of past FPIES reaction.

SUMMARY STATEMENT 23: Recognize that infants with milk or soy FPIES may potentially be at increased risk of having FPIES to other foods. [Strength of Recommendation: Strong; Evidence Strength III; Grade: C]

The majority of children (65-80%) in the literature are reported to have FPIES to a single food, most commonly milk.⁴⁻⁶ In a large US case series at a tertiary care center, about 5-10% of children reacted to more than 3 foods, some to as many as 6 or more foods.⁵

⁴ Children with either milk or soy FPIES may also react to both items, with this likelihood higher among those who developed symptoms of FPIES in the first month of life, though the risk or odds of this occurring is not known. (Table XI)^{8,76} ⁴ In these infants with

early onset of FPIES, it may be prudent to breast-feed or introduce a hypoallergenic formula in the first 12 months of age, though data pertaining to primary/secondary FPIES prevention do not exist. In such potentially dually-reactive children, it is recommended to perform supervised OFC to introduce the uncertain FPIES trigger.

Children with milk or soy FPIES may also have an increased likelihood of reacting to a solid food, most commonly rice or oat. However, current early feeding guidelines do not recommend delay in introducing complementary foods past 6 months of life because of FPIES.^{40 97 98} A practical ordering for introducing solid foods at about 6 months of age at home could start with fruits and vegetables, followed by other complementary foods, for example, red meats and then cereal grains. If an infant tolerates a variety of the early food proteins, subsequent introduction may be more liberal. Tolerance to one food from the food group is considered as a favorable prognostic indicator for tolerance of other foods from the same group.³⁵

In an infant with severe CM and or soy-FPIES, supervised (e.g. in-office) introduction of solid foods may be considered to promote implementation of normal dietary variety and prevent unnecessary avoidance. In such situations, especially, with parental apprehension regarding home introduction, supervised food challenge to a mixture of several solid foods may be considered as a way of excluding the risk of severe reactions to small amounts of the solid foods, followed by gradual build up to regular age-appropriate serving size at home [Miceli Sopo S, personal communication].

1127

1128 **Summary and assessment of future needs**

1129 Management of FPIES relies on dietary elimination of the offending foods, optimizing
1130 nutritional support and management, and providing prompt medical management of
1131 acute FPIES episodes. The cornerstone of management of acute FPIES is volume
1132 repletion to restore hemodynamic balance. Rigorous multi-center clinical trials are
1133 necessary to determine optimal management of the acute FPIES in regards to utilization
1134 of steroids and parenteral ondansetron as adjunct therapies. Regarding long-term
1135 management, optimal timing of the trigger food reintroduction, timing of potentially
1136 cross-reactive food introduction, incorporation of baked milk/egg, and preventative
1137 studies require further investigations. Finally, prospective studies should evaluate the
1138 evolution of specific IgE responses to the FPIES trigger food and determine the role for
1139 sIgE testing during follow up evaluations and decisions regarding the timing of OFCs.

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1141 **SECTION VII: Nutritional Management for FPIES**

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1143 **SUMMARY STATEMENT 24: Provide guidance during the introduction of**
1144 **complementary foods to ensure nutritional adequacy during this time and beyond.**

1145 **[Strength of Recommendation: Strong; Evidence Strength: IIb/III; Grade B/C]**

1146 There are many resources available which detail how to introduce solids into an infant's
1147 diet or prepare complementary (weaning) foods, though these are based on expert
1148 opinion and are not evidenced-based. (Table XII) Consultation with a dietician is highly

recommended to facilitate weaning needs. Parents may need encouragement and support particularly if they have previously not prepared many foods at home, or have limited experience with introducing new foods. It is commonly recommended that caregivers introduce a new food as a single ingredient and with high-risk trigger foods, waiting at least 4 days before introducing another food as sometimes it may take that long for a reaction to develop.⁹⁹

The American Academy of Pediatrics (AAP) recommends introducing complementary foods rich in iron and zinc at about 6 months of age.⁹³ Nutritionally rich complementary foods should be introduced in the diet of the infant with FPIES beginning with a few fruits and vegetables but then progressing to red meats for dietary sources of protein, iron and zinc and iron-fortified *alternative* grains (such as corn, quinoa, millet) to increase the likelihood of meeting the recommended dietary allowance (RDA) requirements for the child's age. A recent scientific opinion published by European Food Safety Authority stated that the dietary intakes of alpha-linolenic acid, docosahexaenoic acid, iron, vitamin D and iodine are low in infants and young children living in Europe and that zinc intake may also be below nutritional requirements. Consequently an appropriate supply of these nutrients should be ensured for infants considered to be at additional risk of having an inadequate intake of nutrients within their diet.¹⁰⁰ Infants and young children following a modified diet due to food allergies are more likely to have a lower intake of macro- and micronutrients than infants and young children not requiring an elimination diet.¹⁰¹⁻¹⁰³

Food allergic children have been noted deficiencies in energy, protein, vitamin A, vitamin D, calcium, iron and zinc and to a lesser extent thiamine, riboflavin and niacin.

¹⁰¹⁻¹⁰⁴ A broad-spectrum nutritional supplement could be considered, but this may limit food diversity. Infants and children with FPIES are at risk for significant dietary restrictions and nutritional deficiencies, due to parental anxiety about trying new foods. Limited food experiences can adversely affect food intake for many years to come. ¹⁰⁵ The National Institute of Allergy and Infectious Diseases (NIAID) Guidelines for the Diagnosis and Management of Food Allergies recommends individualizing dietary advice for food allergic children, though providing patients and families with 'standard' information, which can be given prior to the dietetic consultation, can be useful.¹ Providers should maintain the perspective that even single food elimination can be associated with significant nutritional deficiency if care is not taken to replace the major nutrients. ¹⁰⁶ Table XIII details the typical nutrients associated with the foods most commonly associated with FPIES.

Iron is a critical nutrient for the growth and development of the infant's central nervous system. Although breast milk has lower iron content than most iron-fortified formulas, it has greater iron bioavailability, and the prevalence of iron deficiency anemia is low (3%) among un-supplemented breastfed infants in the first 6 months of life. Normally, a breastfed infant will not require additional iron in the diet until after 6 months of age, when infant body stores normally become depleted. Exclusive breastfeeding beyond 6 months of age has been associated with increased risk of iron deficiency and iron deficiency anemia at 7-12 months of age.^{107 108-110} However, these studies did not report any limitation of the complementary foods in the infant's diets.

ESPGHAN suggests that >90% of the iron requirements of the breastfed infant should be met by complementary foods after the age of 6 months.¹¹¹ Low intake of iron-rich complementary foods (enriched cereal grains, legumes and meat) is associated with a higher prevalence of iron deficiency anemia in infants and young children.¹¹² In many countries iron-enriched cereals are one of the first complementary foods, which might not be an option for some infants with FPIES to grains. Therefore, alternative sources of iron may be important, such as beef and lamb, which are rarely associated with FPIES, as opposed to other iron-rich complementary foods such as enriched grains, poultry, fish, nuts, and legumes.^{3,6,12,13,33,113,114} If non-meat sources of high iron or iron-enriched complementary plant foods are chosen, they can be provided along with a food rich in vitamin C to improve bioavailability. This is consistent with AAP general feeding advice.

The AAP recommends iron supplementation (1 mg iron/kg body weight) after four months of age for infants who continue to breast feed exclusively, with maintenance of iron supplementation until appropriate iron-containing complementary foods have been introduced, and recommends iron-enriched formula for those infants who are bottle-fed.¹¹⁵ The AAP Committee on Breastfeeding has suggested consideration of screening *at-risk infants* for iron deficiency.^{115 116} ESPGHAN does not recommend universal supplementation of iron in infants between 4-6 months of age and recommends instead that iron-rich complementary foods be introduced during the complementary food period, no earlier than 17 weeks and no later than 24 weeks of age.¹¹¹ ESPGHAN does state, however, that preventative iron supplementation may be provided on an individual

basis to infants from high-risk groups if the infant has a low intake of iron-rich complementary food, Table XIII.¹¹²

SUMMARY STATEMENT 25: Do not routinely recommend avoidance of products with precautionary labeling statements in patients with FPIES.

[Strength of Recommendation: Weak; Evidence Strength: IV; Grade D]

It is difficult to predict what threshold doses (TD) may incite an acute FPIES reaction. No studies have identified a reliable TD for trigger foods in FPIES. Out of 28 children receiving diagnostic OFC to CM, 53.6% (15/28) tolerated 121 ml of milk and 82 % tolerated 50 ml before developing a reaction.¹¹ High TDs have been reported.¹² In patients undergoing fish OFC, 45.4% (5/11) developed a reaction after eating a half (9%) or a whole (36.4%) serving size of the trigger fish per age.¹¹⁷ However, further studies have reported a TD of only 0.15g of protein/kg body weight in 15 out of 16 (93.7%) cases of confirmed FPIES caused by CM, soy, egg, rice and oat.⁴² It is unknown if small and frequently ingested amounts of a trigger food can cause chronic (or subclinical) FPIES. Severe reactions due to very low TDs – even by trivial oral mucosal contact – have been reported¹¹⁸ as well as a progressive reduction of TDs in the event of a repeated episode of contact/ingestion of the trigger food.¹¹⁹ Therefore, strict avoidance of trigger foods is recommended.

Regarding products with precautionary statements, only CM, egg, and peanut precautionary statements have been evaluated for associated risk. Crotty *et al.* reported that products with milk precautionary statements had detectable amounts of

milk ranging from 0.027 to 620 mg (non-fat milk powder) per serving, and as high as ~0.22 grams milk protein per serving (~6.5 ml fluid CM).¹²⁰ However, based on the estimated reports of TD for patients with CM-FPIES, these amounts are unlikely to trigger a reaction. Risk for soy precautionary statements has not been evaluated, and consumers are unlikely to find precautionary statements for other common FPIES triggers (e.g., rice, oats, legumes, poultry etc.).

SUMMARY STATEMENT 26: Use hypoallergenic extensively hydrolyzed or amino acid-based formula in formula-fed infants or infants that can no longer breast feed who are diagnosed with FPIES due to CM. [Strength of Recommendation: Strong; Evidence Strength: IIa/IIb; Grade B]

The NIAID Guidelines for the Diagnosis and Management of Food Allergies⁶⁷ recommend a hypoallergenic formula for the treatment of FPIES based on several studies demonstrating most children tolerated extensively hydrolyzed formula (eHF), though there are selected children that only can tolerate amino acid based formula.^{15 10}¹²¹⁻¹²³ The Australasian Consensus guidelines recommend the use of casein-based eHF (eHFc) for the treatment of FPIES, given that the beta-lactoglobulin levels and peptide sizes of CM protein in breast milk and those of eHFc stretch across the same ranges.^{124, 125-128} Thus, children tolerant of CM proteins transferred via breast milk should theoretically tolerate the residual CM peptides in eHFc.

The Diagnosis and Rationale for Action against CM Allergy (DRACMA) guidelines from the World Allergy Organization (WAO) recommend the use of eHF for FPIES.¹²⁹ The European Society for Paediatric Gastroenterology, Hepatology and Nutrition

(ESPGHAN) and the European Academy of Allergy and Clinical Immunology guidelines recommend the use of extensively hydrolyzed formulas for all forms of CM allergy.^{130 98} However, amino acid-based formulas are the only completely non-allergenic formula and they can be effective in patients not responding to extensively hydrolyzed formulas and other sub-groups of children. These include infants with severe growth faltering, those with CM protein allergy with severe symptoms, and non-IgE-mediated syndromes such as food protein-induced enterocolitis and enteropathies, eosinophilic gastroenteropathies. The United Kingdom National Institute of Clinical Excellence (UK NICE) guidelines make no recommendation on formula choice, however.¹³¹

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

SUMMARY STATEMENT 27: Monitor growth (weight and height/length) regularly in all children with FPIES. [Strength of Recommendation: Moderate; Evidence Strength: III; Grade C]

Nowak *et al.* and others have reported infants with FPIES to CM or soy exposed to these proteins on a daily basis typically manifest poor weight gain, weight loss or failure to thrive that resolves with elimination of the implicated food.^{13,21,35,48,114} Poor growth in children with FPIES who have successfully eliminated the implicated food and are subsequently without symptoms has not been reported. Nonetheless, children with inadequate intake of energy, protein and certain micronutrients (e.g., iron and zinc) will

be at increased risk of inadequate growth; hence infants with FPIES and multiple food avoidances or difficulty advancing the diet may be at increased risk.

Food allergy is a risk for poor growth and inadequate nutrient intake^{101,102,132,133} Meyer *et al.* reported that food allergic children were more underweight than the general UK population.¹³⁴ Additionally, elimination of 3 or more foods had a significant impact on weight-for-age. Christie *et al.* reported on an age-matched, consecutive sampling, cross-sectional study of 98 children with food allergy and 99 without and found children with 2 or more food allergies were shorter based on height-for-age percentiles than those with one food allergy.¹⁰¹ Isolauri *et al.* also reported that in CM allergy mean length-for-age and weight-for-length were significantly decreased compared to healthy, age-matched controls.¹³² In this cohort, poor growth was more pronounced in a subset of patients with early onset of food allergy, but not associated with the number of foods eliminated. NIAID Guidelines for the Diagnosis and Management of Food Allergies recommend close growth monitoring of all children with food allergy.¹ Growth (weight, length/height, head circumference) should be assessed at regular intervals based on national standards.^{135,136}

SUMMARY STATEMENT 28: Recommend foods that will enhance developmental skills in infants in the complementary feeding period to prevent the delay in the development of food acceptance and feeding skills or the onset of aversive feeding behaviors. [Strength of Recommendation: Weak; Strength of Evidence: IV; Grade: D]

Timely introduction of a variety of tastes and textures has been reported to directly affect the development of flavor acceptance, feeding skills and eating behaviors.¹³⁷⁻¹⁴³ Children may have difficulty in acquiring specific oral motor feeding skills when foods are not introduced during critical periods and as such, when textured foods are introduced beyond 10 months of age, children are more likely to refuse solid foods.¹⁴² Northstone *et al.* noted that infants introduced to lumpy foods later (10 months of age or older) were more difficult to feed and had more distinct likes and dislikes. Finding appropriate flavors and textures for infants and children with FPIES may require some creativity when multiple solid foods are restricted.¹⁴³ Avoidance of a greater number of foods may increase the likelihood of food refusal and aversions. Many textures may be provided even if only one food is tolerated. For instance, a fruit or vegetable may be prepared into a thin or thick puree, served with lumps and bumps, soft cooked for finger foods or freeze-dried or fried/oven-baked in refined oil for a crispy, crunchy texture.

Summary and assessment of future needs

Nutritional management is critically important in FPIES. When the initial complementary feeding schedule is altered, nutrients may be inadvertently omitted potentially placing infants at risk of nutrient deficiencies. Infants with FPIES will benefit from nutritional evaluation and guidance. These at-risk infants may also benefit from laboratory assessment of iron status. Future studies should systematically evaluate the prevalence of nutrient deficiencies, poor growth and feeding difficulties in FPIES and provide guidance for preventative intervention.

SECTION VIII: Natural History of FPIES

SUMMARY STATEMENT 29: Recognize that the age of development of tolerance in FPIES varies by type of food trigger, and by country of origin. [Strength of Recommendation: Strong; Evidence strength IIa/IIb; Grade B]

The development of tolerance in patients with milk and soy FPIES has been reported to occur at an earlier age than grains or other foods induced FPIES. However, significant heterogeneity and potential selection bias exists in the available data regarding tolerance development in FPIES, and may significantly influence these estimates. There is significant difference noted in this timing internationally, as well. The average reported age for developing tolerance to grains is 35 months, and is 42 months for other solid foods. For soy-induced FPIES, the average reported age for tolerance is approximately 12 months, but ranges from 6 months to >22 years of age.^{5,4,144,17} In a large population-based cohort study from Israel, for milk-induced FPIES, 60% developed tolerance by 1 year, 75% by 2 years, and 85% by 3 years.¹¹ In a large US case series, the median age of resolution was 6.7 years. However, data from a challenge-based study in Korea noted that significant rates of resolution to milk and to soy FPIES may occur more rapidly (12 and 6 months, respectively), than previously assumed.¹⁷ In pooling the available data from multiple small cohorts, the age of tolerance to milk appears to be around 3 years of age, but two recent large cohorts found a later age of tolerance.^{5,6,11,12,16,17,38,42,43,55,60,72,76,119,122,144-149} However, these data come from reports of tolerance, and were not derived from a targeted study to determine a firm age of resolution, and thus may be biased towards older ages. In a large US case series, the median age of resolution for milk FPIES was 5.1 years, and in

the United Kingdom, 25% of the patients had milk FPIES persist at 8 years of age.^{5,134}
 In contrast, data from the same large US case series noted median ages of resolution
 were 4.7 years for rice, and 4.0 years for oat. Several studies have noted that patients
 with IgE positive skin test to milk and milk FPIES have a more protracted course and
 older age of tolerance (~13.8 years) compared to patients with negative skin test.⁴

**SUMMARY STATEMENT 30: Evaluate patients with FPIES at regular intervals,
 according to the patient's age and the food allergen, to determine if he/she is still
 allergic. [Strength of Recommendation: Strong; Evidence Strength IIb/III; Grade:
 C]**

The ideal timing of OFC to determine resolution has not been systematically studied but
 may vary considerably by nation, as well as by individual provider preference. In the US,
 diagnostic OFC is usually attempted within 12-18 months following the most recent
 reaction.^{3,35} However, Korean data suggest children may be ready within a year of
 diagnosis, with tolerance rates to milk and soy 27% and 75% at 6 months, 42% and
 91% and 8 months, and 64% and 92% at 10 months, respectively.¹⁷ Milk-FPIES
 resolved in all children by age 2 years and soy-FPIES resolved by age 14 months--50%
 of milk-FPIES resolved within first year of life, 89% by age 2 years and 90% by age 3
 years.¹¹ In contrast, retrospective series from the US report lower rates of resolution of
 FPIES to milk or soy, 35% by age 2 years, 70% by age 3 years and 85% by age 5
 years.^{5 4} These differences likely reflect various study designs, provider preferences,
 international differences in the approach to such patients, or selection bias towards
 more severe and persistent phenotype among children evaluated at the referral allergy

centers compared to those identified from the general population. There are no data on resolution of FPIES to seafood in older children and adults. Periodic re-evaluations should be similarly considered in adult patients.

Summary and assessment of future needs

Longitudinal cohorts are needed to better determine outcomes and natural history of FPIES, including associations with other immune mediated adverse food reactions, and time to develop tolerance. Geographic variability is evident in terms of reported timing of development of tolerance to triggers, and studies are needed to better understand the nature of such variation.

CONCLUSIONS

The consensus document provides the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES. It also identifies the unmet needs and future directions for research. Research on prevalence, pathophysiology, diagnostic markers, and future treatments is necessary to improve the care of patients with FPIES. These guidelines will be updated periodically, as more evidence becomes available.

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TABLE I Proposed defining features for clinical phenotyping of FPIES

FPIES subtypes	Defining features
Age of onset	
Early	Younger than age 9 months
Late	Older than age 9 months
Severity	
Mild-moderate	Repetitive emesis with or without diarrhea, pallor, mild lethargy
Severe	Repetitive, projectile emesis with or without diarrhea, pallor, lethargy, dehydration, hypotension, shock, methemoglobinemia, metabolic acidosis
Timing and duration of symptoms	
Acute	Occurs with intermittent food exposures, emesis starts usually within 1-4 hours, accompanied by lethargy and pallor; diarrhea may follow within 24 hours, usual onset 5-10 hours. Usual resolution of symptoms within 24 hours following elimination of the food from the diet. Growth is normal and child is asymptomatic during food trigger elimination.
Chronic	Occurs with daily ingestion of the food (e.g., feeding with cow milk or soy-based formula in an infant), symptoms include intermittent emesis, chronic diarrhea, poor weight gain or failure to thrive. Infants with chronic FPIES usually return to their usual state of health within 3 to 10 days of switching to a hypoallergenic formula, although in severe cases, temporary bowel rest and intravenous fluids may be necessary. Subsequent feeding of the offending food following a period of avoidance results in the acute symptoms.
IgE positivity	
Classic	Food-specific IgE- negative
Atypical	Food-specific IgE- positive

TABLE II Proposed defining features of mild and severe acute FPIES

	Mild – moderate acute FPIES	Severe acute FPIES
Clinical features	Required • Vomiting (onset usually 1-3 hours, may range 30 minutes-6 hours): few episodes of intermittent vomiting (1-3), may be bilious • Decreased activity level • Pallor • Self-resolving, the child is able to tolerate oral rehydration at home Optional • Mild watery diarrhea, onset usually within 24 hours, may be bloody (occasionally)	Required • Vomiting (onset usually 1-4 hours, may range 30 minutes-6 hours): projectile (forceful), repetitive (4 or more), bilious and dry heaving • Altered behavior ranging from decreased activity to lethargy • Pallor • Dehydration • Requires intravenous hydration Optional • Hypotension • Abdominal distention • Hypothermia • Diarrhea, onset usually within 24 hours, may be bloody • Hospitalization
Laboratory features (optional, when available)	• Elevated white blood cell count with neutrophilia • Thrombocytosis • Stool may be positive for leukocytes, eosinophils or increased carbohydrate content	• Elevated white blood cell count with neutrophilia • Thrombocytosis • Metabolic acidosis • Methemoglobinemia • Stool may be positive for leukocytes, eosinophils or increased carbohydrate content

TABLE III Differential diagnosis of FPIES

Condition	Features that may distinguish from FPIES
Infectious gastroenteritis (e.g. viral, bacterial)	Single episode of illness, fever, sick contacts
Sepsis	Fluid resuscitation alone not effective
Necrotizing enterocolitis (NEC)	Newborns and younger infants, rapid escalation of symptoms, bloody stools, shock, intramural gas on abdominal radiographs
Anaphylaxis	Symptoms begin within minutes to 2 hours of exposure, positive IgE testing, usually other manifestations (e.g. urticaria)
Food aversion	Look at the familial context
Inborn errors of metabolism: Urea cycle defects, Hereditary fructose intolerance, hyperammonemic syndromes, propionic /methylmalonic aciduria, beta-oxidations defects, hyperinsulinism-hyperammonemia syndrome, Pyruvate dehydrogenase deficiency, mitochondrial disorders, maple syrup urine disease, ketothiolase deficiency.	Developmental delay, neurologic manifestations, organomegaly, reaction to fruits
Lactose intolerance	In severe form, gas, bloating, cramps, diarrhea, borborygmi and vomiting following ingestion of liquid milk and large doses of dairy products with lactose
Neurologic disorders (e.g. cyclic vomiting)	No relation to specific food intake
Gastrointestinal reflux disease	Emesis more chronic and not usually severe (i.e. does not lead to dehydration), only upper GI symptoms present
Hirschsprung's disease	Delay in passage of the first meconium, marked abdominal distention
Food protein-induced enteropathy	Symptoms usually not temporarily associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, most commonly implicated foods cow milk, soy, wheat, egg white
Eosinophilic gastroenteropathies (e.g. eosinophilic esophagitis, eosinophilic gastroenteritis)	Usually not associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, more likely to have positive IgE tests

Celiac disease	No temporal relationship between symptoms and specific food intake; progressive malabsorption; celiac serology is positive
Immune enteropathies (e.g. inflammatory bowel disease, autoimmune enteropathy, immunodeficiency)	Rare in infancy, not related to specific food intake
Obstructive problems (e.g. malrotation, Ladd's bands, volvulus)	Not related to specific food intake, evidence of obstruction on radiological studies
Coagulation defects	No relation to specific food intake
Alpha1-antitrypsine deficiency	No relation to specific food intake; hepatic involvement
Primary immunodeficiencies	No relation to specific food intake; intestinal symptoms, frequent infections.

TABLE IV Diagnostic criteria for patients presenting with possible FPIES

Acute FPIES	
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: 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4 hours after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency room visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 hours (usually 5-10 hours) 8. Hypotension 9. Hypothermia
The diagnosis of FPIES requires that a patient meets the major criterion and at least 3 minor criteria. If only a single episode has occurred, a diagnostic oral food challenge should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group. Further, while not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours, compared to the usual several day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.	
Chronic FPIES	
Severe presentation: when the offending food is ingested in on a regular basis [e.g., infant formula] Intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with	The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days following elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 hours, diarrhea in 24 hours (usually 5-10 hours). Without confirmatory challenge,

dehydration and metabolic acidosis.

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

the diagnosis of chronic FPIES remains presumptive.

TABLE V Diagnostic criteria for the interpretation of oral food challenges in patients with a history of possible or confirmed FPIES

Major criterion	Minor criteria
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	1. Lethargy 2. Pallor 3. Diarrhea in 5-10 hours after food ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of at least 1500 neutrophils above the baseline count
The OFC will be considered diagnostic of FPIES, i.e. positive, if the major criterion is met with at least two minor criteria. However, we would suggest two important caveats to these criteria: 1) with the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor and lethargy may be averted; and 2) not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore, the treating physician may decide that a challenge be considered diagnostic in some instances even if only the major criterion was met. However, in challenges performed for research purposes, stringent criteria for challenge positivity should be adhered to.	

TABLE VI Management of acute FPIES episode at the medical facility

Presenting Symptoms		
Mild	Moderate	Severe
Symptoms		
1-2 episodes of emesis No lethargy	> 3 episodes of emesis and mild lethargy	>3 episodes of emesis, with severe lethargy, hypotonia, ashen or cyanotic appearance
Management		
1. Attempt oral re-hydration (e.g., breast-feeding or clear fluids) 2. If age 6 months and older: Consider ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 3. Monitor for resolution about 4-6 hours from the onset of a reaction	1. If age older than 6 months: administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 2. Consider placing a peripheral intravenous line for normal saline bolus 20 ml/kg, repeat as needed 3. Transfer the patient to the emergency department or intensive care unit in case of persistent or severe hypotension, shock, extreme lethargy, or respiratory distress 4. Monitor vital signs 5. Monitor for resolution at least 4-6 hours from the onset of a reaction 6. Discharge home if patient is able to tolerate clear liquids	1. Place a peripheral intravenous line and administer normal saline bolus 20 ml/kg rapidly, repeat as needed to correct hypotension 2. If age 6 months and older: administer intravenous ondansetron 0.15 mg/kg/dose, maximum 16 mg/dose 3. If placement of intravenous line is delayed due to difficult access and age is 6 months or older administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 4. Consider administering intravenous methylprednisolone 1 mg/kg, maximum 60 to 80 mg/dose 5. Monitor and correct acid base and electrolyte abnormalities 6. Correct methemoglobinemia if present 7. Monitor vital signs 8. Discharge after 4-6 hours from the onset of a reaction when the patient is back to baseline and is tolerating oral fluids 9. Transfer the patient to the emergency department or intensive care unit for further management in case of persistent or severe hypotension, shock, extreme lethargy, respiratory distress

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

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

TABLE VII Management of acute FPIES episode at home

- A. Child **with history of severe FPIES reaction**: call 911 or go to the emergency department if the triggering food was definitely ingested, even in the absence of symptoms or with any symptoms regardless of severity
- B. Child **with no history of severe FPIES reaction**

Current episode	Mild	Moderate-severe
Symptoms	1-2 episodes of emesis No or mild lethargy	More than 3 episodes of emesis and moderate-severe lethargy
Management	Attempt oral re-hydration at home (e.g., breast-feeding or clear fluids)	Call 911 or go to the emergency room

TABLE VIII Common food co-allergies in children with FPIES

FPIES to	Clinical cross-reactivity/co-allergy	Observed Occurrence*
Cow's milk	Soy	<30-40%
	Any solid food	<16%
Soy	Cow's Milk	<30-40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow's milk or soy	<25%
Legumes*	Soy	<80%
Grains: rice, oats, etc*	Other grains (including rice)	about 50%
Poultry*	Other poultry	<40%

*Note: where a child already tolerates a food type in a particular group (e.g. beans), clinical reactions to other members of the same group (e.g. other legumes) are unlikely. Caution is warranted in interpreting these data as they were derived from single centers and from patient populations skewed towards the more severe phenotype of FPIES and may overestimate the actual risk of co-allergy.

TABLE IX Empiric guidelines for selecting weaning foods in infants with FPIES

Ages and Stages	Lower risk foods*	Moderate risk foods*	Higher risk foods*
4-6 months (as per AAP, CoN) If developmentally appropriate and safe and nutritious foods are available. ➤ Begin with smooth, thin, purees and progress to thicker purees ➤ Choose foods that are high in iron ➤ Add vegetables and fruits 6 months (as per WHO) Complementary feeding should begin no later than 6 months of age. ➤ In the breast fed infant, high iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age. ➤ Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated. 8 months of age or when developmentally appropriate. ➤ Offer soft-cooked and bite-and-dissolve textures from around 8 months of age or as tolerated by infant. 12 months of age or when developmentally appropriate. ➤ Offer modified tolerated foods from the family table-chopped meats, soft cooked vegetables, grains and fruits.	Vegetables		
	Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
	Fruits		
	Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
	High iron foods		
	Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Higher iron foods: Fortified, infant rice and oat cereals.
	Other		
	Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish

This table should be considered in the context of the following notes:

- Exclusive breast feeding until 4-6 months of age and continuing breast feeding through the first year of life or longer as long as mutually desired by both mother and child.¹
- If an infant tolerates a variety of early foods, subsequent introduction may be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered as a favorable prognostic indicator for tolerance of other foods from the same group (legumes).²

AAP, CoN= American Academy of Pediatrics, Committee on Nutrition; WHO= World Health Organization

* Risk assessment is based on the clinical experience and the published reports of FPIES triggers.

1. Baker RD, Greer FR, Committee on Nutrition American Academy of P. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 2010;126:1040-50.

2. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *The Journal of allergy and clinical immunology* 2005;115:149-56.

Box 1 Grading of evidence and criteria for strength of recommendation

Category of evidence

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least one randomized controlled trial
- IIa Evidence from at least one controlled study without randomization
- IIb Evidence from at least one other type of quasi-experimental study
- III Evidence from non-experimental descriptive studies, such as comparative studies
- IV Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

Strength of recommendation*

- A Directly based on category I evidence
- B Directly based on category II evidence or extrapolated recommendation from category I evidence
- C Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence
- LB Laboratory Based
- NR Not rated

TABLE I Recommendation Rating Scale

Statement	Definition	Implication
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B)*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.

Moderate (Mod)	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C)*. In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak (Weak)	An option means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.

TABLE II Proposed defining features for clinical phenotyping of FPIES

FPIES subtypes	Defining features
Age of onset	
Early	Younger than age 9 months
Late	Older than age 9 months
Severity	
Mild-moderate	Repetitive emesis with or without diarrhea, pallor, mild lethargy
Severe	Repetitive, projectile emesis with or without diarrhea, pallor, lethargy, dehydration, hypotension, shock, methemoglobinemia, metabolic acidosis
Timing and duration of symptoms	
Acute	Occurs with intermittent food exposures, emesis starts usually within 1-4 hours, accompanied by lethargy and pallor; diarrhea may follow within 24 hours, usual onset 5-10 hours. Usual resolution of symptoms within 24 hours following elimination of the food from the diet. Growth is normal and child is asymptomatic during food trigger elimination.
Chronic	Occurs with daily ingestion of the food (e.g., feeding with cow milk or soy-based formula in an infant), symptoms include intermittent emesis, chronic diarrhea, poor weight gain or failure to thrive. Infants with chronic FPIES usually return to their usual state of health within 3 to 10 days of switching to a hypoallergenic formula, although in severe cases, temporary bowel rest and intravenous fluids may be necessary. Subsequent feeding of the offending food following a period of avoidance results in the acute symptoms.
IgE positivity	
Classic	Food-specific IgE- negative
Atypical	Food-specific IgE- positive

TABLE III Proposed defining features of mild and severe acute FPIES

	Mild – moderate acute FPIES	Severe acute FPIES
Clinical features	Required • Vomiting (onset usually 1-4 hours, may range 30 minutes-6 hours): few episodes of intermittent vomiting (1-3), may be bilious • Decreased activity level • Pallor • Self-resolving, the child is able to tolerate oral rehydration at home Optional • Mild watery diarrhea, onset usually within 24 hours, may be bloody (occasionally)	Required • Vomiting (onset usually 1-4 hours, may range 30 minutes-6 hours): projectile (forceful), repetitive (4 or more), bilious and dry heaving • Altered behavior ranging from decreased activity to lethargy • Pallor • Dehydration • Requires intravenous hydration Optional • Hypotension • Abdominal distention • Hypothermia • Diarrhea, onset usually within 24 hours, may be bloody • Hospitalization
Laboratory features (optional, when available)	• Elevated white blood cell count with neutrophilia • Thrombocytosis • Stool may be positive for leukocytes, eosinophils or increased carbohydrate content	• Elevated white blood cell count with neutrophilia • Thrombocytosis • Metabolic acidosis • Methemoglobinemia • Stool may be positive for leukocytes, eosinophils or increased carbohydrate content

TABLE IV Age of onset or diagnosis of FPIES (cow milk/soy vs. solid food triggers)*

Reference	Country	Only CM/soy FPIES investigated	Overall age of onset/ diagnosis (months)	Age onset/diagnosis of cow milk/soy FPIES (months)	Age onset/diagnosis of solid FPIES (months)	Atypical FPIES*	
						SPT	ssIgE
Nomura et al	Japan	Y (CM)	-	0.28 (0.1-0.82)** 0.59 (0.34-0.1.20) #	-	-	8/14 (57%) 6/16 (38%)#
Powell	USA	Y (CM)	-	0.46 (0.14-2.39)	-	-	-
Gryboski	USA	Y (CM)	-	0.25 (0.07-4)	-	-	-
Katz et al	Israel	Y (CM)	-	1 (0-6.4)	-	2/44 (5%)	-
Nowak-Wegrzyn et al	USA	N	-	1 (0.08-12)	5.5 (3-7)	0/44 (0%)	3/44 (7%)
McDonald et al	USA	Y (CM/soy)	-	1 (0.04-3)	-	-	-
Hwang et al	South Korea	Y (CM/soy)	-	1.28 (0.46-2.1)	-	-	-
Chung et al	South Korea	Y (CM)	1.75 (-)	1.75 (-)	-	0/28 (0%)	0/28 (0%)
Sicherer et al	USA	N	2 (0.25-108)	2.0 (0.25-108)	6 (5-24)	1/20 (5%)	5/20 (25%)
Fogg et al	USA	N	2 (0.25-9)	2 (0.25-4)	4.5 (4-9)	-	-
Sopo et al	Italy	N	5.1 (5.10)	3.5 (2.40) ###	10.6 (6.70)	0/66 (0%)	-
Mehr et al	Australia	N	5.6 (2.70)	4.9 (2.60)	6.1 (1.70)	1/35(3%)	-
Caubet et al####	USA	N	4 (2-6)	5 (2-10)	7 (6-12)	39/160 (24%) had positive SPT and/or ssIgE	
Ruffner et al	USA	N	9.7 (10.20)	7 (0.70)	12.1 (1.10)	26/721 (4%)	-

*Data from studies where age onset/diagnosis recorded. Data represented as either mean age onset/diagnosis (standard deviation) or median age of onset/diagnosis (range) unless otherwise specified

**Figure relates to cluster 1 analysis and #relates to cluster 2 analysis performed (both clusters representative of FPIES cases)

Figure relates to cow milk FPIES only (3 soy cases included with other foods)

Data represented as a median (interquartile range)

TABLE V Case series examining cases of FPIES*

Reference	Year	Study design	Definition used	Country	No. patients	Duration study (yrs)	Data on all triggers [#]	Center	Male (%)	Eczema (%)	IgE FA (%) [#]
Caubet et al	2014	Prospective + retrospective	Their own (modified Powell)	USA	160	10	Yes+; CM, soy, rice, oat, seafood	One allergy clinic	54	57	11
Ruffner et al	2013	Retrospective	Their own	USA	462	5	Yes; CM, soy, rice, oat, egg	One hospital	60	34	-
Fogg et al	2006	Prospective	Sicherer et al	USA	19	1.5	Yes; CM, soy, rice, oat, egg	Single allergy clinic	53	11	-
Nowak-Wegrzyn et al	2003	Retrospective	Sicherer et al	USA	44	5	Yes; CM, soy, rice, oat, barley	2 allergy clinics	59	34	-
Sicherer et al	1998	Retrospective	Their own	USA	20	6	Yes; CM, soy, rice, green pea, poultry	Single allergy clinic	44	31**	15
Burks et al	1994	Prospective	Their own	USA	22	1.5	CM/soy	One hospital	-	-	-
McDonald et al	1984	Prospective	Powell	USA	10	-	CM/soy	One hospital	-	-	-
Powell ^{###}	1976	Retrospective	Their own	USA	9	-	CM/soy	Their own	-	-	-
Gryboski ^{###}	1967	Retrospective	None set	USA	21	16	CM	One hospital	90	14	-
Katz et al	2011	Prospective	Sicherer et al	Israel	44	2	CM	One hospital	52	7 [#]	-
Levy and Danon	2003	Retrospective	Their own	Israel	6	6	Solid food triggers; chicken, turkey, green pea, lentil	One hospital	67	-	-
Hsu and Mehr	2012	Retrospective	Sicherer et al	Australia	38	4	Yes, but only egg presented	One hospital	53	-	-
Mehr et al	2009	Retrospective	Sicherer et al	Australia	35	16	Yes; rice, soy, CM, vegetables	Single allergy clinic	57	51	11
Nomura et al	2011	Retrospective	Powell	Japan	30	3	CM	Japanese database	50	-	-
Hwang et al	2009	Prospective	Powell	Korea	23	4	CM/soy	One hospital	70	0	-
Chung et al	2002	Prospective	Sicherer et al	Korea	28	-	CM	One hospital	-	-	-
Sopo et al	2012	Retrospective	Their own/Powell	Italy	66	7	Yes; CM, fish, egg, rice	Three allergy clinics	61	9	2

*Case series only included where a definition of FPIES provided and consecutive cases presenting to a health care setting were examined

**Data only available for infants with typical FPIES ($n=16$)

[#]CM, cow milk; -, not available; PC, personal communication with corresponding author; FA = IgE-mediated food allergy (that is positive sIgE- and IgE-mediated clinical reaction to a separate food protein not causing FPIES).

+ Most common food allergens listed

^{###}In these series, chronic FPIES or a combination of cases of acute/chronic FPIES was reported.

TABLE VI Differential diagnosis of FPIES

Condition	Features that may distinguish from FPIES
Infectious gastroenteritis (e.g. viral, bacterial)	Single episode of illness, fever, sick contacts
Sepsis	Fluid resuscitation alone not effective
Necrotizing enterocolitis (NEC)	Newborns and younger infants, rapid escalation of symptoms, bloody stools, shock, intramural gas on abdominal radiographs
Anaphylaxis	Symptoms begin within minutes to 2 hours of exposure, positive IgE testing, usually other manifestations (e.g. urticaria)
Food aversion	Look at the familial context
Inborn errors of metabolism: Urea cycle defects, Hereditary fructose intolerance, hyperammonemic syndromes, propionic /methylmalonic aciduria, beta-oxidations defects, hyperinsulinism-hyperammonemia syndrome, Pyruvate dehydrogenase deficiency, mitochondrial disorders, maple syrup urine disease, ketothiolase deficiency.	Developmental delay, neurologic manifestations, organomegaly, reaction to fruits
Lactose intolerance	In severe form, gas, bloating, cramps, diarrhea, borborygmi and vomiting following ingestion of liquid milk and large doses of dairy products with lactose
Neurologic disorders (e.g. cyclic vomiting)	No relation to specific food intake
Gastrointestinal reflux disease	Emesis more chronic and not usually severe (i.e. does not lead to dehydration), only upper GI symptoms present
Hirschsprung's disease	Delay in passage of the first meconium, marked abdominal distention
Food protein-induced enteropathy	Symptoms usually not temporarily associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, most commonly implicated foods cow milk, soy, wheat, egg white
Eosinophilic gastroenteropathies (e.g. eosinophilic esophagitis, eosinophilic gastroenteritis)	Usually not associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, more likely to have positive IgE tests

Celiac disease	No temporal relationship between symptoms and specific food intake; progressive malabsorption; celiac serology is positive
Immune enteropathies (e.g. inflammatory bowel disease, autoimmune enteropathy, immunodeficiency)	Rare in infancy, not related to specific food intake
Obstructive problems (e.g. malrotation, Ladd's bands, volvulus)	Not related to specific food intake, evidence of obstruction on radiological studies
Coagulation defects	No relation to specific food intake
Alpha1-antitrypsine deficiency	No relation to specific food intake; hepatic involvement
Primary immunodeficiencies	No relation to specific food intake; intestinal symptoms, frequent infections.

TABLE VII Diagnostic criteria for patients presenting with possible FPIES

Acute FPIES	
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: 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4 hours after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency room visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 hours (usually 5-10 hours) 8. Hypotension 9. Hypothermia
The diagnosis of FPIES requires that a patient meets the major criterion and at least 3 minor criteria. If only a single episode has occurred, a diagnostic oral food challenge should be strongly considered to confirm the diagnosis, especially since viral gastroenteritis is so common in this age group. Further, while not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours, compared to the usual several day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.	
Chronic FPIES	
Severe presentation: when the offending food is ingested in on a regular basis [e.g., infant formula] Intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with	The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days following elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 hours, diarrhea in 24 hours (usually 5-10 hours). Without confirmatory challenge,

dehydration and metabolic acidosis.

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

the diagnosis of chronic FPIES remains presumptive.

TABLE VIII Diagnostic criteria for the interpretation of oral food challenges in patients with a history of possible or confirmed FPIES

Major criterion	Minor criteria
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	1. Lethargy 2. Pallor 3. Diarrhea in 5-10 hours after food ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of at least 1500 neutrophils above the baseline count
The OFC will be considered diagnostic of FPIES, i.e. positive, if the major criterion is met with at least two minor criteria. However, we would suggest two important caveats to these criteria: 1) with the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor and lethargy may be averted; and 2) not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore, the treating physician may decide that a challenge be considered diagnostic in some instances even if only the major criterion was met. However, in challenges performed for research purposes, stringent criteria for challenge positivity should be adhered to.	

Table IX Management of acute FPIES episode at the medical facility

Presenting Symptoms		
Mild	Moderate	Severe
Symptoms		
1-2 episodes of emesis No lethargy	> 3 episodes of emesis and mild lethargy	>3 episodes of emesis, with severe lethargy, hypotonia, ashen or cyanotic appearance
Management		
1. Attempt oral re-hydration (e.g., breast-feeding or clear fluids) 2. If age 6 months and older: Consider ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 3. Monitor for resolution about 4-6 hours from the onset of a reaction	1. If age older than 6 months: administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 2. Consider placing a peripheral intravenous line for normal saline bolus 20 ml/kg, repeat as needed 3. Transfer the patient to the emergency department or intensive care unit in case of persistent or severe hypotension, shock, extreme lethargy, or respiratory distress 4. Monitor vital signs 5. Monitor for resolution at least 4-6 hours from the onset of a reaction 6. Discharge home if patient is able to tolerate clear liquids	1. Place a peripheral intravenous line and administer normal saline bolus 20 ml/kg rapidly, repeat as needed to correct hypotension 2. If age 6 months and older: administer intravenous ondansetron 0.15 mg/kg/dose, maximum 16 mg/dose 3. If placement of intravenous line is delayed due to difficult access and age is 6 months or older administer ondansetron intramuscular 0.15 mg/kg/dose, maximum 16 mg/dose 4. Consider administering intravenous methylprednisolone 1 mg/kg, maximum 60 to 80 mg/dose 5. Monitor and correct acid base and electrolyte abnormalities 6. Correct methemoglobinemia if present 7. Monitor vital signs 8. Discharge after 4-6 hours from the onset of a reaction when the patient is back to baseline and is tolerating oral fluids 9. Transfer the patient to the emergency department or intensive care unit for further management in case of persistent or severe hypotension, shock, extreme lethargy, respiratory distress

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

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

TABLE X Management of acute FPIES episode at home

- A. Child **with history of severe FPIES reaction**: call 911 or go to the emergency department if the triggering food was definitely ingested, even in the absence of symptoms or with any symptoms regardless of severity
- B. Child **with no history of severe FPIES reaction**

Current episode	Mild	Moderate-severe
Symptoms	1-2 episodes of emesis No or mild lethargy	More than 3 episodes of emesis and moderate-severe lethargy
Management	Attempt oral re-hydration at home (e.g., breast-feeding or clear fluids)	Call 911 or go to the emergency room

TABLE XI Common food co-allergies in children with FPIES

FPIES to	Clinical cross-reactivity/co-allergy	Observed Occurrence*
Cow's milk	Soy	<30-40%
	Any solid food	<16%
Soy	Cow's Milk	<30-40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	Cow's milk or soy	<25%
Legumes*	Soy	<80%
Grains: rice, oats, etc*	Other grains (including rice)	about 50%
Poultry*	Other poultry	<40%

*Note: where a child already tolerates a food type in a particular group (e.g. beans), clinical reactions to other members of the same group (e.g. other legumes) are unlikely. Caution is warranted in interpreting these data as they were derived from single centers and from patient populations skewed towards the more severe phenotype of FPIES and may overestimate the actual risk of co-allergy.

TABLE XII Empiric guidelines for selecting weaning foods in infants with FPIES

Ages and Stages	Lower risk foods*	Moderate risk foods*	Higher risk foods*
4-6 months (as per AAP, CoN) If developmentally appropriate and safe and nutritious foods are available. ➤ Begin with smooth, thin, purees and progress to thicker purees ➤ Choose foods that are high in iron ➤ Add vegetables and fruits	Vegetables		
	Broccoli, cauliflower, parsnip, turnip, pumpkin	Squash, carrot, white potato, green bean (legume)	Sweet potato, green pea (legume)
	Fruits		
	Blueberries, strawberries, plum, watermelon, peach, avocado	Apple, pear, orange	Banana
	High iron foods		
	Lamb, fortified quinoa cereal, millet	Beef, fortified grits and corn cereal, wheat (whole wheat and fortified), fortified barley cereal	Fortified, infant rice and oat cereals.
6 months (as per WHO) Complementary feeding should begin no later than 6 months of age. ➤ In the breast fed infant, high iron foods or supplemental iron (1 mg/kg/day) is suggested by 6 months of age. ➤ Continue to expand variety of fruits, vegetables, legumes, grains, meats and other foods as tolerated.	Other		
	Tree nuts and seed butters* (sesame, sunflower, etc.) *Thinned with water or infant puree for appropriate infant texture and to prevent choking	Peanut, other legumes (other than green pea)	Milk, soy, poultry, egg, fish
8 months of age or when developmentally appropriate. ➤ Offer soft-cooked and bite-and-dissolve textures from around 8 months of age or as tolerated by infant.			
12 months of age or when developmentally appropriate. ➤ Offer modified tolerated foods from the family table-chopped meats, soft cooked vegetables, grains and fruits.			

This table should be considered in the context of the following notes:

- Exclusive breast feeding until 4-6 months of age and continuing breast feeding through the first year of life or longer as long as mutually desired by both mother and child.¹
- If an infant tolerates a variety of early foods, subsequent introduction may be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered as a favorable prognostic indicator for tolerance of other foods from the same group (legumes).²

AAP, CoN= American Academy of Pediatrics, Committee on Nutrition; WHO= World Health Organization

* Risk assessment is based on the clinical experience and the published reports of FPIES triggers.

1. Baker RD, Greer FR, Committee on Nutrition American Academy of P. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). *Pediatrics* 2010;126:1040-50.
2. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *The Journal of allergy and clinical immunology* 2005;115:149-56.

TABLE XIII Nutritionally important FPIES implicated foods and the main nutrients they provide with alternative dietary sources

Provoking Foods	Main Nutrients	Alternative sources
Cow's Milk	Macronutrients: Protein, fat Minerals and trace elements: Calcium , Magnesium, Phosphorus, Iodine Vitamins: A, B6, B12, D , Riboflavin, Pantothenic Acid	Hypoallergenic formula , breast milk* *breast milk alone does not provide adequate vitamin D, iron, zinc or protein for older infants (>6 months)- consider also solid food choices to meet these nutrient needs Older toddlers (>2 years)- Fortified alternative beverages such as soy , rice, hemp, almond, oat, coconut - if tolerated
Rice, oat, barley, and wheat grains	Carbohydrate, Magnesium, Phosphorus, Potassium, Zinc Frequently in enriched cereal products: Iron , Thiamine, Niacin, Riboflavin, Folate, Choline , Calcium, Zinc, Selenium	Flours and especially enriched cereal and cereal products made from quinoa, buckwheat, millet, corn, legumes- B vitamins, iron, zinc, carbohydrates Dark Green Vegetables- B vitamins, vitamin A, B6, folate, vitamin C Starchy vegetables- carbohydrates Sesame seeds (as tahini) – protein, calcium, iron, copper, manganese, zinc, thiamine, riboflavin, niacin, pantothenic acid, vitamin B6, folate, Omega 3 and 6 fatty acids Beef and lamb - iron, zinc, choline
Soy	Calcium, Phosphorus, Magnesium, Iron, Zinc, Thiamine, Riboflavin, Vitamin B6, Folate	Hypoallergenic formula Other legumes
Eggs	Protein, Iron, Selenium, Biotin, Vitamins B12, Pantothenic Acid, Folate, Riboflavin, Choline	Meats- protein, iron, B12, choline
Fish/Shellfish	Protein, iodine Fatty fish: Vitamins A and D, Choline, Omega-3 fatty acids	Seeds such as flax and sesame- Omega 3 fatty acid, protein, fat Iodized salt- small amounts- iodine
Chicken/Turkey/Lamb	Protein , Selenium, Phosphorus, Vitamin B12, Potassium, Choline, Zinc, Iron	Beef and pork - protein, fat, iron, B12, zinc, choline, phosphorous

Note: when choosing plant-based sources of iron (non-heme iron sources), it is beneficial to include dietary sources of vitamin C to improve absorption of iron

Bolded nutrients= main nutrients of concern with eliminated food/food group

Italicized and bolded foods= best nutritional substitutes for main nutrients of concern

eFigure 1. Literature search strategy

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TABLE E1 Age of onset or diagnosis of FPIES (cow milk/soy vs. solid food triggers)*

Reference	Country	Only CM/soy FPIES investigated	Overall age of onset/diagnosis (months)	Age onset/diagnosis of cow milk/soy FPIES (months)	Age onset/diagnosis of solid FPIES (months)	Atypical FPIES*	
						SPT	ssIgE
Nomura et al	Japan	Y (CM)	-	0.28 (0.1-0.82)** 0.59 (0.34-0.1.20) #	-	-	8/14 (57%) 6/16 (38%)#
Powell	USA	Y (CM)	-	0.46 (0.14-2.39)	-	-	-
Gryboski	USA	Y (CM)	-	0.25 (0.07-4)	-	-	-
Katz et al	Israel	Y (CM)	-	1 (0-6.4)	-	2/44 (5%)	-
Nowak-Wegrzyn et al	USA	N	-	1 (0.08-12)	5.5 (3-7)	0/44 (0%)	3/44 (7%)
McDonald et al	USA	Y (CM/soy)	-	1 (0.04-3)	-	-	-
Hwang et al	South Korea	Y (CM/soy)	-	1.28 (0.46-2.1)	-	-	-
Chung et al	South Korea	Y (CM)	1.75 (-)	1.75 (-)	-	0/28 (0%)	0/28 (0%)
Sicherer et al	USA	N	2 (0.25-108)	2.0 (0.25-108)	6 (5-24)	1/20 (5%)	5/20 (25%)
Fogg et al	USA	N	2 (0.25-9)	2 (0.25-4)	4.5 (4-9)	-	-
Sopo et al	Italy	N	5.1 (5.10)	3.5 (2.40) ###	10.6 (6.70)	0/66 (0%)	-
Mehr et al	Australia	N	5.6 (2.70)	4.9 (2.60)	6.1 (1.70)	1/35(3%)	-
Caubet et al####	USA	N	4 (2-6)	5 (2-10)	7 (6-12)	39/160 (24%) had positive SPT and/or ssIgE	
Ruffner et al	USA	N	9.7 (10.20)	7 (0.70)	12.1 (1.10)	26/721 (4%)	-

*Data from studies where age onset/diagnosis recorded. Data represented as either mean age onset/diagnosis (standard deviation) or median age of onset/diagnosis (range) unless otherwise specified

**Figure relates to cluster 1 analysis and #relates to cluster 2 analysis performed (both clusters representative of FPIES cases)

###Figure relates to cow milk FPIES only (3 soy cases included with other foods)

####Data represented as a median (interquartile range)

TABLE E2 Case series examining cases of FPIES*

Reference	Year	Study design	Definition used	Country	No. patients	Duration study (yrs)	Data on all triggers [#]	Center	Male (%)	Eczema (%)	IgE FA (%) [#]
Caubet et al	2014	Prospective + retrospective	Their own (modified Powell)	USA	160	10	Yes+; CM, soy, rice, oat, seafood	One allergy clinic	54	57	11
Ruffner et al	2013	Retrospective	Their own	USA	462	5	Yes; CM, soy, rice, oat, egg	One hospital	60	34	-
Fogg et al	2006	Prospective	Sicherer et al	USA	19	1.5	Yes; CM, soy, rice, oat, egg	Single allergy clinic	53	11	-
Nowak-Wegrzyn et al	2003	Retrospective	Sicherer et al	USA	44	5	Yes; CM, soy, rice, oat, barley	2 allergy clinics	59	34	-
Sicherer et al	1998	Retrospective	Their own	USA	20	6	Yes; CM, soy, rice, green pea, poultry	Single allergy clinic	44	31**	15
Burks et al	1994	Prospective	Their own	USA	22	1.5	CM/soy	One hospital	-	-	-
McDonald et al	1984	Prospective	Powell	USA	10	-	CM/soy	One hospital	-	-	-
Powell ^{###}	1976	Retrospective	Their own	USA	9	-	CM/soy	Their own	-	-	-
Gryboski ^{###}	1967	Retrospective	None set	USA	21	16	CM	One hospital	90	14	-
Katz et al	2011	Prospective	Sicherer et al	Israel	44	2	CM	One hospital	52	7 [#]	-
Levy and Danon	2003	Retrospective	Their own	Israel	6	6	Solid food triggers; chicken, turkey, green pea, lentil	One hospital	67	-	-
Hsu and Mehr	2012	Retrospective	Sicherer et al	Australia	38	4	Yes, but only egg presented	One hospital	53	-	-
Mehr et al	2009	Retrospective	Sicherer et al	Australia	35	16	Yes; rice, soy, CM, vegetables	Single allergy clinic	57	51	11
Nomura et al	2011	Retrospective	Powell	Japan	30	3	CM	Japanese database	50	-	-
Hwang et al	2009	Prospective	Powell	Korea	23	4	CM/soy	One hospital	70	0	-
Chung et al	2002	Prospective	Sicherer et al	Korea	28	-	CM	One hospital	-	-	-
Sopo et al	2012	Retrospective	Their own/Powell	Italy	66	7	Yes; CM, fish, egg, rice	Three allergy clinics	61	9	2

*Case series only included where a definition of FPIES provided and consecutive cases presenting to a health care setting were examined

**Data only available for infants with typical FPIES ($n=16$)

[#]CM, cow milk; -, not available; PC, personal communication with corresponding author; FA = IgE-mediated food allergy (that is positive sIgE- and IgE-mediated clinical reaction to a separate food protein not causing FPIES).

+ Most common food allergens listed

^{###}In these series, chronic FPIES or a combination of cases of acute/chronic FPIES was reported.

TABLE E3 Nutritionally important FPIES implicated foods and the main nutrients they provide with alternative dietary sources

Provoking Foods	Main Nutrients	Alternative sources
Cow's Milk	Macronutrients: Protein, fat Minerals and trace elements: Calcium , Magnesium, Phosphorus, Iodine Vitamins: A, B6, B12, D , Riboflavin, Pantothenic Acid	Hypoallergenic formula , breast milk* *breast milk alone does not provide adequate vitamin D, iron, zinc or protein for older infants (>6 months)- consider also solid food choices to meet these nutrient needs Older toddlers (>2 years)- Fortified alternative beverages such as soy , rice, hemp, almond, oat, coconut - if tolerated
Rice, oat, barley, and wheat grains	Carbohydrate, Magnesium, Phosphorus, Potassium, Zinc Frequently in enriched cereal products: Iron , Thiamine, Niacin, Riboflavin, Folate, Choline , Calcium, Zinc, Selenium	Flours and especially enriched cereal and cereal products made from quinoa, buckwheat, millet, corn, legumes- B vitamins, iron, zinc, carbohydrates Dark Green Vegetables- B vitamins, vitamin A, B6, folate, vitamin C Starchy vegetables- carbohydrates Sesame seeds (as tahini) – protein, calcium, iron, copper, manganese, zinc, thiamine, riboflavin, niacin, pantothenic acid, vitamin B6, folate, Omega 3 and 6 fatty acids Beef and lamb - iron, zinc, choline
Soy	Calcium, Phosphorus, Magnesium, Iron, Zinc, Thiamine, Riboflavin, Vitamin B6, Folate	Hypoallergenic formula Other legumes
Eggs	Protein, Iron, Selenium, Biotin, Vitamins B12, Pantothenic Acid, Folate, Riboflavin, Choline	Meats- protein, iron, B12, choline
Fish/Shellfish	Protein, iodine Fatty fish: Vitamins A and D, Choline, Omega-3 fatty acids	Seeds such as flax and sesame- Omega 3 fatty acid, protein, fat Iodized salt- small amounts- iodine
Chicken/Turkey/Lamb	Protein , Selenium, Phosphorus, Vitamin B12, Potassium, Choline, Zinc, Iron	Beef and pork - protein, fat, iron, B12, zinc, choline, phosphorous

Note: when choosing plant based sources of iron (non-heme iron sources), it is beneficial to include dietary sources of vitamin C to improve absorption of iron

Bolded nutrients= main nutrients of concern with eliminated food/food group

Italicized and bolded foods= best nutritional substitutes for main nutrients of concern