Practice paper

International consensus guidelines for the diagnosis and management of food protein–induced enterocolitis syndrome: Executive summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology

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Food protein–induced enterocolitis (FPIES) is a non-IgE cell-mediated food allergy that can be severe and lead to shock. Despite the potential seriousness of reactions, awareness of FPIES is low; high-quality studies providing insight into the pathophysiology, diagnosis, and management are lacking; and clinical outcomes are poorly established. This consensus document is the result of work done by an international workgroup convened through the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology and the International FPIES Association advocacy group. These are the first international evidence-based guidelines to improve the diagnosis and management of patients with FPIES. Research on prevalence, pathophysiology, diagnostic markers, and future treatments is necessary to improve the care of patients with FPIES. These guidelines will be updated periodically as more evidence becomes available. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Food protein–induced enterocolitis syndrome, guidelines, non–IgE-mediated food allergy*

Abbreviations used
AAF: Amino acid–based formula
CBC: Complete blood cell count
CM: Cow's milk
FPIES: Food protein–induced enterocolitis syndrome
FTT: Failure to thrive
OFC: Oral food challenge
sIgE: Specific IgE
SPT: Skin prick test
TD: Threshold dose

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Food protein–induced enterocolitis (FPIES) is a non-IgE cell-mediated food allergy that can be severe and lead to shock.[1] Despite the potential seriousness of reactions, awareness of FPIES is low; high-quality studies providing insight into pathophysiology, diagnosis, and management are lacking; and clinical outcomes are poorly established. Unmet needs in the field include identification of noninvasive biomarkers, understanding of the pathophysiology and prevalence, and having uniform approaches to diagnosis and management. This document presents an executive summary of the first international consensus based on available evidence and aims to assist practitioners in their care of patients with FPIES. The full report is available online as open access in this article's Online Repository at www.jacionline.org.

An international workgroup was convened through the Adverse Reactions to Foods Committee of the American Academy of Allergy, Asthma & Immunology and the International FPIES Association advocacy group.

A comprehensive literature review was performed with the assistance of a research librarian, with searches run in PubMed/Medline, Web of Science, and Embase. Excluding abstracts, a total of 879 citations were identified through February 2014; of these, 110 were included. Individual sections were written by using subgroup teams, critiqued, and revised based on feedback from all authors until consensus was achieved. Evidence was graded according to the previously established grading system for clinical practice guidelines used by the Joint Task Force on Allergy Practice Parameters.[2]

SECTION I: DEFINITION AND CLINICAL MANIFESTATIONS

Summary Statement 1: Recognize FPIES as a potential medical emergency, which presents as delayed onset of protracted emesis and/or watery/bloody diarrhea, culminating in hemodynamic instability and hypotension in at least 15% of reactions. [Strength of recommendation: Strong; Evidence strength: IIa/IIb; Evidence grade: B]

FPIES is a non–IgE-mediated food allergy that typically presents in infancy, with repetitive protracted vomiting that begins approximately 1 to 4 hours after food ingestion. Vomiting is often accompanied by lethargy and pallor and can be followed by diarrhea. Delayed onset and absence of cutaneous and respiratory symptoms suggest a systemic reaction different from anaphylaxis.[1,3] Severe cases can progress to hypothermia, methemoglobinemia, acidemia, and hypotension, mimicking sepsis.[3-5] The FPIES clinical phenotype is influenced by the age of onset, nationality, timing, and duration of symptoms and associated IgE-mediated food allergy (Table I).

Summary Statement 2: Recognize that the symptom phenotype in patients with FPIES is determined by the frequency of food ingestion. [Strength of recommendation: Strong; Evidence strength: IIa; Evidence grade: B]

The manifestations and severity of FPIES depend on the frequency and dose of the trigger food, as well as the phenotype and age of an individual patient.[6-9] The distinct pattern of emesis starting within 1 to 4 hours after food ingestion (acute FPIES) occurs when the food is ingested intermittently or after a period of avoidance (Tables I and II). Watery diarrhea (occasionally with blood and mucous) develops in some cases within 5 to 10 hours of ingestion and can be present for up to 24 hours.[4,9-13] Symptoms of acute FPIES usually resolve within 24 hours after food ingestion. In most children with acute FPIES, they are well between episodes with normal growth.

Chronic FPIES is less well characterized compared with acute FPIES and only reported in infants younger than 4 months of age fed with cow's milk (CM) or soy infant formula. Chronic FPIES develops on regular/repeated ingestion of the triggering food, presenting as chronic/intermittent emesis, watery diarrhea, and failure to thrive (FTT; Table I) Severe chronic FPIES can lead to dehydration and shock.[6,14] Hypoalbuminemia and poor weight gain can predict chronic CM-induced FPIES in young infants with chronic gastrointestinal symptoms.[10] With elimination of the chronic FPIES food trigger or triggers, symptoms resolve, but subsequent feeding (accidental exposure or oral food challenge [OFC]) induces an acute FPIES reaction within 1 to 4 hours of food ingestion (Table I). The acute symptomatology after food avoidance distinguishes chronic FPIES from food protein–induced enteropathy, eosinophilic gastroenteritis, or celiac disease. Chronic FPIES is uncommon but appears to be diagnosed more frequently in Japan and Korea.[10,13,15]

SECTION II: EPIDEMIOLOGY

There is limited, wide-scale epidemiologic information regarding FPIES.[16] FPIES was recognized and formally defined in the mid-1970s.[6] A 10th revision of the International Statistical Classification of Diseases and Related Health Problems code for FPIES (K52.2) was implemented in October 2015. Before this, no uniform International Classification of Diseases code existed.

FPIES prevalence estimates vary greatly. Katz et al[12] presented the only published prospective birth cohort noting a cumulative incidence of infants with CM-induced FPIES of 3 per 1000 newborns born at a single hospital over 2 years (0.34%).

Summary Statement 3: Recognize that onset of FPIES to CM and soy can occur at younger ages compared with FPIES

TABLE I. Proposed defining features for clinical phenotyping of FPIES

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

TABLE II. Proposed defining features of mild and severe acute FPIES

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

to solid foods. Patients can have a single trigger or multiple triggers. [Strength of recommendation: Strong; Evidence strength: IIb-III; Evidence grade: C]

The most commonly reported FPIES triggers are CM, soy, and grains.[11,12,17] Soy-induced FPIES and combined soy/CM-induced FPIES are common in the United States (approximately 25% to 50% in reported case series) but uncommon in Australia, Italy, and Israel. Most reported solid food–induced FPIES is attributable to rice and oat. Rice is the most commonly reported grain trigger, except in Italy.[18] Combined rice/oat-induced FPIES has been reported in almost a third of cases of rice-induced FPIES in both the United States and Australia.[4,5,9] In contrast, fish-induced FPIES is common in Italy and Spain but less common elsewhere.[18,19] Multiple factors can be involved to explain this geographic variation, including differences in the populations studied in the case series, presence of atopic disease, breast-feeding and dietary practices, and yet-to-be-discovered genetic factors.[11,12,17,20]

FPIES occurs once CM or soy-based formulas, solid foods, or both are introduced into the infant's diet, usually between 2 and 7 months of age.[4,8,9,12,16,18,21] Infants with CM- and soy-induced FPIES typically present at a younger age (<6 months) compared with those with solid food–induced FPIES (6-12 months) reflecting earlier introduction of CM and soy. The median age of solid food–induced FPIES onset is similar between most series (5-7 months), with grain-

induced FPIES presenting before FPIES to fish, egg, and poultry (see Table E1 in this article's Online Repository at www.jacionline.org).[4,5,8,9,16,22]

Infants with CM/soy-induced FPIES at less than 2 months of age were significantly more likely to manifest diarrhea, blood in stool, and FTT compared with those presenting at more than 2 months of age ($P < .05$ for all comparisons).[7,11,13,18,23-26] Older infants were more likely to present with vomiting alone ($P < .05$).[27] An acute-on-chronic phenotype also exists, in which neonates initially present with the chronic FPIES but, on accidental "on-off" exposure, present with acute FPIES.[6,14]

FPIES to fish/shellfish and egg in adults, as described in a small case series, is characterized by delayed-onset vomiting, persistence of the diagnosis, and a history of previous food tolerance.[28,29]

Summary Statement 4: Consider specific IgE testing of children with FPIES to their trigger food because comorbid IgE-mediated sensitization to triggers, such as CM, can infer a greater chance of persistent disease. [Strength of recommendation: Moderate; Evidence strength: IIb-III; Evidence grade: C]

FPIES is immunologically distinct from IgE-mediated disease, but many children with FPIES have comorbid atopy, including eczema and food IgE sensitization. Studies from the United States and Australia report frequent atopic coassociation, especially eczema (31% to 57% of cases, see Table E2 in this article's Online Repository at www.jacionline.org), although this association is rare in Korea, Israel, and Italy (0% to 9%).[18]

Children with FPIES can also have coexisting IgE-mediated food allergy at presentation or on follow-up assessment, as reported in 2% to 12% of patients.[4,9,18] Caubet et al[4] reported that children with CM-induced FPIES and IgE sensitization to CM (ie, atypical FPIES)[8] were more likely to have persistence of CM-induced FPIES after 3 years of age compared with those without sensitization. Sensitization to other food proteins did not appear to delay tolerance acquisition.

Summary Statement 5: Do not recommend any specific prenatal or postnatal food introduction/avoidance or health behaviors or advise patients regarding any specific genetic factors known to moderate the risk of a patient with FPIES. [Strength of recommendation: Weak; Evidence strength: IIb-III; Evidence grade: C]

In the Israeli birth cohort no association was noted between the development of FPIES and gestational age, maternal age, number of siblings, maternal dairy consumption, or age of introduction of CM, although an association was noted with caesarian section and Jewish religion (ie, a greater proportion had FPIES).[12] US, Italian, and Australian case series have not assessed prenatal or postnatal risk factors.[5,8,9,16-18,22,30,31]

Summary Statement 6: Consider FPIES a heterogeneous disorder associated with a number of geographic variations in the features of disease, representing a spectrum of "syndromes" as opposed to a uniform "syndrome." [Strength of recommendation: Strong; Evidence strength: IIb-III; Evidence grade: B]

The majority of reports in the literature are from Western countries and predominantly include subjects of white race.[16] Japanese data suggest that different FPIES phenotypes might exist based on dietary habits, race, or ethnicity.[15] In Japanese infants with FPIES, vomiting was observed in 100%, bloody stools in 47%, and fever in 13% at the initial presentation. Forty-seven percent had detectable serum CM-specific IgE (sIgE), and 10% reported symptoms during breast-feeding.[13,19] This phenotype appears distinct to Japan, which is in contrast to the vomiting-predominant presentation without bloody stools in slightly older infants more commonly reported in most other countries.[16]

SECTION III: DIAGNOSIS OF FPIES

Summary Statement 7: Diagnose FPIES primarily based on a clinical history of typical characteristic signs and symptoms with improvement after withdrawal of the suspected trigger food. Exclude other potential causes and use OFCs to help confirm the diagnosis if the history is unclear and there is a favorable risk/benefit ratio. [Strength of recommendation: Strong; Evidence strength: IIb-III; Evidence grade: B]

A careful history is the most important diagnostic tool in the evaluation of FPIES.[3,32] Acute FPIES presents with a constellation of unique and sometimes dramatic signs and symptoms. The clinician must obtain details of all possible reactions, specific symptoms, timing of symptoms in relation to food intake, all suspected food triggers, and reproducibility of reactions with repeated exposures to the suspect food or foods. In the vast majority of patients with acute FPIES, history alone is sufficient to make a diagnosis and identify trigger foods.

If the diagnosis is unclear after taking a careful history, OFCs should be used as the gold standard to confirm the diagnosis. There is no laboratory or other diagnostic procedure specific for FPIES, although there are a variety of other laboratory tests to help support the diagnosis and, more importantly, to rule out other conditions, as discussed in Table III.

Infants presenting with a convincing history of FPIES likely do not require challenges to confirm their initial diagnosis. The revised diagnostic criteria for acute and chronic FPIES are presented in Table IV. In fact, in the face of a clear history with repeated reactions to the same food or foods, the risk of an OFC might outweigh its benefits. OFCs are best reserved in the initial diagnostic evaluation for cases in which the history is unclear, a food trigger is not identified, the time course of symptoms is atypical, or symptoms persist despite removing the suspected trigger food or foods from the diet. OFCs are highly useful to determine whether FPIES has been outgrown (Table V).

In patients with chronic FPIES, the diagnosis can be unclear based on the history alone. Given the less specific nature of chronic FPIES symptoms, a trial of food elimination followed by supervised OFCs to potential food triggers might be necessary for a conclusive diagnosis. In select cases endoscopy and biopsy might be warranted to exclude other causes.

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

OFCs in patients with FPIES should be conducted with caution; up to 50% of positive OFC results might require treatment with intravenous fluids.[32] Home OFCs to a food suspected of triggering FPIES are not recommended given the potential for severe reactions. Although one recent study reported successful management of OFC reactions with oral rehydration and anecdotally some reactions are managed with oral rehydration,[12] it is advisable to have intravenous hydration readily available.

TABLE III. Differential diagnosis of FPIES

Condition	Features that can distinguish from FPIES
Infectious gastroenteritis (eg, viral or bacterial)	Single episode of illness, fever, sick contacts
Sepsis	Fluid resuscitation alone not effective
Necrotizing enterocolitis	Newborns and younger infants, rapid escalation of symptoms, bloody stools, shock, intramural gas on abdominal radiographs
Anaphylaxis	Symptoms begin within minutes to 2 hours of exposure, positive IgE test results, usually other manifestations (eg, urticaria)
Food aversion	Look at the familial context
Inborn errors of metabolism: urea cycle defects, hereditary fructose intolerance, hyperammonemic syndromes, propionic/methylmalonic acidemia, β-oxidation defects, hyperinsulinism-hyperammonemia syndrome, pyruvate dehydrogenase deficiency, mitochondrial disorders, maple syrup urine disease, ketothiolase deficiency	Developmental delay, neurologic manifestations, organomegaly, reaction to fruits
Lactose intolerance	In its severe form gas, bloating, cramps, diarrhea, borborygmi, and vomiting after ingestion of liquid milk and large doses of dairy products with lactose
Neurologic disorders (eg, cyclic vomiting)	No relation to specific food intake
Gastrointestinal reflux disease	Emesis more chronic and not usually severe (ie, does not lead to dehydration), only upper gastrointestinal symptoms present
Hirschsprung disease	Delay in passage of the first meconium, marked abdominal distention
FPIES	Symptoms usually not temporarily associated with specific food intake; symptoms more chronic than episodic; vomiting less severe; most commonly implicated foods are CM, soy, wheat, and egg white
Eosinophilic gastroenteropathies (eg, eosinophilic esophagitis or eosinophilic gastroenteritis)	Usually not associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, more likely to have positive IgE test results
Celiac disease	No temporal relationship between symptoms and specific food intake, progressive malabsorption, results of celiac serology are positive
Immune enteropathies (eg, inflammatory bowel disease, autoimmune enteropathy, or immunodeficiency)	Rare in infancy, not related to specific food intake
Obstructive problems (eg, malrotation, Ladd bands, or volvulus)	Not related to specific food intake, evidence of obstruction on radiologic studies
Coagulation defects	No relation to specific food intake
α_1-Antitrypsin deficiency	No relation to specific food intake, hepatic involvement
Primary immunodeficiencies	No relation to specific food intake, intestinal symptoms frequent infections

A variety of protocols for FPIES-related OFCs have been published.[3,6,32-34] All OFCs require close supervision with immediate access to intravenous fluids. Some experts strongly recommend that peripheral intravenous access be secured before the OFC. A baseline complete blood cell count (CBC) with differential might be of value, especially in the research setting (as a comparator with a postchallenge CBC) but is considered optional in OFCs performed for clinical indications. Although some protocols provide the entire dose in a single portion, the current consensus is to administer the challenge food at a dose of 0.06 to 0.6 g, usually 0.3 g of the food protein per kilogram of body weight, in 3 equal doses over 30 minutes. It is generally recommended not to exceed a total of 3 g of protein or 10 g of total food (100 mL of liquid) for an initial feeding (which aims to approximate a serving size) and observe the patient for 4 to 6 hours.[34] Lower starting doses, longer observation periods between doses, or both should be considered in patients with a history of severe reactions.[32] When a very low dose of food protein is administered and there is no reaction after 2 to 3 hours of observation, some experts advocate that the patient ingest a full age-appropriate serving of the food, followed by 4 hours of observation. However, in patients with detectable sIgE to the challenge food, a more gradual administration of the challenge food according to protocols for IgE-mediated food allergy is recommended, with a longer postchallenge observation period to account for a possible FPIES reaction.[34] The total dose and dosing regimen for FPIES-related OFCs have not been systematically studied, and therefore practices can vary internationally; it is ultimately at the physician's discretion to modify the regimen per the individual circumstances.

With a positive (eg, failed) OFC result, typical FPIES symptoms, including emesis (usually protracted repetitive emesis), pallor, and lethargy, begin within 1 to 4 hours after ingestion. Diarrhea can occur in about 5 to 10 hours. If a CBC with differential was obtained before and after challenge, there is an increase in the neutrophil count (>1500 cells/mL), peaking 6 hours after food ingestion.[4,6,14] In patients with diarrhea, a stool sample can be assessed for the presence of occult blood, leukocytes, or red blood cells. Revised criteria for interpretation of OFC results are presented in Table V.

See Summary Statement 18 for treatment of acute reactions or positive OFC results.

Summary Statement 9: Do not routinely perform testing for food sIgE to identify food triggers of FPIES because FPIES is not an IgE-mediated process. However, because some patients with FPIES can exhibit coexisting IgE-mediated allergies,

TABLE IV. Diagnostic criteria for patients presenting with possible FPIES

Acute FPIES	
Major criterion: Vomiting in the 1- to 4-h period after ingestion of the suspect food and absence of classic IgE-mediated allergic skin or respiratory symptoms	Minor criteria: 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4 h after eating a different food 3. Extreme lethargy with any suspected reaction 4. Marked pallor with any suspected reaction 5. Need for emergency department visit with any suspected reaction 6. Need for intravenous fluid support with any suspected reaction 7. Diarrhea in 24 h (usually 5-10 h) 8. Hypotension 9. Hypothermia
The diagnosis of FPIES requires that a patient meets the major criterion and ≥3 minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially because viral gastroenteritis is so common in this age group. Furthermore, although not a criteria for diagnosis, it is important to recognize that acute FPIES reactions will typically completely resolve over a matter of hours compared with the usual several-day time course of gastroenteritis. The patient should be asymptomatic and growing normally when the offending food is eliminated from the diet.	
Chronic FPIES	
Severe presentation: When the offending food is ingested on a regular basis (eg, infant formula); intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis. *Milder presentation*: Lower doses of the problem food (eg, solid foods or food allergens in breast milk) lead to intermittent vomiting and/or diarrhea, usually with poor weight gain/FTT but without dehydration or metabolic acidosis.	The most important criterion for chronic FPIES diagnosis is resolution of the symptoms within days after elimination of the offending food(s) and acute recurrence of symptoms when the food is reintroduced, onset of vomiting in 1-4 h, diarrhea in 24 h (usually 5-10 h). Without confirmatory challenge, the diagnosis of chronic FPIES remains presumptive.

TABLE V. Diagnostic criteria for the interpretation of OFCs in patients with a history of possible or confirmed FPIES

Major criterion	Minor criteria
Vomiting in the 1- to 4-h period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms	1. Lethargy 2. Pallor 3. Diarrhea 5-10 h after food ingestion 4. Hypotension 5. Hypothermia 6. Increased neutrophil count of ≥1500 neutrophils above the baseline count
The OFC will be considered diagnostic of FPIES (ie, positive) if the major criterion is met with ≥2 minor criteria. However, we would suggest 2 important caveats to these criteria: (1) with the rapid use of ondansetron, many of the minor criteria, such as repetitive vomiting, pallor, and lethargy can be averted, and (2) not all facilities performing challenges have the ability to perform neutrophil counts in a timely manner. Therefore the treating physician might decide that a challenge be considered diagnostic in some instances, even if only the major criterion was met. However, in challenges performed for research purposes, providers should adhere to stringent criteria for challenge positivity.	

testing can be considered in patients with certain comorbid conditions. Assessment of chemistry or blood counts can help rule out other causes of symptoms if obtained in the acute setting. [Strength of recommendation: Moderate; Evidence strength: III; Evidence grade: C]

The majority of patients with FPIES have negative skin prick test (SPT) responses and undetectable serum food sIgE to the suspect food at the time of their initial diagnosis.[4,8,12,18,22] However, IgE testing can be considered in patients with FPIES at follow-up visits, as dictated by interval history, because 2% to 20% might eventually have positive test responses to the suspect FPIES-related food or foods and 20% to 40% will have positive test responses to other common food allergens.[4,8,18] There are some children who demonstrate sIgE to their trigger food (so-called atypical FPIES) and have slower resolution of FPIES, and these children are important to identify.[8,35] Therefore periodic testing (eg, before an OFC) for food sIgE can be considered in patients with comorbid conditions, such as IgE-mediated food allergy to other foods and atopic dermatitis believed to be influenced by a food allergen, but this is not recommended at the initial evaluation for an FPIES trigger. In patients with CM-induced FPIES, CM sIgE levels should be measured before performing a food challenge, given the risk of conversion to the IgE-mediated CM allergy. Atopy patch tests have been evaluated in 2 small studies as a possible means of identifying specific food sensitivities in patients with FPIES. Because of conflicting results, no recommendation regarding the utility of atopy patch tests can be made.[36,37]

Patients with chronic FPIES demonstrate varying degrees of anemia, hypoalbuminemia, and an increased white blood cell count with a left shift and eosinophilia.[10] This frequently leads to sepsis evaluation in the emergency department.[22] Thrombocytosis was reported in 65% of patients in one acute FPIES series.[9] Metabolic acidosis and methemoglobinemia were reported in patients with acute and chronic FPIES because of hemodynamic shifts.[38]

In patients with acute FPIES with diarrhea, frank or occult blood, mucus, leukocytes, and increased carbohydrate content can all occur.[6] In infants with chronic FPIES with diarrhea, stool examination can reveal occult blood, neutrophils, eosinophils, Charcot-Leyden crystals, and/or reducing substances.[10] Gastric

aspirates were assessed before and 3 hours after an OFC, revealing more than 10 leukocytes/high-power field in 15 of 16 patients with positive OFC results and 0 of 8 patients with negative OFC results.[39] These evaluations do not have clinical utility for routine use, and even the acute leukocytosis seen in patients with positive OFC results rarely adds to the overall interpretation of the OFC outcome.

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

There is no radiographic finding specific to FPIES. Radiologic studies performed in some older studies involving infants with possible chronic FPIES symptoms showed air-fluid levels, nonspecific narrowing and thumb printing of the rectum and sigmoid, and thickening of the plicae circulares in the duodenum and jejunum with excess luminal fluid.[40] Intramural gas has been documented, potentially leading to a misdiagnosis of necrotizing enterocolitis.[9]

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

An infant can present with multiple reactions before FPIES is eventually considered, often leading to extensive diagnostic evaluations, especially when FPIES is caused by solid foods.[9,22] Delayed diagnosis is likely due to a combination of nonspecific symptoms, the absence of definitive diagnostic tests, and an overall lack of familiarity with FPIES. Delayed diagnosis of solid food–induced FPIES might also be due to the fact that rice, oat, and vegetables uncommonly cause IgE-mediated food allergy.

The differential diagnosis of FPIES is extensive, as shown in Table III. The initial episodes can be misdiagnosed as acute viral gastroenteritis or be evaluated for sepsis, especially if they present with profound lethargy, hypotension, and increased white blood cell counts with a leftward shift.[6,9]

Summary Statement 12: Use distinct criteria to diagnose FPIES in the outpatient/community setting compared with the monitored setting in which OFCs are being used to rule in the diagnosis. [Strength of recommendation: Weak; Evidence strength: III/IV; Evidence grade: D]

Revised diagnostic criteria for patients presenting with possible acute and chronic FPIES are presented in Table IV. These criteria differ from Powell and Sicherer's criteria in that they eliminate an age limit for onset of FPIES and emphasize repetitive vomiting as a cardinal feature of acute FPIES based on more recent literature.[5,6,8,9,11,12,18,28,41] Specific major and minor criteria for acute FPIES are provided based on the collective published evidence. The major criterion for acute FPIES is vomiting in the 1- to 4-hour period after ingestion of the suspect food and the absence of classic IgE-mediated allergic skin or respiratory symptoms. Minor criteria include the following:

1. a second (or more) episode of repetitive vomiting after eating the same suspect food;
2. a repetitive vomiting episode 1 to 4 hours after eating a different food;
3. extreme lethargy with any suspected reaction;
4. marked pallor with any suspected reaction;
5. need for emergency department visit with any suspected reaction;
6. need for intravenous fluid support with any suspected reaction;
7. diarrhea in 24 hours (usually 5–10 hours);
8. hypotension; and
9. hypothermia.

The diagnosis of FPIES requires that a patient meets the major criterion and at least 3 minor criteria. If only a single episode has occurred, a diagnostic OFC should be strongly considered to confirm the diagnosis, especially because viral gastroenteritis is so common in this age group.

General criteria are provided for patients with chronic FPIES, but given the paucity of published reports of chronic FPIES, specific major and minor criteria could not be established at this time.

For severe chronic FPIES, when the offending food is ingested on a regular basis (eg, infant formula), intermittent but progressive vomiting and diarrhea (occasionally with blood) develop, sometimes with dehydration and metabolic acidosis. For milder chronic FPIES, lower doses of the problem food (eg, solid foods or food allergens in breast milk) lead to intermittent vomiting, diarrhea, or both, usually with poor weight gain/FTT but without dehydration or metabolic acidosis.

It is important to recognize 2 distinct hallmarks of chronic FPIES: patients are asymptomatic and maintain normal growth when the trigger food is eliminated from the diet, and reintroduction of the trigger food induces acute FPIES symptoms. The diagnostic criteria for the interpretation of OFC results in patients with a history of possible or confirmed FPIES are presented in Table V. These criteria also differ in the degree of neutrophilia and remove the stool laboratory findings, reflecting a possible phenotypic shift represented by a lower frequency of diarrhea and smaller magnitude of neutrophil count increase during OFCs, as reported in the recent literature.[4,11,12]

SECTION IV: PATHOPHYSIOLOGY OF FPIES

FPIES can involve antigen-specific T cells, antibodies, and cytokines as a cause of the inflammation found in the colon and, to variable degrees, the ileum by means of endoscopy, colonoscopy, and biopsy.[39,42-48] This inflammation is believed to cause an increased intestinal permeability and fluid shift into the gastrointestinal lumen.[49]

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

FPIES is classified as a non–IgE-mediated disorder.[1,8,22,50] However, some patients with FPIES have IgE to the trigger food, which might be associated with a more protracted course, in particular casein in patients with CM-induced FPIES.[4,22,32] Phenotypic shifting from IgE-mediated CM-induced allergy to pure FPIES has been reported.[51] Local intestinal mucosal IgE antibodies could facilitate antigen uptake and lead to intestinal inflammation. T_H2 responses similar to those occurring in patients with IgE-mediated allergy have been found in patients with FPIES.[52,53] This corroborates the observation of high rates of atopy in patients with FPIES.[3,4] The relationship between IgE and non-IgE mechanisms in patients with FPIES requires further investigations. Reported successful use of ondansetron

to treat vomiting, abdominal pain, and lethargy during FPIES challenges implies neuroimmune mechanism involvement.[54,55]

SECTION IV: GASTROINTESTINAL MANIFESTATIONS OF FPIES

Summary Statement 14: Do not routinely obtain endoscopic evaluation as part of the evaluation of FPIES. [Strength of recommendation: Weak; Evidence strength: IV; Evidence grade: D]

In patients with chronic FPIES with emesis and FTT, upper endoscopy can reveal gastric edema, erythema, and mucosal friability, with gastric antral erosions.[46] Colonoscopy results can be normal in the absence of rectal bleeding or diarrhea.[42,43,56,57]

In patients with rectal bleeding, loss of vascular pattern, spontaneous and induced friability, and variable degrees of ulceration with spontaneous bleeding can occur. Rectal histology ranges from slight infiltrate of lymphocytes and plasma cells in the lamina propria to polymorphonuclear leukocytic infiltration of the lamina propria or glands, with occasional crypt abscesses and depletion of mucus from rectal glands. Destruction of the surface epithelium can be seen. Colonic macroscopic appearance is similar to that of the rectum, with red, fragile, hemorrhagic mucosa seen within a few hours of ingesting the offending food.[56] Colonic biopsy specimens show severe inflammation with increased eosinophil numbers.[56] In some infants with FPIES, small intestinal damage with variable degrees of villous atrophy has been described.[24] Clinically, enteropathy can cause carbohydrate malabsorption and watery stools, which are positive for reducing substances.[6,57] Gross and histologic abnormalities can revert to normal as soon as 2 days after removal of the trigger food.[42]

Summary Statement 15: Do not use stool tests to make the diagnosis of FPIES. [Strength of recommendation: Weak; Evidence strength: III; Evidence grade: D]

Stool eosinophils, detected by using Hansel's stain, along with eosinophilic debris can be found in infants with FPIES.[57] Results of stool cultures and/or evaluation of stool for pathogenic organisms, including parasites, should be negative. Stool leukocytes noted on trigger food challenge were included among Powell's diagnostic criteria of FPIES, although this specific feature is rarely considered essential in light of Sicherer's modification to the acute FPIES criteria.[57] In addition, patients with chronic FPIES can have occult fecal or frank blood after elimination and then reintroduction of the trigger food to their diets.[12,17,57]

Summary Statement 16: Consider a work-up to rule out other gastrointestinal diseases resulting in symptoms that overlap with FPIES. [Strength of recommendation: Moderate; Evidence strength: III; Evidence grade: D]

A broad differential must be considered given that many infantile gastrointestinal disorders cause symptoms overlapping with chronic FPIES (Table III).

SECTION VI: MANAGEMENT OF ACUTE FPIES

Summary Statement 17: Treat acute FPIES as a medical emergency and be prepared to provide aggressive fluid resuscitation because approximately 15% of patients can have hypovolemic shock. [Strength of recommendation: Strong; Evidence strength: IIa; Evidence grade: B]

Summary Statement 18: Manage acute FPIES individually according to severity and review treatment strategies with the caregivers of each patient. [Strength of recommendation: Moderate; Evidence strength: IIb/III; Evidence grade: C]

Acute FPIES can result readily in hypovolemic shock and should be managed appropriately whether from a positive OFC result or accidental exposure. The priority in management of severe FPIES is restoration of stable hemodynamics through aggressive isotonic fluid resuscitation (eg, 10-20 mL/kg boluses of normal saline) repeated as needed and dextrose saline as a continuous intravenous maintenance infusion (Table VI). A single dose of intravenous methylprednisolone (1 mg/kg; maximum, 60-80 mg), can decrease presumed cell-mediated inflammation, although no studies support this recommendation.[33] In severe reactions patients might require supplemental oxygen, mechanical ventilation, or noninvasive positive pressure ventilation for respiratory insufficiency or failure, vasopressors for hypotension, bicarbonate for acidemia, and methylene blue for methemoglobulinemia.[3,28,32,38,58,59] Epinephrine autoinjectors are not routinely recommended/prescribed for FPIES, although those with concomitant IgE-mediated allergy should be prescribed epinephrine autoinjector at the physician's discretion if the patient is deemed at risk for food-induced anaphylaxis.[1] Mild-to-moderate acute FPIES can resolve with oral rehydration, including breast-feeding, at home (Table VII).

Summary Statement 19: Consider ondansetron as an adjunctive management of emesis in patients with acute FPIES. [Strength of recommendation: Weak; Evidence strength: IV; Evidence grade: D]

Ondansetron is a serotonin 5-HT_3 receptor antagonist used to treat nausea and vomiting, often after chemotherapy, but is used also in patients with viral gastroenteritis. Special caution might be warranted in children with heart disease because of the potential to prolong the QT interval.[60] Two small case series reported that use of intravenous ondansetron was helpful in stopping emesis during FPIES-related OFCs.[54,55] This intervention is promising, but its use is poorly studied at present. Rigorous trials are needed to determine the role and efficacy of ondansetron in the management of acute FPIES.

Summary Statement 20: Use dietary elimination of the trigger food or foods for the primary management of FPIES and educate caregivers and other care providers regarding avoidance strategies. [Strength of recommendation: Strong; Evidence strength: IIb/IIIIV; Evidence grade: C]

Long-term FPIES management involves elimination of the trigger food or foods, plans for dietary advancement, treatment of symptoms at presentation or on re-exposure (including emergency treatment planning), and monitoring for FPIES resolution. Nutritional consultation should be strongly considered for any patient, irrespective of the number of food avoidances recommended, to ensure adherence to dietary avoidance and adequate nutrition.

Infants with suspected CM- or soy-induced FPIES are generally advised to avoid all forms of these foods, including baked and processed foods, unless they are already included in the diet.[1,3,61] There are no conclusive studies to date evaluating tolerance to CM and egg proteins in baked products in children with FPIES, although a small case series reported tolerance of baked CM and egg in some children. Introduction of baked CM and egg should be done under physician supervision

TABLE VI. Management of acute FPIES episode at the medical facility

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

Strong consideration should be lent to performing food challenges in children with a history of severe FPIES in the hospital or other monitored setting with immediate availability of intravenous resuscitation. Oral challenges in the physician's office can be considered in patients with no history of a severe FPIES reaction, although caution should be urged because there are no data that can predict the future severity of FPIES reactions.

TABLE VII. Management of acute FPIES episode at home

Current episode	Mild[A,B]	Moderate-to-severe
Symptoms	1-2 Episodes of emesis No or mild lethargy	>3 Episodes of emesis and moderate-to-severe lethargy
Management	Attempt oral rehydration at home (eg, breast-feeding or clear fluids)	Call 911 or go to the emergency department

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

because there are unclear long-term outcomes associated with this practice.[62-67]

Infants with CM/soy-induced FPIES can be breast-fed or use a hypoallergenic formula, such as casein-based extensively hydrolyzed formula. When possible, breast-feeding should be continued, which is consistent with official recommendations for infant feeding.[68] Ten percent to 20% might require an amino acid–based formula (AAF).[4,22] In infants with CM-induced FPIES, introduction of soy formula should be considered under a physician's supervision and *vice versa*.

The risk of coreactivity to CM and soy is reported in approximately 20% to 40% of US patients but is noticeably absent in similar reports from Australia, Israel, and Italy.[9,12,18] Based on high homology of the protein sequences in these animal milks, goat and sheep milk are not recommended in patients with CM-induced FPIES.[61] It is possible that milks from donkeys, camels, or both might be tolerated in patients with CM-induced FPIES because they are usually well tolerated in those with IgE-mediated CM allergy. Infants with chronic FPIES usually return to their usual state of health within 3 to 10 days of switching to a hypoallergenic formula, although in severe cases temporary bowel rest and intravenous fluids might be necessary.[6,14]

Summary Statement 21: Do not recommend routine maternal dietary elimination of offending triggers while breast-feeding if the infant is thriving and remains asymptomatic. [Strength of recommendation: Moderate; Evidence strength: III-IV; Evidence grade: C]

The majority of infants do not react to food allergens present in maternal breast milk. In the case of symptomatic FPIES occurring in an exclusively breast-fed infant, the mother should eliminate

the suspected trigger food or foods from her diet if reactions occur after breast-feeding or the infant has FTT; the mother should seek immediate consultation with an allergy specialist.[15,69] Nutritional consultation should be considered to assist the elimination diet. If resolution of symptoms is not accomplished with a maternal dietary elimination diet, discontinuation of breast-feeding and introduction of a hypoallergenic formula should be considered.[68]

Summary Statement 22: Reintroduce the foods triggering FPIES under a physician's supervision. [Strength of recommendation: Strong; Evidence strength: Ia/IIb; Evidence grade: B]

Foods that triggered FPIES reactions in the past should generally be reintroduced under a physician's supervision during a formal OFC or supervised feeding. The timing of such reintroduction is variable. Placement of secure peripheral intravenous access before the OFC might be warranted in patients with past severe reactions requiring an emergency department visit or hospitalization, as well as in infants and patients with anticipated difficult intravenous access. Between 45% and 95% of the challenge reactions were treated with intravenous fluids, steroids, or both.[8,18] In patients with milder reactions, oral rehydration might be sufficient (Table VII).[12] Although some providers might elect to allow families to try certain foods at home, this should be a shared decision between medical care providers and caregivers, accounting for access and distance to local emergency departments, caregiver comfort, the nature of the trigger food, and the severity of past FPIES reactions.

Summary Statement 23: Recognize that infants with CM- or soy-induced FPIES might be at increased risk of having FPIES to other foods. [Strength of recommendation: Strong; Evidence strength: III; Evidence grade: C]

The majority of children (65% to 80%) have FPIES to a single food, most commonly CM.[4,5,9] In a large US case series at a tertiary care center, about 5% to 10% of children reacted to more than 3 foods, some to as many as 6 or more foods.[4,5] Children with either CM- or soy-induced FPIES can also react to both foods, with this likelihood being higher among those who had symptoms of FPIES in the first month of life, although the risk (Table VIII) or odds of this occurring are not known.[4,6,57] In these infants with early onset of FPIES, it might be prudent to breast-feed or introduce a hypoallergenic formula in the first 6 to 12 months of life, although data pertaining to primary/secondary FPIES prevention do not exist. In such potentially dually reactive children, it is recommended to perform supervised OFCs to introduce the uncertain FPIES trigger.

Children with CM- or soy-induced FPIES can also have an increased likelihood of reacting to a solid food, most commonly rice or oat. Current early feeding guidelines do not recommend delay in introducing complementary foods past 6 months of life because of FPIES.[70-72] A practical ordering for introducing solids at about 6 months of age at home could start with fruits and vegetables, followed by other complementary foods, such as red meats and cereals (Table IX). If an infant tolerates a variety of early food proteins, subsequent introduction might be more liberal. Tolerance to one food from the food group is considered a favorable prognostic indicator for tolerance to other foods from the same group.[32]

In an infant with severe CM- and/or soy-induced FPIES, supervised (eg, in-office) introduction of solids can be considered to promote implementation of normal dietary variety and prevent unnecessary avoidance. Supervised OFCs to a mixture of several solids can be considered as a way of excluding the risk of severe reactions to small amounts, followed by gradual build up to regular age-appropriate serving size at home (S. Miceli Sopo, personal communication).

TABLE VIII. Common food coallergies in children with FPIES

FPIES to:	Clinical cross-reactivity/ coallergy	Observed occurrence*
CM	Soy	<30% to 40%
	Any solid food	<16%
Soy	CM	<30% to 40%
	Any solid food	<16%
Solid food (any)	Another solid food	<44%
	CM or soy	<25%
Legumes*	Soy	<80%
Grains: rice, oats, etc*	Other grains (including rice)	About 50%
Poultry*	Other poultry	<40%

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

SECTION VII: NUTRITIONAL MANAGEMENT FOR FPIES

Summary Statement 24: Provide guidance during the introduction of complementary foods to ensure nutritional adequacy during this time and beyond. [Strength of Recommendation: Strong; Evidence Strength: III; Grade C]

Children with food allergy have been noted to have deficiencies in energy, protein, vitamin A, vitamin D, calcium, iron, and zinc.[73-76] Infantile FPIES is a risk for deficiencies caused by dietary restrictions and delayed introduction of new foods. Limited food experiences can adversely affect food intake for many years to come.[77] It is commonly recommended that caregivers introduce a new food as a single ingredient and, in the case of high-risk foods, to wait at least 4 days before introducing another food to observe for the development of a reaction.[78] Providers should recognize that even single-food elimination can be associated with significant nutritional deficiency.[79] Consultation with a dietitian is highly recommended to facilitate weaning. Table E3 in this article's Online Repository at www.jacionline.org details the nutrients typically provided by the foods most commonly triggering FPIES.

Summary Statement 25: Do not routinely recommend avoidance of products with precautionary allergen labeling in patients with FPIES. [Strength of recommendation: Weak; Evidence strength: IV; Evidence grade: D]

No studies have identified a reliable threshold dose (TD) in patients with FPIES. Among 28 children undergoing OFC to CM, 53.6% tolerated 121 mL of CM and 82% tolerated 50 mL of CM before having a reaction.[12] High TDs have been reported.[18] However, further studies have reported a TD of only 0.15 g of protein/kg body weight in 15 (93.7%) of 16 cases of confirmed FPIES caused by CM, soy, egg, rice, and oat.[36] Therefore strict avoidance of trigger foods is recommended.

Summary Statement 26: Use hypoallergenic formula in formula-fed infants or infants who can no longer breast-feed and are given a diagnosis of FPIES caused by CM. [Strength of recommendation: Strong; Evidence strength: IIa/IIb; Evidence grade: B]

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

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

This table should be considered in the context of the following notes:
A. Exclusive breast-feeding until 4 to 6 months of age and continuing breast-feeding through the first year of life or longer as long as mutually desired by both mother and child (Baker RD, Greer FR, Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 2010;126:1040-50).
B. If an infant tolerates a variety of early foods, subsequent introduction can be more liberal. Additionally, tolerance to one food in a food group (green pea) is considered a favorable prognostic indicator for tolerance of other foods from the same group (legumes; Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol 2005;115:149-56).
AAP, CoN, American Academy of Pediatrics, Committee on Nutrition; *WHO*, World Health Organization.
*Risk assessment is based on the clinical experience and published reports of FPIES triggers.

The official guidelines[1] recommend a hypoallergenic formula for the treatment of FPIES based on several studies demonstrating that most children tolerated extensively hydrolyzed formula, although there are selected children who exclusively tolerate AAFs.[7,8,80-82] AAFs are the only completely nonallergenic formulas and can be effective in patients not responding to extensively hydrolyzed formulas and those with FTT. Soy formula might be an acceptable alternative, especially in infants older than 6 months; however, cautious introduction is warranted because of the potential for coreactivity between patients with soy-induced FPIES and those with CM-induced FPIES.

Summary Statement 27: Monitor growth (weight and height/length) regularly in children with FPIES. [Strength of recommendation: Moderate; Evidence strength: III; Evidence grade: C]

Nowak and others[22,32,42,83,84] reported that infants with CM- or soy-induced FPIES exposed to these proteins on a daily basis typically manifest poor weight gain, weight loss, or FTT that resolves with elimination of the implicated food. Poor growth in children with FPIES who have successfully eliminated the implicated food and remain asymptomatic has not been reported. Children with FPIES and multiple food avoidances or difficulty advancing the diet might be at increased risk. Growth (weight, length/height, and head circumference) should be assessed at regular intervals based on national standards.[1,85,86]

Summary Statement 28: Recommend foods that enhance developmental skills in infants in the complementary feeding period to prevent aversive feeding behaviors and delay in the development of food acceptance and feeding skills. [Strength of recommendation: Weak; Evidence strength: IV; Evidence grade: D]

Timely introduction of various tastes and textures affects flavor acceptance, feeding skills, and eating behaviors.[87-93] Finding appropriate flavors and textures for infants and children with FPIES requires creativity when multiple solid foods are restricted.[93] Many textures can be provided, even if only 1 food is tolerated, because a single fruit or vegetable can be prepared into a thin or thick puree, pureed with lumps, soft cooked for finger foods, or freeze-dried or fried/oven baked in refined oil for a crispy crunchy texture (Table IX).

SECTION VIII: NATURAL HISTORY OF FPIES

Summary Statement 29: Recognize that the age of development of tolerance in patients with FPIES varies by type of food trigger and country of origin. [Strength of recommendation: Strong; Evidence strength: IIa/IIb; Evidence grade: B]

Development of tolerance in patients with CM-induced FPIES, soy-induced FPIES, or both has been reported to occur at an earlier age than tolerance in patients with grain- or other food-

induced FPIES. Significant data heterogeneity and potential selection bias influence these estimates. The average reported age of tolerance to grains is 35 months, and that to other solid foods is 42 months. The average reported age of tolerance to soy is approximately 12 months but ranges from 6 months to greater than 22 years of age.[4,5,17] In a large population-based cohort study from Israel, for patients with CM-induced FPIES, 60% had tolerance by 1 year, 75% by 2 years, and 85% by 3 years.[12] In a large US case series the median age of tolerance was 6.7 years. However, data from a challenge-based study in Korea noted that significant rates of tolerance to CM- and soy-induced FPIES might occur more rapidly (12 and 6 months, respectively) than previously assumed.[11] In pooling the available data from multiple small cohorts, the age of CM tolerance appears to be around 3 years, but recent large cohorts found a later age of tolerance.[5,9-12,18,36,37,49,54,57,81,94-102] However, these data were not derived from a targeted study to determine a firm age of resolution and thus might be biased toward older ages. In a large US case series the median age of resolution for CM-induced FPIES was 5.1 years, and in the United Kingdom 25% of the patients had CM-induced FPIES persist at 8 years of age.[5,103] Data from the same large US case series noted that median ages of resolution were 4.7 years for rice and 4.0 years for oat. Several studies observed that patients with CM-induced FPIES and positive CM-induced SPT responses have a more protracted course and older age of tolerance (approximately 13.8 years) compared with those with negative SPT responses.[4]

Summary Statement 30: Evaluate patients with FPIES at regular intervals according to the patient's age and food allergen to determine whether she or he is still allergic. [Strength of recommendation: Strong; Evidence strength: IIb/III; Evidence grade: C]

The ideal timing of OFCs to determine resolution has not been systematically studied but can vary considerably by country, nutritional and social food importance, and individual preference. In the United States diagnostic OFCs are usually attempted within 12 to 18 months after the most recent reaction.[3,32] Korean data suggest children might be ready within a year of diagnosis, with tolerance rates to CM and soy ranging between 27% and 75% at 6 months, 42% and 91% and 8 months, and 64% and 92% at 10 months, respectively.[11] CM-induced FPIES resolved in all children by age 2 years, and soy-induced FPIES resolved by age 14 months; 50% of CM-induced FPIES resolved within first year of life, 89% by age 2 years, and 90% by age 3 years.[12] In contrast, retrospective series from the United States report lower rates of resolution of FPIES to CM or soy: 35% by age 2 years, 70% by age 3 years, and 85% by age 5 years.[4,5] These differences likely reflect various study designs, provider preferences, international differences in the approach to such patients, or selection bias toward more severe and persistent phenotype among children evaluated at the referral allergy centers compared with those identified from the general population.[4,11,104] There are no data on resolution of FPIES to seafood in older children and adults. Periodic re-evaluations should be similarly considered in adult patients.

ASSESSMENT OF FUTURE NEEDS

The following areas have been identified as priorities for advancing the care of patients with FPIES:

1. characterize chronic FPIES;
2. establish FPIES prevalence;
3. identify FPIES risk factors;
4. validate the proposed diagnostic criteria;
5. standardize the OFC protocol and criteria for challenge positivity;
6. determine the pathophysiology of acute and chronic FPIES;
7. understand the relationship between atopy and FPIES;
8. develop noninvasive biomarkers for diagnosis and for monitoring for resolution;
9. develop therapeutic approaches to accelerate FPIES resolution;
10. determine the role of ondansetron in managing FPIES reactions;
11. determine whether extensively heated (baked) CM and egg white proteins can be tolerated by children with FPIES to these foods;
12. perform systematic evaluation of the prevalence of nutrient deficiencies, poor growth, and feeding difficulties in patients with FPIES and provide guidance for preventative intervention; and
13. perform longitudinal cohort studies to better determine outcomes and the natural history of FPIES in children and adults.

CONCLUSION

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

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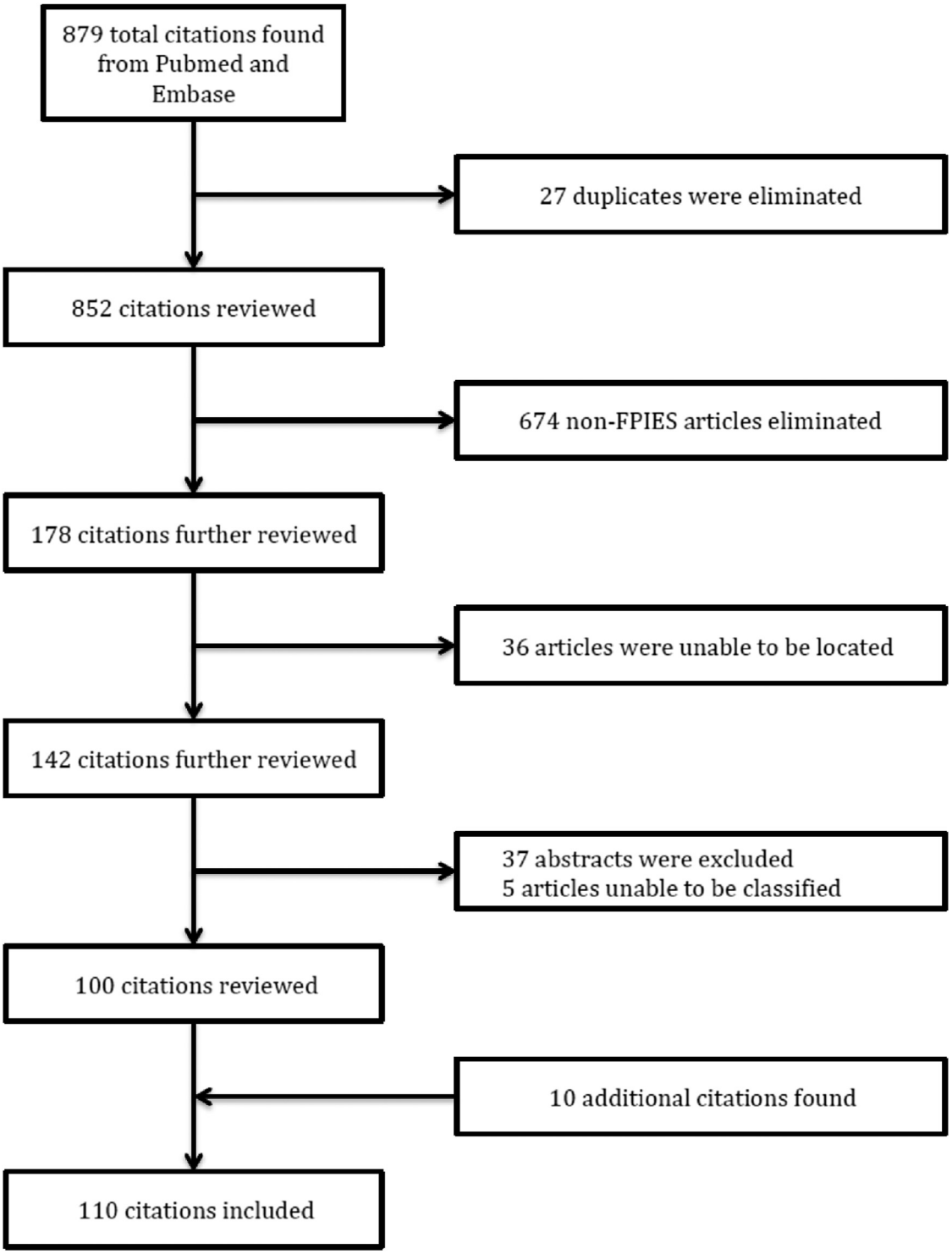

FIG E1. Scheme of a comprehensive literature search run in PubMed/Medline, Web of Science, and Embase.

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

Reference	Country	Only CM/soy FPIES investigated	Overall age of onset/ diagnosis (mo)	Age onset/ diagnosis of CM/ soy FPIES (mo)	Age onset/ diagnosis of solid-food FPIES (mo)	Atypical FPIES*	
						SPT	ssIgE
Nomura et al[13]	Japan	Yes (CM)	—	0.28 (0.1-0.82)†	—	—	8/14 (57%)
				0.59 (0.34-1.20)‡			6/16 (38%)‡
Powell[14]	United States	Yes (CM)	—	0.46 (0.14-2.39)	—	—	—
Gryboski[42]	United States	Yes (CM)	—	0.25 (0.07-4)	—	—	—
Katz et al[12]	Israel	Yes (CM)	—	1 (0-6.4)	—	2/44 (5%)	—
Nowak-Wegrzyn et al[22]	United States	No	—	1 (0.08-12)	5.5 (3-7)	0/44 (0%)	3/44 (7%)
McDonald et al[26]	United States	Yes (CM/soy)	—	1 (0.04-3)	—	—	—
Hwang et al[11]	South Korea	Yes (CM/soy)	—	1.28 (0.46-2.1)	—	—	—
Chung et al[24]	South Korea	Yes (CM)	1.75 (—)	1.75 (—)	—	0/28 (0%)	0/28 (0%)
Sicherer et al[8]	United States	No	2 (0.25-108)	2.0 (0.25-108)	6 (5-24)	1/20 (5%)	5/20 (25%)
Fogg et al[36]	United States	No	2 (0.25-9)	2 (0.25-4)	4.5 (4-9)	—	—
Sopo et al[18]	Italy	No	5.1 (5.10)	3.5 (2.40)§	10.6 (6.70)	0/66 (0%)	—
Mehr et al[9]	Australia	No	5.6 (2.70)	4.9 (2.60)	6.1 (1.70)	1/35 (3%)	—
Caubet et al[4]‖	United States	No	4 (2-6)	5 (2-10)	7 (6-12)	39/160 (24%) had positive SPT and/or ssIgE results	
Ruffner et al[5]	United States	No	9.7 (10.20)	7 (0.70)	12.1 (1.10)	26/721 (4%)	—

ssIgE, Serum sIgE antibody.
*Data are from studies in which age of onset/diagnosis was recorded. Data are represented as either mean age of onset/diagnosis (SD) or median age of onset/diagnosis (range), unless otherwise specified.
†Figure relates to cluster 1 analysis performed (both clusters representative of FPIES cases).
‡Figure relates to cluster 2 analysis performed (both clusters representative of FPIES cases).
§Figure relates to CM-induced FPIES only (3 soy cases included with other foods).
‖Data are represented as medians (interquartile ranges).

TABLE E2. Case series examining cases of FPIES*

Reference	Year	Study design	Definition used	Country	No. of patients	Study duration (y)	Data on all triggers	Center	Male sex (%)	Eczema (%)	IgE FA (%)
Caubet et al[4]	2014	Prospective + retrospective	Their own (modified Powell)	United States	160	10	Yes‡; CM, soy, rice, oat, seafood	One allergy clinic	54	57	11
Ruffner et al[5]	2013	Retrospective	Their own	United States	462	5	Yes; CM, soy, rice, oat, egg	One hospital	60	34	—
Fogg et al[36]	2006	Prospective	Sicherer et al	United States	19	1.5	Yes; CM, soy, rice, oat, egg	Single allergy clinic	53	11	—
Nowak-Wegrzyn et al[22]	2003	Retrospective	Sicherer et al	United States	44	5	Yes; CM, soy, rice, oat, barley	Two allergy clinics	59	34	—
Sicherer et al[8]	1998	Retrospective	Their own	United States	20	6	Yes; CM, soy, rice, green pea, poultry	Single allergy clinic	44	31†	15
Burks et al[7]	1994	Prospective	Their own	United States	22	1.5	CM/soy	One hospital	—	—	—
McDonald et al[26]	1984	Prospective	Powell	United States	10	—	CM/soy	One hospital	—	—	—
Powell[14]§	1976	Retrospective	Their own	United States	9	—	CM/soy	Their own	—	—	—
Gryboski[42]§	1967	Retrospective	None set	United States	21	16	CM	One hospital	90	14	—
Katz et al[12]	2011	Prospective	Sicherer et al	Israel	44	2	CM	One hospital	52	7	
Levy and Danon[20]	2003	Retrospective	Their own	Israel	6	6	Solid food triggers; chicken, turkey, green pea, lentil	One hospital	67	—	—
Hsu and Mehr, PC	2012	Retrospective	Sicherer et al	Australia	38	4	Yes, but only egg presented	One hospital	53	—	—
Mehr et al[9]	2009	Retrospective	Sicherer et al	Australia	35	16	Yes; rice, soy, CM, vegetables	Single allergy clinic	57	51	11
Nomura et al[17]	2011	Retrospective	Powell	Japan	30	3	CM	Japanese database	50	—	—
Hwang et al[11]	2009	Prospective	Powell	Korea	23	4	CM/soy	One hospital	70	0	—
Chung et al[24]	2002	Prospective	Sicherer et al	Korea	28	—	CM	One hospital	—	—	—
Sopo et al[18]	2012	Retrospective	Their own/Powell	Italy	66	7	Yes; CM, fish, egg, rice	Three allergy clinics	61	9	2

—, Not available; *FA*, IgE-mediated food allergy (ie, a positive serum sIgE antibody and IgE-mediated clinical reaction to a separate food protein not causing FPIES); *PC*, personal communication with corresponding author.
*Case series were only included where a definition of FPIES was provided and consecutive cases presenting to a health care setting were examined.
†Data were only available for infants with typical FPIES (n = 16).
‡Most common food allergens listed.
§In these series chronic FPIES or a combination of cases of acute/chronic FPIES was reported.

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

Provoking foods	Main nutrients	Alternative sources
CM	Macronutrients: **protein, fat**	***Hypoallergenic formula***, breast milk*
	Minerals and trace elements: **calcium**, magnesium, phosphorus, iodine	Older toddlers (>2 y): ***fortified alternative beverages such as soy***, rice, hemp, almond, oat, coconut, if tolerated
	Vitamins: A, B6, B12, **D**, riboflavin, pantothenic acid	
Rice, oat, barley, and wheat grains	Carbohydrate, magnesium, phosphorus, potassium, **zinc**	Flours and especially ***enriched cereal and cereal products*** made from quinoa, buckwheat, millet, corn, legumes: B vitamins, iron, zinc, carbohydrates
	Frequently in enriched cereal products: **iron**, thiamine, niacin, riboflavin, folate, **choline**, calcium, zinc, selenium	Dark green vegetables: B vitamins, vitamin A, B6, folate, vitamin C
		Starchy vegetables: carbohydrates
		Sesame seeds (as tahini): protein, calcium, iron, copper, manganese, zinc, thiamine, riboflavin, niacin, pantothenic acid, vitamin B6, folate, omega 3 and 6 fatty acids
		Beef and lamb: iron, zinc, choline
Soy	Calcium, phosphorus, magnesium, iron, zinc, thiamine, riboflavin, vitamin B6, folate	Hypoallergenic formula
		Other legumes
Eggs	Protein, iron, selenium, biotin, vitamin B12, pantothenic acid, folate, riboflavin, choline	Meats: protein, iron, B12, choline
Fish/shellfish	Protein, iodine	Seeds, such as flax and sesame: omega 3 fatty acids, protein, fat
	Fatty fish: Vitamins A and D, choline, omega-3 fatty acids	Iodized salt- small amounts- iodine
Chicken/turkey/lamb	**Protein**, selenium, phosphorus, vitamin B12, potassium, **choline**, **zinc**, **iron**	***Beef*** and pork: protein, fat, iron, B12, zinc, choline, phosphorous

Note: When choosing plant-based sources of iron (nonheme iron sources), it is beneficial to include dietary sources of vitamin C to improve iron absorption. Boldface nutrients are the main nutrients of concern with eliminated foods/food groups. Italicized and boldface foods are the best nutritional substitutes for the main nutrients of concern.
*Breast milk alone does not provide adequate vitamin D, iron, zinc, or protein for older infants (>6 months); consider also solid-food choices to meet these nutrient needs.