Workshop summary

Current status and future directions in food protein–induced enterocolitis syndrome: An NIAID workshop report of the June 22, 2022, virtual meeting

Anna Nowak-Wegrzyn, MD, PhD,[a,b] Scott H. Sicherer, MD,[b] Cem Akin, MD, PhD,[c] Sara Anvari, MD, MSc,[d] Lisa M. Bartnikas, MD,[e] M. Cecilia Berin, PhD,[f] Theresa A. Bingemann, MD,[g] Scott Boyd, MD, PhD,[h] Terri Brown-Whitehorn, MD,[i] Supinda Bunyavanich, MD,[j] Antonella Cianferoni, MD, PhD,[k] George du Toit, MBBCh, FRCPCH,[l] John E. Fortunato, MD,[m] Jeffrey D. Goldsmith, MD,[n] Marion Groetch, MS, RD,[o] Stephanie A. Leonard, MD,[p] Meenakshi Rao, MD,[q] Fallon Schultz, MSW, LCSW, CAM,[r] Julie M. Schwaninger, MS,[s] Carina Venter, PhD, RD,[t] Amity Westcott-Chavez, MA, MFA,[u] Robert A. Wood, MD,[v] and Alkis Togias, MD[w]

Ann Arbor, Mich; Baltimore and Rockville, Md; Boston, Mass; Chicago, Ill; Denver, Colo; Houston, Tex; London, United Kingdom; New York and Rochester, NY; Olsztyn, Poland; Palo Alto and San Diego, Calif; Philadelphia, Pa; and Point Pleasant, NJ

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated gastrointestinal food allergy characterized by delayed, protracted vomiting and accompanied by lethargy and pallor, usually 1 to 4 hours after ingesting the food allergen. The pathophysiology of FPIES remains unknown, and currently there are no diagnostic biomarkers available to assess disease activity or its resolution. Over the last 2 decades, FPIES has become increasingly recognized in both pediatric and adult patients. Forty years after the initial FPIES description, the first FPIES code appeared in the *International Classification of Diseases, Tenth Revision* (ICD-10), and the first international consensus guidelines for the diagnosis and management of FPIES were published. On June 22, 2022, the National Institute of Allergy and Infectious Diseases (NIAID) held its first virtual multidisciplinary workshop on FPIES. Various clinical and translational aspects of FPIES as well as important areas of unmet needs were discussed as priorities for future research during this 2-day virtual workshop. Our report provides a summary of content of the workshop, including updated literature on the topic areas, and also provides critical commentary on the state of FPIES. (J Allergy Clin Immunol 2025;155:336-56.)

Key words: *Food allergy, food protein–induced enterocolitis syndrome, FPIES, dysautonomia, gut neurophysiology, mast cell, serotonin, enteroendocrine cell*

On June 22, 2022, the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, held a virtual multidisciplinary workshop on food protein–induced enterocolitis syndrome (FPIES). The workshop was organized in

From [a]the Department of Pediatrics, Hassenfeld Children's Hospital, NYU Grossman School of Medicine, New York, and the Department of Pediatrics, Gastroenterology and Nutrition, Collegium Medicum, University of Warmia and Mazury, Olsztyn; [b]the Department of Pediatrics, Division of Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York; [c]the Department of Medicine, University of Michigan, Division of Allergy and Clinical Immunology, Ann Arbor; [d]the Division of Immunology, Allergy and Retrovirology, Texas Children's Hospital, Baylor College of Medicine, Houston, and Texas Children's Hospital, William T. Shearer Center for Human Immunobiology, Houston; [e]the Department of Medicine, Division of Immunology, Boston Children's Hospital, Boston, and Harvard Medical School, Boston; [f]the Department of Medicine, Division of Allergy/Immunology, Northwestern University Feinberg School of Medicine, Chicago; [g]the Department of Allergy, Immunology and Rheumatology and the Department of Pediatric Allergy and Immunology, University of Rochester School of Medicine, Rochester; [h]the Stanford University School of Medicine, Palo Alto; [i]the Division of Pediatric Allergy and Immunology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia; [j]the Department of Pediatrics, Division of Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York; [k]the Division of Pediatric Allergy and Immunology, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia; [l]the Department of Women and Children's Health (Paediatric Allergy), School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, London, and the Children's Allergy Service, Evelina London Children's Hospital, Guy's and St Thomas' Hospital, London; [m]Gastroenterology, Hepatology and Nutrition, Northwestern University Feinberg School of Medicine, Chicago; [n]the Department of Pathology, Boston Children's Hospital, Boston, and Harvard Medical School, Boston; [o]the Department of Pediatrics, Division of Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York; [p]the Division of Pediatric Allergy & Immunology, Rady Children's Hospital San Diego, University of California, San Diego; [q]the Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, and Harvard Medical School, Boston; [r]the Division of Allergy, Immunology, and Transplantation, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Rockville; [s]the International FPIES Association (IFPIES), Point Pleasant; [t]Children's Hospital Colorado, University of Colorado, Denver; [u]IFPIES, Point Pleasant; [v]the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore; and [w]Allergy, Immunology and Transplantation, NIAID, National Institutes of Health, Rockville.

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Corresponding author: Anna Nowak-Wegrzyn, MD, PhD, Pediatric Allergy and Immunology, 160 East 32nd Street, LM3, New York, NY 10016. E-mail: Anna.nowak-wegrzyn@nyulangone.org.

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Abbreviations used
ANS: Autonomic nervous system
EEC: Enteroendocrine cells
FPIES: Food protein–induced enterocolitis syndrome
GI: Gastrointestinal
HRQOL: Health-related quality of life
5-HT: Serotonin
I-FPIES: International FPIES Association
IgE-FA: IgE-mediated food allergy
IM: Intramuscular
IV: Intravenous
NIAID: National Institute of Allergy and Infectious Diseases
OFC: Oral food challenge
PROMIS: Patient Reported Outcomes Measurement System
QOL: Quality of life

response to the efforts of the International FPIES Association (I-FPIES), which represents the community of people living with FPIES and advocates for progress in FPIES research and clinical care. The invited speakers discussed the currently available evidence on various aspects of FPIES and identified the important areas of unmet needs as priorities for future research. This report summarizes the content of the workshop with updated literature on the topic areas, provides a critical commentary on the state of FPIES, and outlines directions for future investigations.

BACKGROUND OF THE FPIES WORKSHOP

Patient and caregiver perspectives

FPIES is a disorder in which symptoms present episodically; however, living with FPIES involves daily, constant management of the disease.[1,2] While great strides have been made to represent the full spectrum of food allergic disorders, limitations in awareness and representation in the literature have contributed to the challenges patients and families face while navigating FPIES.[1,3]

Over the last decade, patient advocacy efforts have given the patient experience a platform for recognition. This has included the recognition of so-called outliers of FPIES: FPIES in adults; acute and chronic phenotypes, multiple food reactions, breast milk reactions, high rates of comorbid diseases, and atypical FPIES.[3] Often the patient perspective has been denied, dismissed as poor adherence to treatment recommendations, or, worse, falsely attributed to factitious disorder (formerly known as Munchausen by proxy).[4] When the realities of living with FPIES are not validated, it fuels patient fear and provider mistrust, resulting in broken patient and clinician rapport. Early food introduction guidelines may have spotlighted inadvertently FPIES, with a rise in reports of FPIES reactions to peanut.[5] This gives credence to the dire need for further research of FPIES, which ultimately benefits the full spectrum of food allergic disorders.

To date, studies with the largest cohorts and patient representation have come from the patient-reported data surveyed through I-FPIES.[6] Of the 410 patients and caregivers, 403 reported self-management of their child's most severe reactions. These reports demonstrate how the lack of funding and research has placed the clinical burden and decision-making, as well as the risk and detriment, onto the patient and family. Additionally, recent patient-reported data coupled with empiric clinical data reveal multiple food FPIES and FPIES to grains and solid foods, including fruits and vegetables, to be more prevalent than previously appreciated.[6-8] Patient accounts serve as a guide to reduce further delays in clinical care and to avoid unnecessary spending of desperately needed research dollars.

Obtaining a diagnosis may be a revolving door of specialist appointments and invasive, unnecessary testing, with several exposures landing patients in emergency departments requiring resuscitation.[9] Nearly 20% of FPIES patients experience hypovolemic shock; the long-term effects of this episodic catastrophe are unknown and have not been studied.[10,11] More recently, the first case of cardiac arrest was reported in the literature.[12] Patients are told they have a virus, that their symptoms are not food related, that they can only be allergic to the top 9 allergens, or —much worse—that they are imagining or purposely inflicting these reactions on themselves or their children. Reliable, easy-to-implement diagnostics would alleviate this experience. It would also reduce the need for oral food challenges (OFCs), which, although considered the reference standard, are not fully standardized, and many providers report apprehension in conducting this procedure as a result of the severity of these reactions.[13] If a provider is reluctant to conduct an OFC, the patient and family have every right to feel the same.[13-15]

For those who are fortunate to find an FPIES specialist, its diagnosis comes with assurances that they will outgrow this disorder; however, the need remains for a longitudinal study to confirm that this is indeed the case for all patients. Patients must be open to several years of trial and error versus strict avoidance, which translates to "risk versus detriment" to an FPIES patient who has endured multiple rounds of profuse vomiting, bloody stools, and shock. This is often when patients begin to express their autonomy in their clinical care and face the choice of avoidance versus exposure to food. For those who choose avoidance for safety concerns, the consequences can be provider mistrust, compromised nutrition, emergence of secondary conditions, and a disjointed relationship with food. For those who choose exposure, a decision is made to put the patient at risk of a reaction, often with caretaker consent. When challenge reveals an allergy, caregiver guilt can be traumatizing.[16,17]

This fragmented approach to management is reactionary, episodic, and supportive, but it is not corrective or preventative, and it does not reduce the risk or the trauma the condition induces.[18] FPIES may become a patient- and parent-managed disease, increasing risk and placing significant financial, psychosocial, and clinical burdens on patients and families.[2] Patients and providers begin to rely on anecdotal information from their peers for clinical management. The quality of life (QOL) for FPIES patients is significantly reduced in every measured domain compared to the same index reports in IgE-mediated food allergy (IgE-FA), yet all of this is preventable with appropriate research defining the pathophysiology, identifying diagnostics and prognostic biomarkers, delivering effective therapeutic interventions, and providing supportive psychologic management.[17]

DEFINITIONS AND EPIDEMIOLOGY OF FPIES

FPIES is a non-IgE–mediated food allergy manifesting with repetitive, projectile emesis within 1 to 4 hours after ingesting the offending food.[10] Emesis can be accompanied by lethargy, pallor, low muscle tone, and diarrhea, which starts within 5 to 10 hours; 15% to 20% of patients become hypotensive or develop a hypovolemic, distributive shock, attributed to intense

intestinal inflammation. There is striking absence of "typical" skin (hives, angioedema) and respiratory (coughing, wheezing) allergic symptoms.

Laboratory testing may reveal an elevated white blood count with predominance of neutrophils, thrombocytosis, and a modest increase in C-reactive protein. In more severe reactions, metabolic acidosis, electrolyte derangements, or methemoglobinemia might be present.[19,20]

Because of our limited insights into its pathophysiology and its lack of biomarkers, FPIES diagnosis is based on the recognition of symptom constellation and depends on clinical expertise. This frequently leads to a delay in diagnosis and to an extensive diagnostic work-up to identify alternative etiologies.[1,21] It also contributes to uncertainty regarding the accuracy of current, population-based, epidemiologic data.

FPIES usually has an onset in infancy, within the first year of life, soon after the initial introduction of the food into the diet. Symptoms are most commonly caused by direct feeding; however, occasionally, an infant might react to food allergens in maternal breast milk. The majority of infants react to 1 or 2 foods, although 1 in 10 might have reactions to multiple foods. The specific food triggers seem to be influenced by the local dietary patterns and age at time of food introduction. The most common triggers are cereal grains (eg, oat, rice, wheat), cow's milk, vegetables (eg, sweet potato, carrot) and fruits (eg, avocado, banana, apple).[7] In the United States and South Korea, where infant soy formulas are in use, soy FPIES is also seen. Recently, peanut and egg have emerged as newer FPIES triggers, raising the possibility that earlier introduction of allergenic foods might be a contributing factor.[5,8,22]

Onset of FPIES in older children and adults is less common than in infants, and it is usually triggered by seafood, although other foods, including cow's milk, egg, and wheat, have also been reported.[23-25]

Since the first published report on FPIES in 1978 and until the past decade, FPIES was considered an exceedingly rare form of food allergy (Fig 1). In the following years, birth cohort studies from Israel and Spain reported the incidence of FPIES between 0.3% and 0.7%.[26] The US population-based study that captured data from 2015-16 estimated the prevalence of FPIES at 0.51% in children and 0.22% in adults (Fig 2).[27] A 2014-17 birth cohort from the suburban Boston area reported a FPIES cumulative incidence of 0.92% over 3 years.[28] Few studies have reported FPIES in non-White children or in children from disadvantaged backgrounds, raising the possibility of a disparity resulting from limited access to specialist care.[27,29]

Infantile FPIES usually resolves by age 3 to 5 years, with the exception of fish FPIES, which only resolves in a small subset by that age.[30-32] Egg FPIES also tends to have a later age at resolution, with a median age of 5 years.[33] A recent report highlights a more protracted course of peanut FPIES, with 57% of those challenged to peanut at a median age of 42 months reacting with FPIES symptoms.[5] Atypical FPIES is defined as FPIES symptoms with detectable specific IgE to the FPIES food trigger. Atypical cow's-milk FPIES been shown to be more persistent than classic cow's-milk FPIES. The natural history of adult-onset FPIES is not well documented; however, the limited data suggest a prolonged course for the majority of affected adults.[23,32]

FPIES at all ages is associated with allergic comorbidities, including atopic dermatitis, IgE-FA, asthma, allergic rhinitis, and eosinophilic esophagitis, suggesting shared immunopathophysiology.[27,29,34] However, unlike IgE-FA, the typical infantile FPIES triggers include foods with low protein content, like oat, rice, and fruits and vegetables—traditionally considered to have a low allergenic potential. These low-allergenicity FPIES triggers suggest that host factors might be more important, potentially including the gut microbiome, immaturity of the gut barrier, and oral tolerance. The impact of the earlier food introduction on increased prevalence of FPIES to peanut and egg needs to be better understood.

Phenotypes

The 2017 International Consensus Guidelines on FPIES identified 4 phenotypes that were based on the following: (1) age at onset (under vs older than 9 months); (2) severity; (3) timing and duration of symptoms resulting in "acute" versus "chronic" presentation; and (4) IgE positivity (typically negative specific IgE for the culprit food, but also some "atypical" cases that are positive).[6,10,19] This report also identified the role of frequency and dose of allergen ingestion on severity and chronicity, recognized an "acute on chronic" phenotype, and also noted that dietary habits and race/ethnicity may influence phenotypes. Given that phenotypes are "observable characteristics," additional examples of FPIES phenotypes not discussed in the guidelines could include single versus multiple foods, categories of foods such as cereal grains versus fruits, persistence versus resolution versus recurrence, and phenotypes based on symptom pattern.

The age-related phenotypes are particularly disparate, but there are few studies on adults.[23] The usual age at onset of FPIES is 2 to 7 months. Additional characteristics in infants include the fact that cow's milk or soy are typically triggers under age 6 months; those affected under age 2 months experience bloody diarrhea and growth failure more often than older infants; and older infants more commonly have isolated vomiting.[35,36] Adults, compared to infants or children, are more commonly female, are triggered by shellfish, have previously tolerated the culprit food, experience more abdominal pain without vomiting, have low resolution rates, and may have higher rates of comorbid gastrointestinal (GI) pathologies, such as irritable bowel syndrome or celiac disease.[23,32,37,38]

While FPIES is characterized as a non-IgE, cell-mediated allergy, patients with disease fulfilling the diagnosis are sometimes noted to have detectable food-specific IgE to the trigger or develop sensitization over time, referred to as atypical FPIES. The frequency of IgE positivity varies among reports up to as high as 24%.[39] A subset (about 1 of 3) of patients with atypical FPIES to cow's milk might eventually develop classic acute IgE-mediated reactions (eg, urticaria) and are more likely to have a more persistent cow's-milk FPIES.[40] As noted before, based on clinical experience, atypical FPIES can have a highly variable clinical presentation and might involve immediate or delayed cutaneous symptoms, in addition to delayed, repetitive emesis. Thus, atypical FPIES might represent a fluid phenotype on a spectrum of mixed cell-mediated and IgE-mediated pathophysiology.

An important aspect of phenotyping FPIES regards eventually determining endotypes that could then reveal pathways toward better diagnosis, prognosis, treatment, and prevention. To pursue endotyping, it is important to consider subphenotypes of FPIES that could relate to differences in immune or other underlying

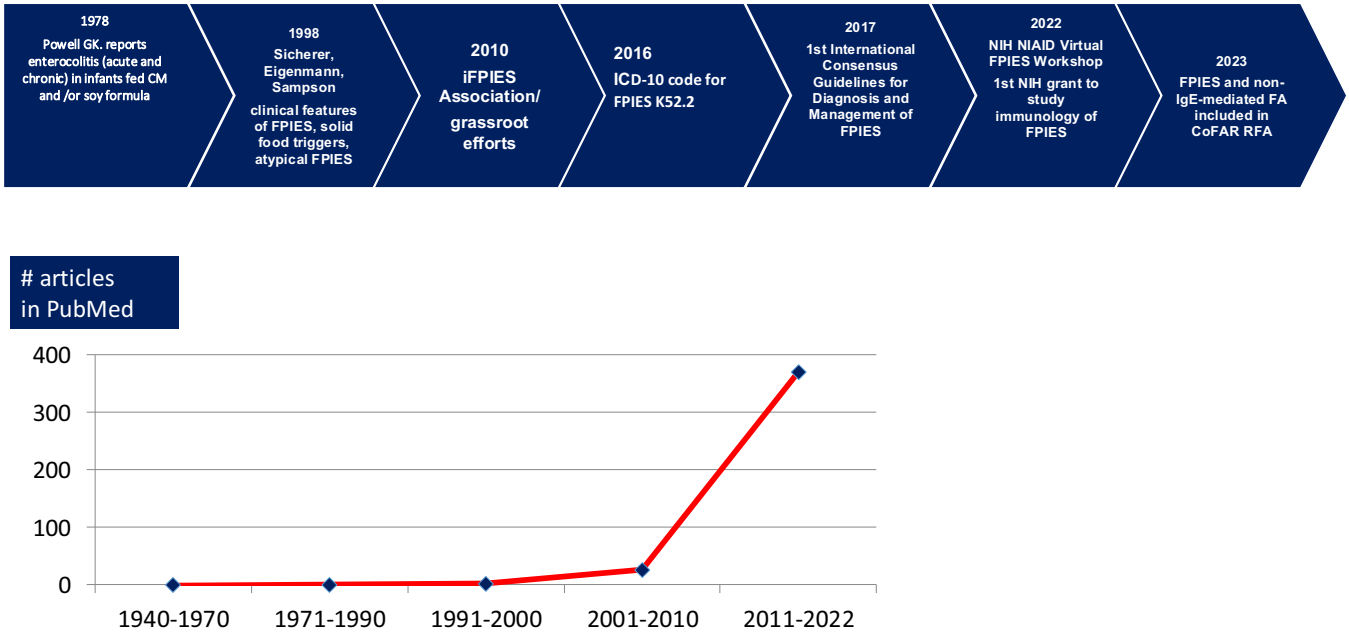

FIG 1. FPIES recognition and research progress. Historical milestones in FPIES, starting from first description of symptom constellation documented with OFCs, recognition of various food triggers, establishment of lay patient organizations, obtaining ICD-10 diagnostic code for FPIES, 2017 consensus guidelines, and NIAID National Institutes of Health workshop, paralleled by increasing numbers of publications in peer-reviewed literature. *ICD-10, International Classification of Diseases, Tenth Revision.*

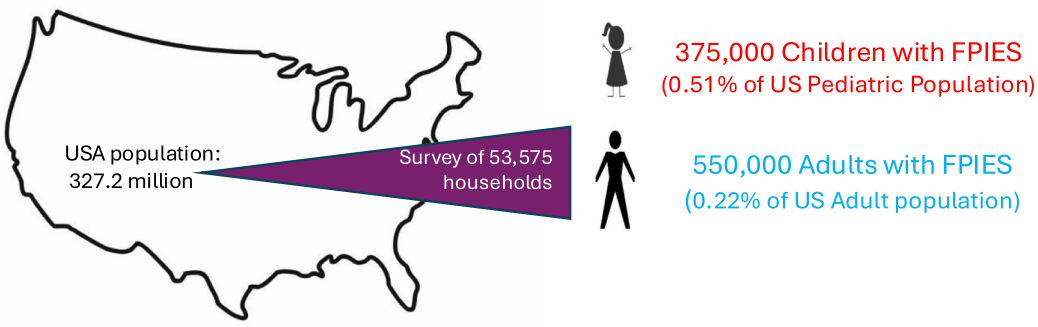

FIG 2. FPIES prevalence in US population-based survey. Population estimates based on data of Nowak-Wegrzyn et al.[27] Self-report data were collected for 40,443 adults. On the basis of population-weighted estimates obtained from this nationally representative sample, physician-diagnosed FPIES was reported by 0.28% (0.24-0.33%) of Americans, corresponding to over 900,000 people.

mechanisms. The purest classic phenotype is arguably the acute form of FPIES, without detectable food-specific IgE. Importantly, there are presentations or features of FPIES that are not the classical delayed reaction, with no evidence of IgE to the trigger food. Given that FPIES is often associated with other atopic disorders, it may not be surprising to have conversion/transition to or concomitant IgE sensitization. Is IgE-positive atypical FPIES a different endotype? In those with straightforward IgE-FA, isolated, delayed GI symptoms sometimes (albeit rarely) occur, which can also mimic the FPIES phenotype. Thus, in some cases, atypical FPIES may be an artificial or circumstantial phenotype that may not easily inform an endotype. However, considering that the majority (2 of 3) with atypical FPIES continue to manifest solely FPIES symptoms, it would not be appropriate to exclude this subphenotype in studies aiming to determine endotypes.

Should severity be considered a subphenotype in FPIES? Severity may be related to the amount of food ingested, the robustness of the host response, or other factors. There is a need to better define the criteria for severe and mild FPIES that considers these factors. A patient manifesting more severe symptoms (eg, unresponsiveness, lethargy, requirement for intravenous [IV] fluids) after an ingestion of a very low dose of food on more than one occasion could be considered as having a more severe FPIES phenotype. Operationally, we might refer to severe versus mild reactions rather than the overall FPIES phenotype. Additionally, phenotyping by age may need to be considered. The distinction in phenotypes by age is notable and raises questions about environmental influences considering the distinction in foods (ie, rice or oat compared to shellfish), among other aspects.

Regarding phenotyping toward a goal of endotyping, the acute versus chronic phenotypes are particularly difficult to disentangle, given that many infantile disorders may include characteristics of chronic FPIES, so unless phenotyping includes OFC showing acute responses to administration of the triggering food, a secure diagnosis of chronic FPIES may be questioned, or a disorder fulfilling the diagnosis of chronic FPIES may have a different pathophysiology. For the purposes of endotyping, lumping chronic and acute disease together could be misleading unless patients are carefully identified by OFC after avoidance results in amelioration of symptoms. Given the overlapping subphenotypes of FPIES, it may ultimately be necessary to apply agnostic approaches to explore endotypes, such as multiomic systems biology approaches.

Are there clues among these phenotypes as to etiology/pathophysiology? Although only noted in case reports, descriptions of drug-induced enterocolitis syndrome suggests the trigger may not always be a protein, and this may be a clue for FPIES; perhaps toxins, carbohydrate moieties, chitin, and other chemicals in foods are also triggers.[41] Another clue may regard timing and a window of immunologic opportunity. Because the existing phenotypes suggest that in infants there is a window of time when 1 or more foods, often unrelated, become triggers, there may be an immunologic window or gut barrier defect window (perhaps triggered by infection, dysbiosis, or other insults) at work. In adults, it is possible that oral tolerance may get attenuated when a food is only consumed periodically, and/or that gut barrier function may be partly compromised when that food is coingested with alcohol, exercise, antacid medications, or nonsteroidal anti-inflammatory drugs, or are due to hormone changes, intestinal infection, or inflammation. Future phenotyping and attention to patterns of reactivity may benefit from seeking history on coingestions, infections, timing of exposure, receipt of antacids or antibiotics, environmental exposures, and various additional potential cofactors.

Risk factors

There appears to be some hereditary risk to FPIES, but it has not been well characterized. In the US population-based study, 4.9% reported multiple siblings affected, and 1.9% had an affected parent.[27] In an Australian population-based study, the calculated risk was 15.4/100,000 per year without an affected sibling versus 16.4/100,000 per year with—a marginal increase in risk calculated from 7% of infants with FPIES having an affected sibling.[27,39] However, there are multiple case reports of affected monozygotic twins,[42-44] suggesting a modest hereditary component and the need for genetic studies. Infants with trisomy 21 appear to be at increased risk of developing a higher severity of FPIES.[45-47] In Italian and Japanese cohorts of children with trisomy 21, approximately 11% were diagnosed with FPIES to various foods—an over 10-fold higher rate than population estimates of FPIES. Four genes located on human chromosome 21q22.11 encode α and β subunits of the IFN-α receptor, the β subunit of the IL-10 receptor, and the second subunit of the IFN-γ receptor. Overexpression of chromosome 21 gene products in patients with trisomy 21 leads to an increase of TNF-α and IFN-γ levels with a decrease in IL-10 concentration in plasma, which can lead to exaggerated inflammatory responses. This should be investigated as a potential mechanism of predisposition to FPIES.[48,49]

Population-based studies and even some referral-based studies in children mostly favor an even sex distribution or a slight male preponderance, with one exception being a primary care cohort in Philadelphia (214 with FPIES from a cohort of 158,510) having a significant male preponderance at 64%.[29] In an US adult population-based cohort, 53.5% of the cases occurred in female patients, whereas in a Spanish adult referral population, 93.5% were female.[23,27] In sum, there may be a weak male predominance in infants and female predominance in adults.

Multiple studies suggest high rates of comorbid atopic disease, such as IgE-FA, atopic dermatitis, allergic rhinitis, and asthma.[27,29,34] A cohort study in children from Philadelphia noted statistically significant higher rates of atopic disease in those with FPIES compared to the population without FPIES, the largest difference being in IgE-FA (24% in FPIES vs 4% in the general population).[29]

Several other potential risk factors have been described, but there are few data available. A birth cohort from Philadelphia noted 77% with FPIES were White, but diagnosis bias cannot be ruled out, and the US population-based prevalence study showed a higher rate of FPIES among Asian/non-Hispanic children.[27] An Israeli study suggested cesarean section delivery was a risk factor, which may raise research interest in the role of the microbiome.[50] Indeed, a small study reported longitudinal differences in gut microbiome in infants with FPIES compared to age-matched, nonallergic healthy infants in the first year of life.[28] Another case–control study found gut microbiome differences in older children with fish FPIES (mean age, 7.5 ± 3.2 years) compared to age-matched, nonallergic healthy children (mean age, 6.9 ± 2.7 years).[51]

Another potential risk factor regards timing of food introduction. Based on the timing of onset being typically within the first 9 months, and most foods involved may not be common allergens but rather the first foreign proteins introduced, there appears to be a window of time where an infant may be more prone to experience FPIES. In support, an increase in peanut- and egg-induced FPIES has been noted since guidelines for early introduction as a means of prevention have been promulgated.[5,8,22] However, 2 studies did not identify timing as a risk, although there may be ascertainment issues related to a focus on milk.[33] In one of the earliest studies, egg was used as a control allergen for infants with suspected milk or soy FPIES.[52] At a mean age of 5.5 months, 3 of 10 infants with challenge-confirmed milk or soy FPIES developed acute FPIES symptoms at first egg ingestion, suggesting that early introduction might increase the risk of FPIES.

Ultimately, impactful modifiable risk factors have not yet been identified, but the clear atopic disposition suggests FPIES has some degree of allergic etiology aligned with other atopic diseases.

PATHOPHYSIOLOGY AND MECHANISMS

Current knowledge and gaps in FPIES immunology

The role of immunoglobulins in FPIES has been carefully examined. Initial reports indicated that infants with active FPIES had higher levels of specific IgA and IgG to milk, soy, and ovalbumin at baseline and an increase in food-specific IgA after OFC than infants who had outgrown their FPIES. Subsequent investigations have not found differences in IgA, $IgG_{1\text{-}4}$, IgM, IgD, IgE, or free light chains specific for foods or specific for

milk components when comparing active FPIES to outgrown FPIES or other controls.[53,54] A decrease in milk-specific IgA and IgG has been reported in FPIES, but this is in comparison to children with nonmilk FPIES or other controls who are not avoiding milk, and therefore differences may be due to lack of ingestion.[55] Again, food-specific IgE can be found in a subset of individuals with FPIES, referred to as atypical FPIES, and is associated with a prolonged time to resolution.[40]

The role of T cells in FPIES is more controversial. McDonald et al reported that peripheral blood mononuclear cells from individuals with a positive FPIES challenge result had higher proliferation compared to individuals with a negative challenge result.[52] However, no difference in proliferation was later reported by Hoffman et al.[56] Recall assays examining cytokine production from milk-restimulated peripheral blood mononuclear cells demonstrated a predominantly T_H2 profile, or an absence of T-cell response.[53,54] It is difficult to reconcile how a T_H2 profile similar to IgE-FA could play a pathogenic role in a food allergy with such distinct clinical manifestations. On the one hand, Goswami et al used a CD154-based detection assay for milk-, soy-, or rice-responsive T cells and found no difference in T-cell frequency or phenotype compared to healthy controls.[57] On the other hand, measurement of cytokines before and after FPIES challenge clearly demonstrates a potential role for T cells. IL-2 is elevated after challenge, as are the T_H17 cytokines IL-17A, IL-17F, and IL-22.[58,59] T-cell activation can be detected after challenge by expression of the activation marker CD69, although expression is so widespread that it does not appear to be antigen specific. Analysis of T-cell subsets by mass cytometry demonstrated that CD69 was most highly upregulated on $CD3^+CD4^-CD161^+$ cells, including γδ T cells, indicative of preferential activation of nonconventional T-cell subsets.[58]

In addition to pan–T-cell activation, mass cytometry analysis demonstrated activation of multiple innate cell subsets, including monocytes, eosinophils, neutrophils, and natural killer cells after food challenge. RNA sequencing analysis of blood obtained before and after OFC showed an upregulation of monocyte-associated gene signatures during FPIES reactions.[57] This is consistent with data from Mehr et al, who demonstrated an innate immune signature associated with FPIES reactions.[60] Analysis of signaling in whole blood by mass cytometry identified an elevation in phospho-STAT3 in myeloid cells and T cells after food challenge. This suggests that activation of these cell subsets was downstream of systemic release of cytokines including IL-6, IL-10, IL-22, and oncostatin M.[58] Untargeted metabolomics of serum samples obtained before and after OFC found elevated levels of a total of 34 metabolites, including inosine and urate of the purine signaling pathway in those with symptomatic FPIES compared to those without symptoms after challenge.[61] Expression of the purine receptors P2RX7 and P2RY10 and the ectonucleotidase CD73 in peripheral blood was significantly reduced after symptomatic FPIES challenge, also implicating the purine pathway in reactions. The level of the serotonin metabolite 5-hydroxyindoleacetate was significantly elevated after reaction, suggesting a role for peripheral serotonin in reactions. Adenosine, a purine metabolite, triggered serotonin release from gastric and duodenal biopsy specimens from FPIES-free donors, suggesting a link between purinergic pathway activation and serotonin release.

Taken together, these results suggest a model (Fig 3) in which tissue-resident memory T cells localized to the GI tract react to OFC with a rapid release of T_H17-associated cytokines. There is subsequent cytokine-mediated activation of innate immune cells, and an additional release of proinflammatory cytokines and potentially ATP that could yield adenosine to drive serotonin release, resulting in the classic symptoms of repetitive vomiting, pallor, and lethargy.

Roles of B-cell isotypes and switching in upper GI tract

Recent analyses of B-cell and plasma cell populations in the blood and GI tissues of patients with IgE-FA could have relevance to FPIES. Immunoglobulin heavy chain transcripts sequenced from biopsy samples of esophagus, stomach, and duodenum and peripheral blood of peanut-allergic adults at baseline showed increased numbers of somatically mutated, clonally expanded peanut IgE^+ B-lineage cells and cells with a plasma cell phenotype in the stomach and duodenum.[62] The observed cooccurrence of B-cell clones between the blood and GI tissue biopsy samples supports the idea that blood-based immune monitoring is likely to capture at least a fraction of the B-cell repertoires that are present in less accessible tissue sites. The implications of these observations for FPIES include the value of obtaining GI biopsy tissues for research, when this can be safely carried out in FPIES patients, to test for the possibility that the pathologic mechanisms involve immune cell populations such as B cells that may be localized to specific GI tissue sites.[63,64]

Possible role of mast cells

The clinical spectrum of mast cell activation is diverse and involves many different organ systems, including the digestive tract with symptoms such as abdominal cramping, diarrhea, nausea, and vomiting, which are also common symptoms in FPIES. While mast cells are best known for their activation through the IgE pathway, it is important to note the heterogeneity in mast cells populating different anatomical locations.[65,66] Connective tissue mast cells are produced in embryonic yolk sac and seed the tissues, where they have a long life-span. They express tryptase, chymase, carboxypeptidase, cathepsin G, and MRGPRX-2, a G protein–coupled receptor important in mediating mast cell activation via various ligands through non-IgE receptor pathways. In contrast, mucosal mast cells are dynamically maintained in tissues, expanding in type 2 inflammation, and replaced by bone marrow–derived mast cells; these cells have a much more limited protease and mediator profile. In an animal model exploring mast cell involvement in different manifestations of food allergy, systemic anaphylaxis was associated with activation of connective tissue type mast cells, while GI manifestations such as diarrhea without anaphylaxis was mediated by both mucosal and connective tissue mast cells.[67]

There is little known about mast cell involvement in FPIES other than they are found as part of the mixed inflammatory infiltrate in GI biopsy samples.[10] Caubet et al reported no acute rise in tryptase levels before and after a positive OFC in children with FPIES to cow's milk.[53] Baseline tryptase levels were within a normal range in all patients, although patients with positive results to OFC had higher levels. This finding is unlikely to be of diagnostic significance; the difference was small, and the tryptase levels were overlapping between children who did not react versus those who did react to the OFC. One possible explanation

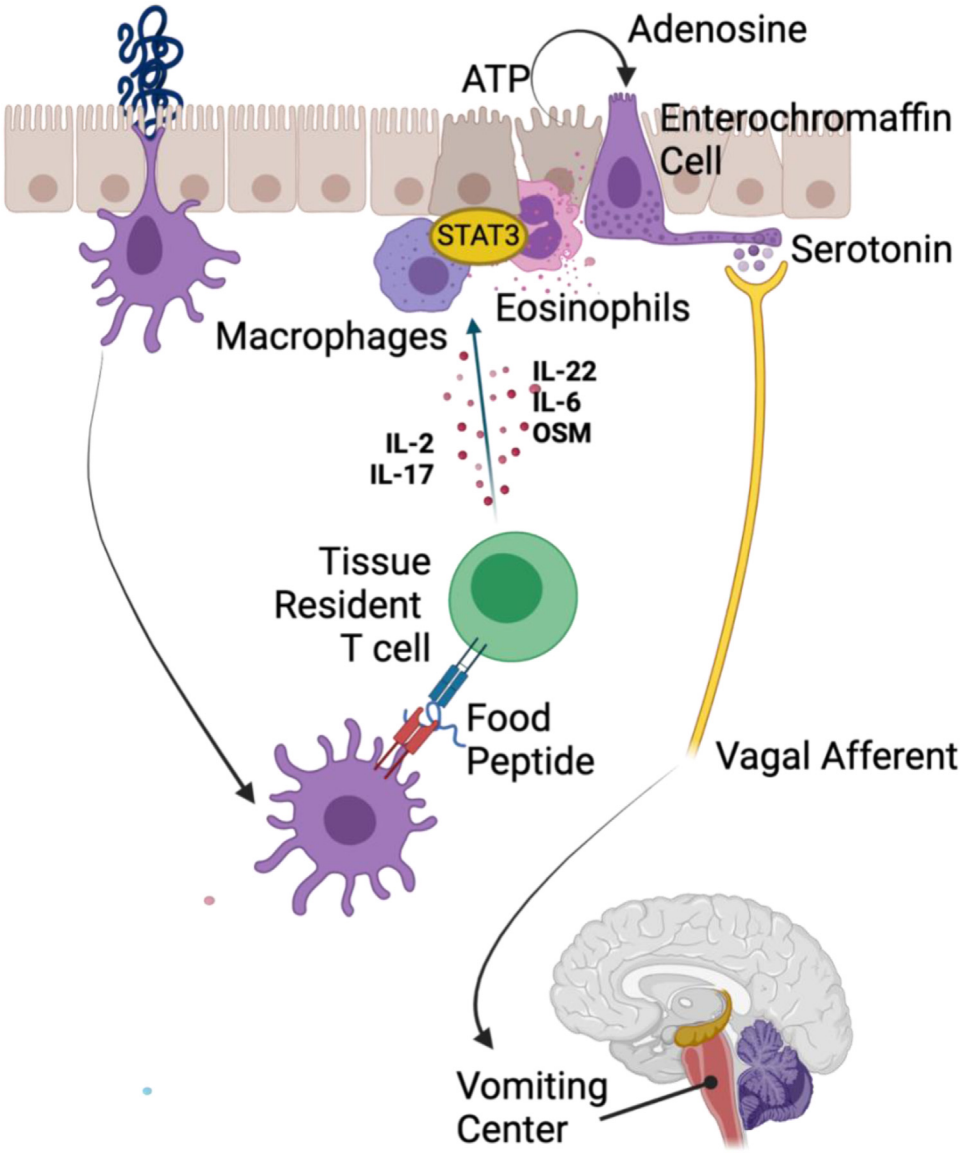

FIG 3. Immune pathophysiology of acute FPIES. Food antigen is absorbed and activates tissue-resident T cells to make cytokines, including IL-2, IL-17, and IL-22. OSM and IL-6 are also produced, but source may also include tissue macrophages. IL-22, OSM, and IL-6 activate STAT3, which is observed in multiple innate immune cell types. ATP can be released by activated immune cells and damaged epithelial cells, and its metabolite, adenosine, acts on enterochromaffin cells to drive serotonin release, linking inflammation to vomiting, pallor, and lethargy. *OSM,* Oncostatin M.

for this finding may be reactive mast cell hyperplasia induced by the inflammatory milieu (perhaps by cytokines, including IL-9 and stem cell factor) in patients with active FPIES.

Because of the complex and largely unknown pathogenesis of FPIES, mast cell–directed therapies alone are unlikely to be effective, although they may provide adjunctive treatment options. Knowledge gaps exist in terms of quantitative and qualitative changes in mast cells in acute and chronic FPIES, and how they correlate with disease resolution. Single-cell RNA sequencing experiments, similar to those investigated in other disorders, may provide mechanistic insights into the role of mast cells in FPIES pathogenesis. It would also be of interest to investigate whether different food components, protein or nonprotein, can directly activate mast cells through non-IgE–mediated pathways.[66]

Possible role of GI microbiome. Microbial communities residing in anatomic locations throughout our bodies can exert influence on health and disease.[68] Epidemiologic studies from around the world have identified many environmental factors associated with allergy risk (eg, birth mode, pet ownership, birth order, farming environment) that are also linked to differential microbiome exposure.[69,70]

While definitive evidence for microbial dysregulation in FPIES is currently lacking, several studies have suggested gut dysbiosis preceding and persisting in FPIES in infants and children.

A small study reported longitudinal differences in the gut microbiome in infants with FPIES compared to age-matched, nonallergic healthy infants in the first year of life.[71] Another case–control study found gut microbiome differences in older children with fish FPIES (mean age, 7.5 ± 3.2 years). Children with FPIES

had significantly higher proportions of Lachnospiraceae spp and lower proportions of Ruminococcaceae spp, Lactobacillaceae spp, and Leuconostocaceae spp than healthy controls.[51]

More extensive findings about the GI microbiome in individuals with IgE-FA support the need for GI microbial features getting more thoroughly investigated to assess their contribution to FPIES pathophysiology. For example, in studies of an early life cohort of 512 children from the Consortium for Food Allergy Research, investigators examined stool and saliva samples and identified GI microbiota associated with food allergy status, food allergy development, and resolution of food allergy over time.[72-74] Findings from these and other studies support the notion that individuals with and without food allergy have distinct GI microbiota, and early-life GI microbiota might influence the development and trajectory of disease. Recently, investigators also identified GI microbial features associated with reaction threshold in food allergy.[73] Research in murine models has been instrumental in uncovering mechanisms by which GI microbiota may modulate food allergy susceptibility. In the absence of specific microbial signals in the GI system, T_H2-promoting pathways are augmented. In turn, colonization by some microbiota has been observed to influence T-regulatory cell expansion, basophil-mediated allergic inflammation, and intestinal IgA secretion.[75]

Although preliminary data raise the possibility that GI microbiota may also be associated with FPIES, rigorous and systematic data addressing this particular question are needed.[28,51] If distinct microbial features are found to be associated with FPIES, then GI microbiome manipulation by diet, probiotics, prebiotics, synbiotics, postbiotics, and/or microbiota transfer could be considered as potential modalities for prevention and/or treatment of FPIES.

GI pathology in FPIES

The pathology of FPIES has not been comprehensively described. This is chiefly because pathology samples are difficult to obtain in patients during an acute FPIES event; endoscopy is often not feasible as a result of the clinical status of the patients. Thus, our knowledge of this topic is limited to case reports and small case series; in all these publications, the pathology is not completely described.

Most review articles of FPIES refer to a case report in which a 6-month-old had repeated FPIES events due to chicken ingestion.[76] The patient underwent endoscopy during one of these events, which revealed hemorrhagic, fragile mucosa. Biopsy samples showed "severe inflammation with eosinophils," with no additional pathologic description provided.

Additional descriptions come from a small case series of 4 infants, who, in retrospect, had clinical features of FPIES.[77] Endoscopy showed hemorrhagic and friable mucosa; however, the study also noted a loss of vascular pattern. Histologically, mild to moderate acute colitis was described, without mention of mucosal eosinophilia.

Other descriptions include duodenal villous atrophy with increased lamina propria inflammation.[67] One article reported increased major basic protein using immunohistochemistry; however, histology did not reveal increased lamina propria eosinophils.[78] TGF-β1 expression was generally depressed in 28 infants diagnosed with FPIES on the bases of clinical criteria and oral challenge. Expression of type 1 TGF-β receptor was significantly lower in the patients who had villous atrophy compared to patients who did not, and was negatively correlated with the severity of atrophy. Expression of type 2 TGF-β receptor showed no significant difference between the patients with or without villous atrophy. The immunoreactivity for both TGF-β receptors on lamina propria cells was low. TNF-α expression was detected on both epithelial and lamina propria cells; it was significantly greater in patients who had villous atrophy compared to patients who did not.[78]

Given the incomplete evidence base and understanding of the pathology of FPIES, additional studies need to be undertaken.

Possible role of GI neurophysiology

There are many ways that the nervous system may contribute to the pathophysiology of FPIES, but confirmatory evidence is lacking. The nervous system regulates or mediates nearly every aspect of GI function, including motility, epithelial barrier integrity, fluid/ion flux across the epithelium, gut hormone responses, sensations of nausea or abdominal pain, and mucosal immunity. Because these functions are fundamentally linked to the symptoms of FPIES (nausea, vomiting, and diarrhea), the nervous system is certain to have roles in FPIES symptomatology. Neural circuits, furthermore, store memories of experiences and link these memories to specific behavioral responses that can be conscious, autonomic, or both. Thus, the GI nervous system may also directly underlie FPIES pathophysiology, producing specific autonomic responses in response to specific food exposures. The digestive tract contains its own intrinsic nervous system called the enteric nervous system; it is also extensively innervated by projections from extrinsic neurons located outside the gut, including vagal afferent and efferent neurons, spinal afferent neurons, and sympathetic postganglionic neurons. All these components of the nervous system are potential actors in FPIES.

Clinical experience and a case–control study suggest that ondansetron, an antagonist of the serotonin type 3 receptor (aka $5HT_3R$) is highly effective in terminating FPIES symptoms in many patients.[79] $5HT_3Rs$ are expressed by vagal afferents, enteric neurons, spinal afferents, intestinal epithelial cells, and mucosal immune cells including macrophages and dendritic cells, meaning that this signaling pathway could be a central node in FPIES pathogenesis.[80] In the gut, serotonin (5-HT) is primarily released by a subset of enteroendocrine cells (EEC), a type of secretory epithelial cell that detects mechanical and chemical stimuli from the gut lumen, and releases 5-HT and peptides in response. These molecules signal in paracrine fashion to cells and nerve endings in the lamina propria, and in an endocrine fashion to more distant targets. It will be important to determine if the density, response thresholds, or outputs of EEC are altered in FPIES and contribute to maladaptive 5-HT signaling. EEC are diverse and release a wide variety of potent peptide hormones, such as peptide YY, motilin, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide 1. Measurement of these hormones at baseline and in response to food challenges in FPIES patients may provide additional insights on the contributions of this neurohormonal axis to FPIES pathophysiology.

There is increasing evidence that cells in the enteric nervous system directly link immune responses to changes in motility. For example, inhibitory motor neurons in the myenteric plexus release vasoactive intestinal peptide and the gaseous

neurotransmitter nitric oxide onto the cells of the smooth muscle syncytium to regulate gut motility. Remarkably, these same neurons were recently shown to release the cytokines IL-18 and IL-6 to influence epithelial antimicrobial peptide secretion and T-regulatory cell differentiation, respectively.[81,82] Enteric neuronal dysfunction could link food exposures with aberrant immune and motility responses. Consistent with this possibility, high-affinity IgE receptors have been reported on enteric neurons and exposure to an antigen after preincubation with antigen-specific IgE, stimulated calcium responses in these neurons.[83] Glia, the abundant nonneuronal cells of the nervous system, have also been implicated in intestinal motility and inflammation.[84] For example, a recent study showed that a subset of enteric glia in the myenteric plexus are responsive to IFN-γ and play an essential role in organizing the immune response to helminth infection.[85] There is a large population of enteric glia in the mucosa that interact with EEC-derived signals, dietary components that penetrate the epithelial barrier, and the cellular components of the mucosal immune system. Determining if these mucosal glia are altered in FPIES and if they potentially contribute to its pathophysiology would not only advance understanding of this disorder but may also help us uncover new therapeutic targets.

Dedicated studies focused on identifying the contributions of the nervous system to FPIES may be highly valuable for both extinguishing maladaptive responses to food exposures and relieving acute symptomatic episodes.

Role of dysautonomia

On the basis of the observed GI symptoms and severe hemodynamic response often associated with FPIES, it is likely that the autonomic nervous system (ANS) plays an important role in the manifestation of these symptoms. If this is the case, it is unknown whether dysregulation of the ANS is causal versus a compensatory consequence to the cascade of inflammatory events associated with FPIES. The ANS facilitates homeostasis and regulates adaptive responses to both internal and external stimuli.[86,87] With changes in the body's environment, the ANS coordinates compensatory responses to maintain organ perfusion and function. When these compensatory mechanisms are overwhelmed, symptoms of autonomic dysregulation manifesting as suppressed or excessive activity can be the result.[88,89] Further, the GI tract is extensively integrated with the ANS. Thus, when this delicate coordination fails, symptoms of diarrhea, abdominal pain, nausea, or vomiting can occur.

Both ANS and GI symptoms are part of FPIES reactions, but the mechanistic relationship between the two has not been explored, in part because of the heterogeneous nature of this condition with a spectrum of clinical phenotypes. For example, it is not known whether the autonomic response to FPIES is secondary to GI symptoms, a consequence of the neuroimmune response, or some combination of both (Fig 4). While the 2017 International Consensus Guidelines have streamlined diagnostic cohorts of acute FPIES, there remains a considerable gap in comprehensively classifying clinical FPIES phenotypes. To effectively accomplish this, it is probably important to identify disease subtypes based not simply on GI symptoms but also on associated comorbidities outside the GI tract. This is exemplified in the case of the work that led to understanding the potential causes of functional nausea in children, in which defining key symptom attributes and cluster analyses allowed identification of 2 distinct patient groups necessitating distinct treatment strategies.[89]

To establish a framework toward defining FPIES phenotypes, the use of clinical instruments such as comprehensive symptom intakes and patient-reported outcomes can be extremely useful. These tools can improve a clinician's understanding of the patient illness, including psychosocial and family impact, using a structured format. In particular, the National Institute of Health Patient Reported Outcomes Measurement System (PROMIS) offers a diverse set of validated multisystem questionnaires that measure patient-reported or proxy reported symptoms to assess a patient's disease state.[90] PROMIS can also be combined with other multidimensional assessment tools to further assess the ANS-GI relationship in FPIES. These tools include the Composite Autonomic Symptom Score 31 (COMPASS 31) and the Nausea Profile Questionnaire, both of which address symptoms spanning from GI to somatic to emotional.[91,92] It will also be important not simply to choose or design the right questionnaire but also to determine the best way to collect data.[93]

In the absence of distinct laboratory diagnostic tests or radiologic findings to classify FPIES, comprehensive symptom questionnaires, including patient-reported outcomes, offer the potential to define distinct and clinically meaningful subgroups. Better clinical characterization of FPIES is necessary to understand its complex and multifactorial nature, particularly as this is related to the interplay of underlying GI, immunologic, and autonomic mechanisms.

FPIES DIAGNOSIS

Clinical diagnosis

FPIES diagnosis is made clinically; there is no confirmatory biomarker. There is also no prognostic biomarker that allows families and clinicians to identify trigger foods in advance of ingestion. When the history is not sufficient to make the diagnosis, OFC remains the reference standard for confirmation of diagnosis, but this has practical limitations. Lack of diagnostic biomarkers remains one of the most burning needs in FPIES because the OFC experience can be unpleasant, leading to patient and family reluctance to repeat the procedure frequently to monitor for tolerance development.

The lack of a standardized FPIES OFC protocol, the need for prolonged observation, and the potential for severe reactions necessitating IV fluid resuscitation contribute to apprehension among clinicians and the limited availability of practices performing FPIES OFC.[13,15] Clear guidance on food dose and regimen, and the criteria for placement of peripheral venous access before OFC are needed. Acute FPIES is the most common type of FPIES. Current consensus guidelines suggest that patients must have 1 major criterion and at least 3 of minor criteria.[10] The major criterion is delayed symptoms (1 to 4 hours after ingestion) with repetitive vomiting after eating the suspected food in the absence of IgE-mediated skin or respiratory symptoms. The minor criteria include 3 of the following: second episode of vomiting after ingestion of same food, similar reaction with a different food, extreme lethargy, marked pallor, need for emergency department evaluation, need for IV fluid support, diarrhea within 24 hours of reaction, and hypotension and/or hypothermia. While these criteria seem to work for many, a recent cohort of patients has been described who have milder presentations and may not meet the above strict criteria.[94]

Chronic FPIES occurs in infants in whom chronic exposure to high doses of food allergen (eg, feeding with cow's milk or

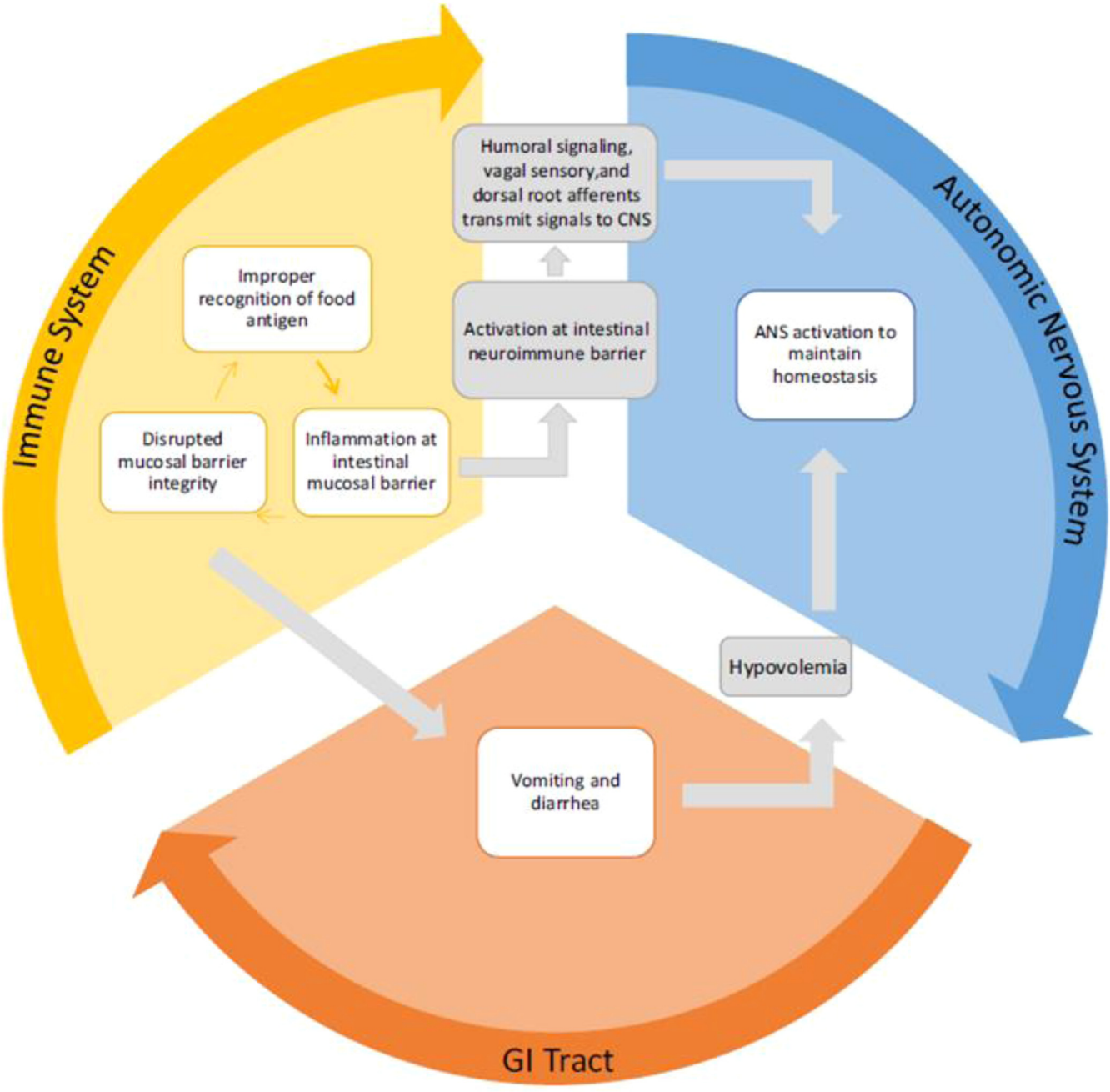

FIG 4. Potential fluid relationship between GI, immune, and ANS responses in FPIES. Reprinted with permission from Hoffman NV, Ahmed A, Fortunato JE, "Food protein–induced enterocolitis syndrome. Dynamic relationship among gastrointestinal symptoms, immune response, and the autonomic nervous system," Ann Allergy Asthma Immunol 2021;126:498-505. *CNS,* Central nervous system.

soy-based infant formula) leads to vomiting, diarrhea, and severe gastroesophageal reflux symptoms daily. Progressive growth concerns and symptoms ensue, and often these infants appear very ill.[35,36] Removal of the offending food leads to improvement, and adding the food back in leads to an acute FPIES reaction. Older children with chronic symptoms that suggest FPIES need further evaluation to exclude alternative diagnoses (Table I), which are more likely.

In adolescent and adult patients with FPIES, presentation is more delayed in nature (up to 6 hours) after food ingestion but often includes more severe abdominal pain and diarrhea, whereas vomiting may be absent in a subset of patients.[23] Diagnostic criteria for FPIES in adults are needed.

Differential diagnosis

Given the delay in the onset of nonspecific symptoms after allergen ingestion, the diagnosis of FPIES is typically only made after repeated exposures to the allergen.[95,96] In the absence of a clear biomarker for the diagnosis of FPIES, until such time a

TABLE I. Differential diagnosis and features that distinguish these conditions from FPIES

Characteristic	Features	Diagnosis
Infectious gastroenteritis	Fever, sick contacts, and single episode of illness and vomiting unrelated to ingestion of the same food	Stool testing for pathogens
Sepsis (pediatric/adult)	Fluid resuscitation alone not effective	Laboratory abnormalities and positive blood cultures, and/or appropriate sepsis biomarkers—eg, procalcitonin, presepsin (soluble CD14), sTREM-1
IgE-FA or anaphylaxis (pediatric/adult)	Immediate onset (<1 hour) of cutaneous, respiratory, and/or GI symptoms; typically present with hives or lip swelling; anaphylaxis may progress to hypotension and responds to epinephrine	Presence of food-specific IgE on blood or skin test
Gastroesophageal reflux disease (pediatric/adult)	Symptoms may occur after ingestion of many or all meals and are not restricted to select FPIES trigger foods; vomiting is less likely to be protracted or end in bilious vomiting; there are no neurologic features associated with GERD, and features are restricted to upper GI symptoms.	Antacids improve symptoms, and upper GI series can provide evidence of reflux
Obstructive GI problem (eg, pyloric stenosis, intussusception, Meckel diverticulum, ileus and volvulus) (pediatric)	Each condition has a typical age at presentation, and symptoms are not related to intake of specific foods	Evidence of obstruction on radiologic studies
Celiac disease (pediatric/adults)	No temporal relationship between symptoms and food intake, and symptoms gradually progress to malabsorption	Celiac serologic testing, mucosal histologic testing, and HLA marker testing positive for HLA-DQ2, -DQ8, family history
Lactose intolerance (pediatric/adults)	Abdominal bloating, flatulence, cramps, diarrhea, nausea, and/or vomiting after ingesting dairy products containing lactose	Positive hydrogen breath test result, lactose elimination diet, genetic
Fructose intolerance (pediatric/adults)	Bloating, flatulence, or diarrhea after ingestion of fruit and fruit-based sweeteners	Positive hydrogen breath test result, fructose elimination diet, genetic screening
Intolerance of short-chain fermentable carbohydrates	FODMAPs	Positive hydrogen breath test result, short-chain fermentable carbohydrate elimination diet, genetic screening
Inborn errors of metabolism (pediatric)	Developmental delay, neurologic features with gradual decline in physical and developmental well-being, and specific triggers may be required to induce symptoms	Testing to examine the specific pathway deficiency or metabolite accumulation, genetic testing
Neurologic disorders (pediatric)	No relation to specific food intake	Neurologic evaluation necessary for diagnosis
Eosinophilic gastroenteropathies (eg, eosinophilic esophagitis, gastritis, colitis) (pediatric/adult)	Typically not associated with specific food intake, and symptoms are more chronic than episodic	Intestinal biopsy and clinical symptom history
Inborn errors of immunity (pediatric)	Frequent infection history and no specific relation to food intake	Immune phenotyping or genetic testing (eg, whole-exome or whole-genome sequencing)
FPIAP (pediatric)	Infant well appearing and thriving, exclusively breast-fed or formula-fed, symptoms are of the lower GI tract (eg, fresh blood and mucus in stools)	Guaiac-positive stools and elimination leads to symptom improvement; delayed symptoms with reexposure
Food protein–induced enteropathy (pediatric)	Vomiting less prominent than nonbloody diarrhea, and less severe presentation without methemoglobinemia or acidemia	No acute reaction at reexposure
Inflammatory bowel disease (pediatric/adults)	GI symptoms include bloody and mucus-containing diarrhea, rectal bleeding and weight loss/failure to thrive, perianal skin tags, or fistulas; not related to specific food intake; systemic symptoms and/or extraintestinal symptoms (eg, fever, arthritis, arthralgia, folliculitis, uveitis, dermatologic manifestations)	Tissue biopsy, highly elevated inflammatory markers (eg, CRP and calprotectin)
Irritable bowel syndrome (adults)	Abdominal pain and changes in bowel habits (constipation and/or diarrhea) and in stool form	No specific test, but will need to exclude other GI problems (eg, celiac disease, infection, or IBD)
SIBO (adults)	Bloating, flatulence, and abdominal discomfort with diarrhea or constipation	Small intestine aspirate and fluid culture (reference standard); breath hydrogen test (less specific)
Food poisoning (pediatric/adults)	Abdominal pain, diarrhea, and/or vomiting	History of eating raw or undercooked food; positive stool sample
Anisakiasis (pediatric/adults)	Acute severe epigastric pain within few hours of ingestion, along with nausea, vomiting, and low-grade fever	History of eating raw or undercooked food; parasite seen during upper endoscopy, radiography, or surgery

CRP, C-reactive protein; *FODMAP,* fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; *FPIAP,* food protein–induced proctocolitis; *GERD,* gastroesophageal reflux disease; *HLA,* human leukocyte antigen; *IBD,* inflammatory bowel disease; *SIBO,* small intestinal bacterial overgrowth; *sTREM-1,* soluble factor triggering receptor expressed on myeloid cells 1.

causal association between food ingestion and symptom onset is clear, interim differential diagnoses are likely to focus on the dominant presenting symptoms and signs, typically those conditions that affect the GI and/or nervous systems. Table I lists potential differential diagnoses.

An additional challenge to making the diagnosis arises from the wide array of allergens that may induce symptoms, which include not only those allergens that are typically associated with IgE-FA (eg, egg, cow's milk), but more commonly those that rarely cause IgE-mediated allergy (eg, oat, rice, fruit, root vegetables).

It remains common for patients to have been assessed by other specialists before seeking care from a physician who is familiar with the condition, such as an allergist or gastroenterologist. Knowledge of FPIES remains low among emergency health care professionals and pediatricians, even though the condition frequently presents in acute-care settings.[1,6]

Diagnostic biomarkers

Recognition of a disease and its correct diagnosis often rely on the availability of a biomarker—a measurable substance, the presence of which indicates disease, infection, or environmental exposure. However, for the diagnosis of FPIES, no biomarker has been identified.[10]

Table II lists immunologic and biochemical markers that have been evaluated in peripheral blood at baseline and during acute FPIES reactions induced by an OFC. At baseline, none can predict the outcome of the OFC, but some change after the OFC and differ between active FPIES and resolved FPIES, and between FPIES and IgE-FA.[40,53-55,57,58,61,97-100] None of those, however, differentiate these conditions well enough to be regarded as true diagnostic biomarkers.

Our ability to identify a diagnostic biomarker is seriously hampered by the lack of understanding of the pathophysiology of FPIES; we do not know which cells recognize and mount the specific responses to culprit foods. This is further hindered as the mechanisms of emesis or those of other clinical manifestations during acute FPIES episodes remain unknown. In fact, solely examining the immune system may limit our view because symptoms may be caused by the nervous system through serotonin pathways or other neural mechanisms of emesis, diarrhea, and other GI symptoms.

TREATING AND MANAGING FPIES

Long-term FPIES management

Long-term management of FPIES includes prevention through dietary management, preparation via emergency planning, and prognosis, as well as assessing for tolerance.

There are 3 main approaches for dietary management, and which approach is the best may depend on age and country of origin of the patient, which food triggered the initial FPIES reaction, if the patient has single versus multiple food FPIES, and what other foods are already part of the diet.

One approach is to recommend avoidance of only the specific food or foods that triggered FPIES. Up to 65% to 80% of pediatric patients have FPIES to a single food, most often cereal grain (oat or rice) or cow's milk.[7,8] Another approach is to also delay introduction of related or potentially coreactive foods in infants This is based on observations, for example, that approximately 50% of patients with grain FPIES are reactive to more than one grain, and 20% to 40% of patients in US cohorts with cow's milk or soy FPIES are reactive to the other.[10]

The more conservative approach may be appropriate for patients at high risk for multiple food FPIES or patients with severe symptoms. In the US cohort 5% to 10% of patients had FPIES to >3 foods, and in another cohort 5% were reactive to ≥6 foods.[6-8,10] It has been observed that patients with cow's milk/soy FPIES can be at risk for solid food FPIES, often rice or oat. In addition, younger infants may be more likely to have multiple food FPIES.[39] Recommending lower-risk foods for introduction first may also help families with young infants in whom first FPIES reactions were to some of the first solid foods introduced to them or who have experienced severe or multiple FPIES reactions. Knowing more about risk factors for multiple food FPIES as well as the degree of coreactivity between and within food groups will help guide dietary management.

For cow's milk and/or soy FPIES, continued breast-feeding or an extensively hydrolyzed casein formula is recommended; up to 10% to 20% may need elemental formula.[10,101] Chronic FPIES, which is predominantly triggered by cow's milk and soy, usually resolves within 3 to 10 days of switching to a hypoallergenic formula. In acute FPIES, while coreactivity between cow's milk and soy in the United States is significant, this has not been observed in Australia, Israel, and Italy, potentially because of the much lower use of soy-based infant formula in these countries compared to the United States. Thus, if one of these two foods is a culprit, a careful introduction of the other might be considered, if preferable over a hypoallergenic formula because of taste or cost, if FPIES symptoms were mild and the infant is older than 6 months. Empirically, the coreactivity between cow's milk and soy is highest in infants younger than 6 months. Similarly, avoidance of the related foods from the same food group may be appropriate in the initial stages of new food introduction after an FPIES reaction, but it should be modified and relaxed based on the successful introduction of other foods.

Breast-feeding of infants with FPIES is encouraged, and maternal avoidance of FPIES trigger or triggers is not recommended if the infant is asymptomatic and growing well. While there are mostly case reports of FPIES symptoms after breast-feeding in the United States, higher rates of infants with FPIES symptoms during exclusive breast-feeding have been reported in Japanese (10%) and Australian (5%) cohorts.[39,102] Additional studies on the prevalence of acute and chronic FPIES symptoms during breast-feeding will improve anticipatory guidance.

Reviewing an emergency treatment plan with patients and families in case of an FPIES reaction is vital. Management of acute reactions is primarily based on severity.[10,103] If symptoms are mild—for example, one or two episodes of vomiting and no lethargy—oral rehydration can be attempted about 20 minutes after the last emesis (Fig 5).[103] If available, ondansetron can be provided to infants aged >6 months. If there is continued vomiting and lethargy, or if there is a concern about dehydration, it is recommended that the patient go to the emergency department for further management, primarily with IV fluids and intramuscular (IM) or IV ondansetron. Giving FPIES patients an emergency letter that explains what FPIES is and suggests treatment can help patients receive the care that they need and avoid a misdiagnosis and/or extensive work-up. If symptoms are severe, such as severe lethargy, hypotonia, or a gray or ashen appearance, it is recommended that emergency services are sought immediately because there is concern for hypotension, hypovolemia, and distributive

TABLE II. Potential biomarkers described in FPIES

Characteristic	Acute FPIES	Diagnosis of FPIES trigger	Chronic FPIES
Specific IgE to foods (SPT, sIgE)	Absent by definition[1]	Absent by definition[1]	IgE to milk elevated in persistent milk-induced FPIES
IgG_{1-4}	Similar to general population and IgE-FA	Similar to general population and IgE-FA	NA
IgM	Similar to general population and IgE-FA	Similar to general population and IgE-FA	NA
IgA	Similar to general population and IgE-FA	Similar to general population and IgE-FA	NA
APT	No	Low sensitivity, specificity, PPV, NPV	NA
T-cell activation	Similar to general population and IgE-FA	Similar to general population and IgE-FA	NA
Neutrophil	Elevated. Minor criteria of FPIES diagnosis >1500/mm	NA	NA
Eosinophil	Elevated in stools	NA	NA
Tryptase	Elevated at baseline. No difference during acute reaction	NA	NA
TARC	Elevated during acute reaction	NA	NA
CRP	Elevated or normal during acute reactions	NA	NA
TNF-α	Elevated	NA	NA
TGF-β	Reduced	NA	NA

APT, Atopy patch test; *CRP,* C-reactive protein; *NA,* not applicable; *NPV,* negative predictive value; *PPV,* positive predictive value; *sIgE,* serum-specific IgE; *SPT,* skin prick test; *TARC,* thymus and activation-regulated chemokine.

shock. Studies are needed to evaluate the use of corticosteroids to treat acute FPIES reactions; in severe reactions, corticosteroids may be considered to treat the inflammation in the gut.

There are limited data on use of ondansetron to treat acute FPIES reactions. Small studies of IV and IM ondansetron have demonstrated rapid symptom resolution (<15 minutes). A larger retrospective study reported that vomiting persisted in 19% of children treated with IV ondansetron versus 93% treated with IV fluids and steroids, and that children treated with ondansetron were less likely to be hospitalized.[79] Only oral ondansetron can be prescribed for patients to use at home, and data are limited regarding its effectiveness. In one small study, oral ondansetron worked for 5 of 7 symptomatic food challenges; the other 2 required an IV dose.[104] Randomized studies on treatment with oral versus IM versus IV ondansetron are needed, as well as investigations into other possible antiemetic or GI agents.

Age at development of tolerance varies by type of food trigger and country of origin.[26] Cow's milk and soy FPIES resolution appears to occur at an earlier age than grains or other solid foods. Periodic evaluation is recommended, and OFC to test for resolution could be considered 12 to 18 months after the last reaction. However, the specific food to be challenged and the severity of previous reactions should be factored in when deciding when to perform the OFC, as the resolution rates may vary based on these factors. There are no data on resolution to seafood in older children and adults, but reevaluations should be similarly considered in adult patients. Prospective studies on the age at development of tolerance and studies using serial OFC are needed to elucidate prognosis. A standardized OFC protocol is necessary to properly conduct these evaluations. Finally, studies on the potential for desensitization, as in IgE-FA, would be a start to the conversation about possible treatment.

Feeding practices

Dietary management of FPIES entails avoidance of the trigger food or foods, guidance on introduction of safe and nutritious complementary foods to support growth and development, and advancement of skill- and age-appropriate food textures to support feeding skill development.[8,40,105] Even with only one identified trigger food, it is common practice to delay introduction of other foods considered higher risk thus, resulting in more limited food choices. An analysis of surveys representing 441 children with FPIES reported that 69.4% were avoiding at least 2 food groups, most commonly cow's milk and grains.[6] Assisting caregivers in creating an individualized, well-designed complementary feeding plan to meet the infant's nutritional needs for optimal growth and development is an essential management strategy.

Children with food allergies are at increased risk of inadequate nutrient intake and poor growth.[106-108] Pooled data from an international survey of 430 children with both IgE-mediated and non-IgE–mediated food allergy from 12 allergy centers found that length/height was particularly impacted, with 9% of the population stunted (length- or height-for-age z score of less than -2).[108] In a retrospective chart review of 74 patients with FPIES from one tertiary-care center, 16 (22%) had failure to thrive documented in the medical record. Ten of these patients had further nutrition assessment; the cause of failure to thrive was attributed to suboptimal oral intake and limited food choices (6/10), and to knowledge deficits related to FPIES food introduction guidelines (4/10). A retrospective multicenter study of children with FPIES reported that patients with 3 or more triggers were significantly more likely to develop food aversion and to have poor weight gain than those with 2 or fewer triggers.[109] Food aversion can result in less variety and exacerbation of poor nutritional intake.

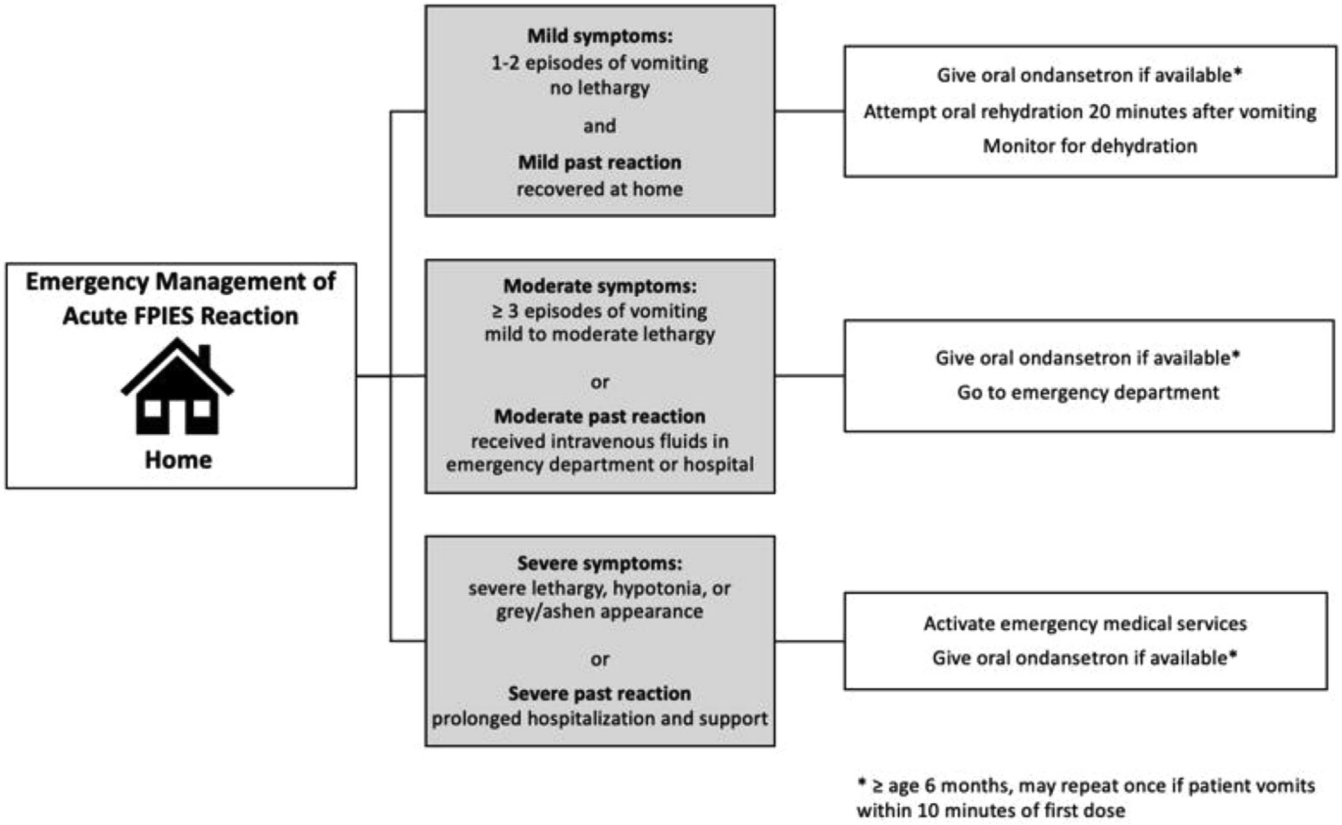

FIG 5. Management of acute FPIES reactions at home. Proposed approach to managing acute reactions at home based on severity of symptoms. Reprinted with permission from Leonard SA et al, "Management of acute food protein–induced enterocolitis syndrome emergencies at home and in a medical facility," Ann Allergy Asthma Immunol 2021;126;482-8.

Caregivers of infants and children with FPIES report higher rates of feeding difficulties compared to those with IgE-FA.[110]

The 2017 International Consensus Guidelines published guidance for complementary feeding which includes a table suggesting categories of foods from lower to higher risk that can potentially trigger FPIES reactions.[10] These practical protocols have recently been updated (Fig 6).[111,112] Many of the lower risk foods are fruits and vegetables with some fortified alternative grains, nuts and seeds, and meats. The alternative enriched grains and meats are recommended to address nutrients of concern for the breast-fed infant, such as iron, zinc, and protein, identified by the Dietary Guidelines for Americans.[113] The American Academy of Pediatrics also addresses the importance of iron intake in infants and children, and notes that breast-fed infants not given iron-rich complementary foods are at risk of iron deficiency.[114] However, the practical application of these recommendations is difficult. It is difficult to purchase grains other than rice, oat, barley, and wheat, which are fortified with iron and zinc, and it is not commonplace culturally in the United States to offer meats as a first food. A recent national study on early feeding practices in US infants reported on foods eaten in infancy and found meats are infrequently fed before 9 months of age, which is too late to start supplying nutrients that are inadequately provided in breast milk alone.[115] As a result, breast-fed infants with FPIES frequently consume only fruits and vegetables long after 6 months of age; they do not have good dietary sources of the nutrients vital for appropriate growth and development.[115]

Children with FPIES are at increased nutritional risk especially when avoiding multiple food groups. No studies to date have evaluated the micronutrient intake of infants with FPIES with altered complementary feeding practices. Additionally, no studies have evaluated whether delaying the introduction of multiple foods, beyond the identified trigger food, negatively affects growth. Most infants with FPIES are reported to have just one food trigger, so is it good policy to delay introduction of other food groups to prevent additional triggers? If this is indeed good policy, can we encourage better nutrition by being more specific about food group patterns to help address the nutrients of concern in this population and decrease the risk of poor nutrition and poor growth? Guidance for feeding in FPIES may require a greater focus on nutrients of concern by prioritizing variety among food groups and individualizing recommendations based on primary milk feeding. Understanding the prevalence and characteristics of poor growth and feeding difficulties and assessing dietary intake in patients with FPIES may elucidate specific areas for targeted nutrition interventions and future research.

Food reintroduction

Food reintroduction is defined as the introduction of food into an infant's or child's diet after a period of avoidance, either directly or indirectly via maternal diet in those receiving breast milk.

Serve 1 new food over 5-10 days. Start with 1/4 tsp and double amount with each serving. Serve twice per day (separated by 6 hours). Stop feeding if any symptoms.
Example: DAY ONE: ¼ tsp at 9am and ½ tsp at 5pm
DAY TWO: 1 tsp at 9am and 2 tsp at 5pm
Continue increasing until reaching an infant serving size
Infant serving size: 1-3 Tablespoons meat, 2 ounces fruit or vegetable, ¼ - ½ cup grains
Multiple servings (1-3) may be needed per day depending on age and nutritional needs

Food Group	Lower Risk	Higher Risk (unless already tolerated)
Milk and alternatives	Breast milk Hypoallergenic formula Fortified coconut, flax, hemp milk (for cooking only)	Milk, Soy, Pea, Oat, and Rice beverages
Meat, Seafood, Poultry	Lamb, Beef, Pork	Chicken Fish (adults), Shellfish (adults)
Grains	Quinoa, Millet, Amaranth	Rice, Oats
Vegetables	Broccoli, Cauliflower, Parsnip, Turnip, Pumpkin	Pea, Sweet Potato
Fruit	Blueberries, Plum, Peach, Strawberries, Watermelon	Avocado, Banana

FIG 6. Empirical approach to introduction of new foods at home. This is an expert opinion–based pragmatic approach to introducing foods at home to infants with FPIES developed during the coronavirus disease 2019 pandemic. Reprinted with permission from Groetch M et al, "Dietary management of food protein–induced enterocolitis syndrome during the coronavirus disease 2019 pandemic," Ann Allergy Asthma Immunol 2021;126;124-26.

If maternal diet was modified because of a concern of possible reactions to food allergen in breast milk in the child, home reintroduction may be feasible after consultation with an allergist using normal portions of food. The amounts of food allergens present in breast milk is usually very low, irrespective of the amounts of intake. Levels may depend on the food involved and may differ between breast-feeding mothers.[116] Among exclusively breast-fed infants, ≤10% of cases of FPIES reactions are attributed to the allergen in breast milk.[111,117] Clinically many mothers prefer to put food back in their diet using a gradual "ladder" approach, as opposed to reintroduction of normal portions of the foods, although more information is needed to understand if graded introduction of food allergens into the mother's diet is required in these cases.

In a child avoiding the food because of the FPIES reaction to that food, it is safest to perform the reintroduction under physician supervision, usually 12 to 18 months after the most recent reaction, although the timing of the OFC can be modified based on the nutritional value of the food and the social/economic implications of that food's avoidance.[20] Recent reports suggest that a subset of children with cow's milk and egg FPIES might tolerate these foods in a baked form.[118,119] As information about measured levels of protein in milk and egg ladders becomes more available, this approach may become clinically more relevant.[120,121] No rigorous studies have been performed to set reliable thresholds or starting doses in children or adults with FPIES, but data published elsewhere may provide some insights into appropriate starting doses.[50,122,123] In addition, Wang et al have provided data on timing and severity of reactions.[124] A recent rostrum indicates that certain factors may be favorable indicators for milk introduction in children with IgE-mediated cow's milk allergies using a ladder approach at home, but such issues remain unclear for FPIES.[120]

A case series from Italy reported baked egg tolerance by 30.2 months of age in 77% of children with egg FPIES.[118] However, the 2017 FPIES guidelines suggested that OFC to baked milk and egg should be conducted under supervision because the long-term effect is unclear. While using a ladder approach for reintroduction of milk at home, parents reported that they felt uncertain recognizing potential symptoms and severity of symptoms. Parents did, however, enjoy the convenience of introducing food at home, which reduces the need for multiple doctors' appointments.[120]

Overall, there are currently no standardized protocols for food reintroduction defining the setting, starting dose, dose escalation, final dose, and format of foods. There may be situations in the management of an individual with FPIES that will necessitate food reintroduction at home. Medical management of reactions

during reintroduction outside of a clinical setting needs to be addressed.

QUALITY OF LIFE (QOL)

Patients and families with FPIES face unique challenges that can lead to a high degree of burden and psychosocial distress.[1] Greenhawt et al performed an exploratory validation study of the Food Allergy Quality of Life–Parental Burden questionnaire in FPIES.[17] This study found that caregivers of children of FPIES had worse health-related QOL (HRQOL) compared to those with IgE-FA, both overall and in all individual domains. Female caregivers reported worse HRQOL than male caregivers. Caregivers of children with both solid and liquid FPIES reported worse HRQOL than those with a single food FPIES.

Maciag et al conducted a study of 410 I-FPIES caregiver members utilizing multiple validated measures and found a high degree of psychosocial burden among caregivers and their affected children.[2] Similar to Greenhawt et al, they found that HRQOL was negatively impacted. On the Parent Perceived Stress Scale 10, caregivers reported a mean score of 20.6, corresponding to moderate stress. On the Penn State Worry Questionnaire, caregivers reported a mean score of 54.0, corresponding to moderate worry. Notably, 77% of respondents had scores suggestive of generalized anxiety disorder, which is much higher than the 6.6% lifetime prevalence among the general population.[125] Parental confidence in their ability to assess their child's food allergy was assessed by the Food Allergy Self-Efficacy Scale for Parents. Using a 2015 UK-based validation cohort, food allergy management self-efficacy was significantly lower in caregivers of children with FPIES compared to IgE-FA.[126] In the FPIES cohort, there was a positive correlation between caregiver HRQOL, stress, worry, and anxiety, and all these correlated negatively with food allergy self-efficacy. Lower household income and avoiding a greater number of food groups due to FPIES were associated with lower caregiver HRQOL and food allergy self-efficacy. After adjustment for other FPIES food triggers, caregivers whose child avoided cow's milk because of FPIES reported lower food allergy-related self-efficacy and HRQOL, and higher stress.

The only study to date evaluating psychosocial function of children with FPIES was conducted by Maciag et al, based on surveys administered to caregiver members of I-FPIES and their children, with responses representing 100 children.[2] Children and their parents were administered the Spence Children's Anxiety Scale, a set of validated assessments of anxiety symptoms. Caregivers' ratings of their preschoolers' separation anxiety, obsessive-compulsive, and general anxiety symptoms were all higher than published norms. Avoiding a greater number of food groups was associated with higher total anxiety among preschool- and elementary school-age children.[2]

In the studies by Maciag et al, 46% of families reported their children <5 years old with FPIES did not attend school/day care, and of those not attending, 54% did not attend because of concerns regarding FPIES.[2] Avoiding multiple food groups because of FPIES was associated with increased likelihood of not attending school/day care. Compared to caregivers whose children were not attending for other reasons, caregivers whose children were not attending school/day care as a result of FPIES reported worse HRQOL, higher stress and worry, and higher total anxiety among their preschool-age children.

Few studies have evaluated the psychosocial impact of FPIES. The participants in these studies were predominantly White, non-Hispanic, educated families with higher incomes recruited from the I-FPIES patient support organization. Additional research is needed into the psychosocial impact of FPIES in more diverse cohorts of patients and families. Unmet needs include developing FPIES-specific assessment tools, identifying risk factors associated with impaired HRQOL, and developing interventions to improve HRQOL in FPIES.

Emotional support

Emotional support is providing care and comfort for another person. It provides a sense of connection. It includes being empathic and fostering a sense of security.[127]

Emotional support is sorely needed for families of children with FPIES. Caregivers report being afraid to feed their child because they fear causing FPIES reactions. They report struggling to find accurate and reliable information, and they experience feelings of isolation and fear of having others care for their child.

Given the stress and challenges of managing food allergies, Marsac and Wurth recommend routine screening for all families/patients with IgE-FA for emotional distress and providing anticipatory coping guidance and education regarding the emotional impact of food allergy.[128] Referral to a mental health provider may be necessary, along with more frequent follow-up visits with their regular clinician. Emotional support, guidance, and education for caregivers and patients with FPIES would also be beneficial.

It is critical that clinicians managing FPIES patients are empathetic and recognize concerns about nutritional adequacy of the child's diet, or when feeding has become stressful for the caregiver or an associated feeding disorder has developed as a result of FPIES, in order to provide the necessary guidance and resources to support families. Furthermore, it is important to recognize and provide the necessary support to FPIES caregivers when there is fear of sending the child to day care or school, or when there are concerns regarding food insecurity and financial stress, as these issues may exist.[1]

It is important to recognize that there may be a disconnect between the amount of support providers feel they are offering and perceived support by the caregivers or patients. There is a need for studies to examine the emotional support, QOL, and self-efficacy in FPIES. Caregivers want a better understanding of FPIES, increased FPIES awareness, accurate and reliable information, and collaborative, proactive care.[4] Emphasizing the importance of and soliciting patient/caregiver concerns and challenges while communicating respectfully and working to enhance the knowledge and understanding of this disorder will provide emotional support for patients and caregivers with FPIES.

CURRENT PRACTICES AND UNMET NEEDS

Current needs in FPIES span the full range of the disease, from identification of risk factors to diagnosis, management, assessment, and resolution. Ideally, all of the needs listed in Table III, including prevention of FPIES and treatments that might enhance disease resolution, should be addressed, but right now, a few areas should be prioritized.

First and foremost, we have the means and resources in hand to continue to improve education about FPIES for both affected

TABLE III. Research needs in FPIES

Area of research	Proposed future directions
Patients' perspective on unmet needs	● Engage patient advocacy organizations to identify the most urgent unmet needs from the patients' perspective.
Epidemiology, phenotyping and genetics	● Conduct large epidemiologic studies in economically diverse populations and populations of diverse descendance, and in different areas of the world to better define the prevalence and burden of FPIES. ● Construct comprehensive FPIES registry/cohort of patients with infant, childhood, and adult onset of FPIES involving collection of diverse biological samples to: ○ Define FPIES phenotypes/endotypes. ○ Examine, through long-term follow-up, factors associated with FPIES resolution and conversion/transition to IgE-FA or delayed comorbidities. ● Perform case–control or case–cohort studies within large population birth cohorts with collection of diverse biological samples to: ○ Assess risk factors associated with disease development in pediatric and adult FPIES. ○ Define FPIES phenotypes/endotypes. ○ Look for acute and chronic FPIES during exclusive breast-feeding. ○ Assess risk of reaction at ingestion of coallergens in FPIES patients. ○ Perform genetic studies of FPIES patients and their first-degree relatives.
Pathophysiology and endotypes	● Acquire blood and stool multiomic data and use system biology before-and-after OFCs in patients with FPIES and controls. ● Obtain targeted measurements of hormones like PYY, motilin, GIP, and GLP-1 to assess the role of EEC during FPIES reactions and to identify additional mediators of acute FPIES. ● Perform GI biopsy studies in adults with FPIES and develop intestinal organoids to study mucosal immunology and responses to trigger foods. ● Examine chemical/biochemical components of common FPIES foods regarding their ability to penetrate the epithelial barrier and activate innate immune cells of the GI mucosa. ● Examine mucosal glia alterations in FPIES and whether glial cells contribute to its pathophysiology. ● Further analyze the intestinal microbiome and develop animal models of FPIES to study the role of the microbiome using fecal transplants from affected infants. ● Screen for pathogens at time of presentation as potential causes or contributors to FPIES. ● Conduct studies of intestinal permeability in FPIES patients and the role of environmental exposures (eg, detergents).
Diagnosis	● Develop diagnostic criteria for adult-onset FPIES. ● Develop and validate standardized FPIES OFC protocols focusing on total dose of the tested food, dosing regimen, and criteria for placement of peripheral venous access before OFC. ● Perform comprehensive diagnostic biomarker analyses utilizing biosamples before and after OFC.
Management of acute reactions	● Perform randomized trials of: ○ The role of ondansetron administration and its effects on FPIES symptoms in adults. ○ Oral versus IM versus IV ondansetron. ○ Alternative antiemetic or GI agents.
Long-term management and strategies for tolerance development	● Perform randomized trials of: ○ Immunomodulatory approaches with food in pediatric and adult FPIES. ○ Baked milk and egg consumption in pediatric FPIES where these foods are triggers. ○ Standardized protocols for new food introduction (timing, type of food) after an initial reaction. ○ Standardized OFC protocols and optimal timing for periodic evaluations to assess tolerance to the culprit food.
Nutrition	● Assess the: ○ Micronutrient intake of infants with FPIES with altered complementary feeding practices. ○ Impact of delaying the introduction of multiple foods beyond the identified trigger food on growth.
Surveys and follow-up	● Develop and validate an FPIES-specific QOL survey. ● Identify risk factors associated with impaired QOL and interventions to improve QOL in FPIES. ● Establish optimal visit frequency for effective emotional support, QOL, and self-efficacy. ● Assess the impact of referral to dietician/feeding specialist, psychologist, and other medical subspecialists (eg, gastroenterologist) to allow for team-based care and proactive assessment of parental concerns on perceived support.

GIP, Glucose-dependent insulinotropic polypeptide; *GLP-1,* glucagon-like peptide 1; *PYY,* peptide YY.

families and clinicians. While a great deal of progress has already been accomplished in this area over the past few decades, there is still a need for improvement and expansion. Many infants still present with substantial delays in diagnosis, with negative consequences, emphasizing the need for improved education for primary caretakers as well as specialists in both pediatric allergy and gastroenterology.

Second, the pathophysiology of this disease remains poorly understood. In addition, while acute and chronic FPIES are often spoken of in the same sentence, the reality is, these labels may

represent different conditions. After all, how could an otherwise healthy baby with acute FPIES to rice and avocado really have the same disease as the breast-fed infant admitted to the intensive care unit with chronic vomiting and diarrhea, failure to thrive, and metabolic imbalances that only improve on an elemental formula, devoid of all intact food proteins?

Third, it is essential that new and improved diagnostic tools for FPIES be developed, including identifying biomarkers that would assist in the diagnosis as well as the assessment of disease resolution. It is a huge deficiency to rely on OFC as the only measure of resolution. This goal is fully intertwined with the unmet need regarding pathophysiology, given that it will be difficult, if not impossible, to develop more sophisticated diagnostic tools and biomarkers of resolution until our understanding of both acute and chronic FPIES is substantially improved.

To address and accomplish these priorities, it is essential that longitudinal cohort studies be performed to truly unravel the complexities of FPIES and recognize FPIES as a disorder with a spectrum of disease manifestations that may involve multiple mechanisms. Such studies would not only allow us to fully describe the outcomes and natural history of both acute and chronic FPIES, but would also provide the opportunity to interrogate mechanisms, biomarkers, and genetics, setting the stage for effective management approaches in the years to come.

WORKSHOP RECOMMENDATIONS

Table III provides more specific recommendations.

- FPIES is a delayed non-IgE food allergy that presents with protracted vomiting and can progress to dehydration and shock if not treated promptly. FPIES food triggers and natural history vary across the globe.
- The prevalence of FPIES has increased since it was first described in 1978, with an estimated US prevalences of 0.5% in children and 0.2% in adults.
  - Develop a comprehensive FPIES epidemiologic tracking system using standardized criteria.
- FPIES has been classically known to be a disease of infancy with high rates of resolution. However, FPIES may not always resolve in early childhood.
  - Determine the natural history of FPIES for different foods and in various regions.
- Following the guidelines for early introduction of allergenic foods to prevent food allergy, peanut and egg FPIES appear to be emerging as new triggers.
  - Determine the risk factors associated with peanut and egg FPIES susceptibility.
- No reliable biomarker exists to diagnose FPIES, with OFC remaining the standard. Conducting FPIES OFC for diagnosis or to assess resolution should be a shared decision-making process between the family and health care provider.
  - Develop diagnostic and prognostic biomarkers to minimize the need for OFC.
- Several phenotypes of FPIES have been recognized—for example, acute, chronic, atypical (IgE^+), multifood, and adult onset. It is likely that the pathophysiology varies from one phenotype to another.
  - Take phenotypes into account when conducting studies examining the mechanisms of FPIES.
- The pathophysiology of FPIES is poorly understood despite new knowledge.
  - Investigate the role of localized GI immune responses, neuroimmune mechanisms, and gut microbiome dysbiosis.
- When managing acute FPIES reactions, ondansetron, a serotonin receptor (5-HT3) antagonist, appears to be of value.
  - Assess the benefit of ondansetron and possibly other antiemetics that can be delivered at home.
- Management of FPIES should focus on avoidance of food triggers and coallergens and ensuring complementary food introduction that is age appropriate and diverse to prevent nutritional deficiencies and avoid growth and developmental delays.
- Assessing the family's struggle with FPIES should be incorporated in all visits, and various support services, including dietetic and psychosocial therapy, should be sought to manage the psychosocial impact of the disease and allay its many associated stressors.
- Reintroduction guidelines after an FPIES diagnosis have yet to be fully validated.
  - Assess the starting dose and rate of escalation for home reintroductions.
  - Determine the optimal timing of food reintroduction.

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