Non–IgE-mediated gastrointestinal food allergy

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Non–IgE-mediated gastrointestinal food-induced allergic
disorders (non-IgE-GI-FAs) account for an unknown proportion
of food allergies and include food protein–induced enterocolitis
syndrome (FPIES), food protein–induced allergic proctocolitis
(FPIAP), and food protein–induced enteropathy (FPE).
Non-IgE-GI-FAs are separate clinical entities but have many
overlapping clinical and histologic features among themselves
and with eosinophilic gastroenteropathies. Over the past decade,
FPIES has emerged as the most actively studied non-IgE-GI-FA,
potentially because of acute and distinct clinical features.
FPIAP remains among the common causes of rectal bleeding in
infants, while classic infantile FPE is rarely diagnosed. The
overall most common allergens are cow's milk and soy; in
patients with FPIES, rice and oat are also common. The most
prominent clinical features of FPIES are repetitive emesis,
pallor, and lethargy; chronic FPIES can lead to failure to thrive.
FPIAP manifests with bloody stools in well-appearing young
breast-fed or formula-fed infants. Features of FPE are
nonbloody diarrhea, malabsorption, protein-losing enteropathy,
hypoalbuminemia, and failure to thrive. Non-IgE-GI-FAs have a
favorable prognosis; the majority resolve by 1 year in patients
with FPIAP, 1 to 3 years in patients with FPE, and 1 to 5 years
in patients with FPIES, with significant differences regarding
specific foods. There is an urgent need to better define the
natural history of FPIES and the pathophysiology of non-IgE-
GI-FAs to develop biomarkers and novel therapies. (J Allergy
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Allergic reactions to foods affecting the gastrointestinal tract
have been known since ancient times. Hippocrates noted that
cow's milk (CM) caused gastrointestinal symptoms, as well as
urticaria, and that some infants fed CM had diarrhea, vomiting,
and failure to thrive (FTT) that resolved only after removal of CM
from their diets.[1] At present, non–IgE mediated gastrointestinal
reactions to food proteins (non-IgE-GI-FAs) are less well studied
than other food allergies. The major reason for the limited under-
standing of non-IgE-GI-FAs is lack of access to target gastroin-
testinal tissue; many patients' symptoms improve with empiric food
avoidance, and endoscopy and biopsy are not performed. Even if
biopsies are performed, they might not capture the myenteric
plexus, where the inflammatory response is localized, or in the
case of a patchy inflammatory process, the histology might be
normal. Furthermore, mast cell staining and careful enumeration
of intraepithelial lymphocytes (IELs) is not performed routinely.

CLASSIFICATION

Non–IgE-mediated food allergy encompasses a wide range of
disorders affecting the gastrointestinal tract (food protein–
induced enterocolitis syndrome [FPIES], food protein–induced
allergic proctocolitis [FPIAP], food protein–induced enteropathy
[FPE], celiac disease, and CM allergy–induced iron deficiency
anemia), skin (contact dermatitis to foods and dermatitis
herpetiformis), and lungs (Heiner syndrome, also known as
pulmonary hemosiderosis).[2-5] Celiac disease, eosinophilic
esophagitis, and extragastrointestinal manifestations of food
allergies will not be discussed in this review. We will focus on
new developments and areas of controversy, predominantly
concerning FPIES. Once considered to be a very rare food allergy,
over the past decade, FPIES has emerged as the most actively
studied non-IgE-GI-FA. It can be hypothesized that the potential
for severe reactions, improved recognition of the symptom
pattern, emergence of lay patient organizations raising awareness,
and an increase in prevalence are all potential contributing
factors.[6-8] Recently, features of FPIES and non-IgE-GI-FAs
have been reviewed extensively; Table I summarizes the cardinal
features of non-IgE-GI-FAs discussed in this review.[9] It has
been demonstrated that isolated gastrointestinal dysmotility
(too rapid, too slow, disturbed, or retrograde) is caused by
non-IgE-GI-FAs in a subset of patients manifesting as
pathologic gastroesophageal reflux, vomiting, delayed gastric

Abbreviations used	
CM:	Cow's milk
EC:	Eosinophilic colitis
EGID:	Eosinophilic gastrointestinal disorder
FPE:	Food protein–induced enteropathy
FPIES:	Food protein–induced enterocolitis syndrome
FPIAP:	Food protein–induced allergic proctocolitis
FTT:	Failure to thrive
IEL:	Intraepithelial lymphocyte
Non-IgE-GI-FA:	Non–IgE-mediated gastrointestinal food-induced allergic disorder
OFC:	Oral food challenge

emptying, diarrhea, constipation, or irritable bowel syndrome (Table II).[4,10-26]

MANIFESTATIONS

Recent studies from large, geographically diverse pediatric populations have defined the features of FPIES (Table I).[27-31] FPIES to CM and soy usually starts within the first 3 to 6 months of life; FPIES to solid foods usually starts at 4 to 7 months, reflecting the sequence of introduction of these foods to the diet. In patients with FPIES, the symptom pattern is determined by the frequency and dose of food allergen in the diet. Acute symptoms develop with intermittent exposure or re-exposure after a period of food avoidance and manifest as severe, projectile, and repetitive emesis starting within 1 to 3 hours of food ingestion. Associated features include pallor and lethargy, with or without diarrhea. Hypotension has been reported in up to 15% of reactions. FPIES is a systemic reaction distinct from IgE-mediated anaphylaxis (eg, lacking urticaria/angioedema or respiratory symptoms).[32] Chronic symptoms develop in young infants with regular intake of the food (eg, infant formula) and include intermittent but progressive emesis, diarrhea (with or without blood), and FTT.[33,34] Transition from chronic to acute symptoms in patients with FPIES resembles IgE-mediated food allergy associated with atopic dermatitis, in which avoidance of the offending food results in an anaphylactic reaction on subsequent exposure.[35] In contrast, such acute symptoms on reintroduction of food after a period of avoidance are not a feature of FPIAP and FPE.

FPIAP typically starts in the first 6 months of life, with blood-streaked and mucous stools.[2,36-39] FPIAP is estimated to account for up to 60% of healthy infants with rectal bleeding. Breast-fed infants are often older at the time of initial presentation and have less severe histologic findings.[38,40,41] New-onset FPIAP can also occur in older children and adults.[42,43] Onset is usually insidious, with a prolonged latent period after introduction of the food, although rarely, onset can be acute, within 12 hours after the first feeding. Infants typically appear well; however, increased gas, colicky behavior with pain on defecation, intermittent emesis, or increased frequency of bowel movements can be present. FTT is absent. Even when the offending food remains in the diet and bleeding continues, children grow well, although they can experience anemia despite iron supplementation.[38,40] FPIAP represents an infantile form of eosinophilic colitis (EC). In young adults EC is rare, has a chronic relapsing course, and is typically more severe, with symptoms including diarrhea,

abdominal pain, and weight loss. In the majority of cases of adult EC, there is no evidence of food allergy.[44]

FPE presents with protracted diarrhea in the first 9 months of life, typically the first 1 to 2 months, within weeks after the introduction of the food.[45,46] More than 50% of affected infants have FTT, and some present with abdominal distension, early satiety, and malabsorption. In many infants symptom onset is gradual; in others it mimics acute gastroenteritis complicated by protracted diarrhea caused by secondary lactose intolerance with transient emesis and anorexia. It might be difficult to distinguish FPE from postenteritis syndrome, especially because FPE can develop after infectious gastroenteritis.[47]

OFFENDING FOODS

The single most common food allergen in patients with non-IgE-GI-FAs is CM, followed by soy and cereals, including rice and oats. FPIES is caused by a single food in the majority of children (65% to 80%), usually CM or soy. US studies report that about 30% to 50% of infants react to both CM and soy,[28,48,49] whereas most non-US studies report a far smaller percentage.[27,31,50] About 5% to 10% are allergic to more than 3 foods, although very few are allergic to 6 or more foods.[28,29] In addition to CM and soy, different cereals, egg, vegetables, fruit, poultry, and the probiotic yeast *Saccharomyces boulardii* have been reported in young children, whereas fish, shellfish (crustaceans and mollusks), and mushroom have been reported in older children and adults.[31,48,50-63] Fish was a common trigger in infants from Italy and Spain.[50,57] Feeding routines, age of introduction of the specific food into the diet, and genetic predisposition might underpin geographic differences in patients with FPIES.

FPIAP in formula-fed infants is typically caused by CM and soy; extensively hydrolyzed formulas cause FPIAP in about 4% to 10%.[38,40,41] FPIAP in breast-fed infants is usually caused by CM, soy, egg, or corn in the maternal diet.[38,64] In older children and adults CM, egg, and wheat have been reported as FPIAP triggers.[42,43]

Infantile FPE is usually caused by CM formula. Soybean, wheat, and egg have also been confirmed as frequent triggers in children with allergy to multiple foods and coexistent CM-induced FPE.[45,46]

BREAST-FEEDING AND NON–IgE-MEDIATED FOOD ALLERGY

Infants with FPIES and FPE are usually asymptomatic during exclusive breast-feeding without maternal dietary restrictions, whereas up to 60% of FPIAP develops during exclusive breast-feeding.[51] FPIES to the food allergens transmitted through breast milk is rare, and the symptoms of acute FPIES develop on direct feeding with the offending food.[65,66] However, in Japanese infants with challenge-proved FPIES, symptoms are reported during breast-feeding in approximately 10%, highlighting potential ethnic, dietary, and geographic differences.[67,68] It is not clear how exclusive breast-feeding moderates the onset of FPIES; it has been hypothesized that breast milk IgA, either alone or as a complex with secreted antigens, might play a protective role by modulating the local gut mucosal immune responses and limiting the amount of available antigen.[40] In addition, the lower dose of food allergen in breast milk might mitigate the full expression of FPIES by not reaching the threshold of clinical reactivity.

TABLE I. Comparison of FPIES, FPIAP, and FPE

	FPIES	FPIAP	FPE
Age at onset	Dependent on age of exposure to antigen; usually 1 d to 1 y; might be older in case of solid foods, such as chicken, eggs, and seafood	Days to 6 mo, usually 1-4 wk; later onset in older children has been reported to CM, egg, and wheat	Dependent on age of exposure to antigen; CM and soy up to 2 y
Food proteins implicated			
Less common	CM, soy, rice, oat, egg	CM, soy	CM, soy
Most common	Multiple other food proteins have been described	Wheat, egg	Wheat, egg
React to ≥2 different foods	Up to 35%; in the United States up to 40% react to both CM and soy	Up to 20% might react to CM and soy or multiple foods	Rare
Transition to IgE positivity	Up to 35 %, especially in patients with CM-induced FPIES	None reported in infants; in older children up to 19% have detectable CM-specific IgE	None reported
Feeding at the time of onset	Formula or breast milk in solid food–induced FPIES	Breast milk or CM or soy formula	CM or soy formula
Atopic background	Variable	Variable	Variable
Family history of atopy	40% to 70%	Up to 25%	Unknown
Personal history of atopy	Up to 30%	Up to 20%	22%
Symptoms			
Emesis	Prominent, repetitive	Absent	Intermittent
Diarrhea	Severe in patients with chronic FPIES	Mild	Moderate
Bloody stools	Severe in patients with chronic FPIES	Prominent	Rare
Edema	Severe in patients with chronic FPIES	Mild, infrequent	Moderate
Shock	15%	Absent	Absent
FTT	Moderate-to-severe in patients with chronic FPIES	Absent	Moderate
Hypothermia	Present (<25%)	Absent	Absent
Laboratory findings			
Anemia	Moderate	Mild, infrequent	Moderate
Hypoalbuminemia	Acute	Mild, infrequent	Moderate
Methemoglobinemia	Might be present	Absent	Absent
Acidemia	Might be present	Absent	Absent
Malabsorption†	Absent	Absent	Present
Leukocytosis with neutrophilia	Prominent	Absent	Absent
Thrombocytosis	Moderate	Mild	Absent
Allergy evaluation			
Food skin prick test*	Can be positive in 4% to 30%	Negative	Negative
Serum food allergen IgE*	Can be positive in 4% to 30%	Negative	Negative
Total IgE	Normal or increased	Normal or increased	Normal
Peripheral blood eosinophilia	Absent	Occasional	Absent
Biopsy findings in infants with chronic symptoms			
Villous atrophy	Patchy, variable	Absent*	Variable†
Colitis	Prominent; rectal ulceration	Focal	Absent
Mucosal erosions	Occasional	Occasional, linear	Absent
LNH	Absent	Common	Duodenum and colon
Eosinophils	Prominent; cryptal abscesses	Prominent; cryptal abscesses; >60 eosinophils per 10 high-power fields in the lamina propria strongly suggest FPIAP	Few Increased IEL numbers
Supervised OFC	Vomiting, lethargy, pallor in 1-3 h; diarrhea in 5-8 h	Usually not necessary; visible or occult fecal blood in 12 h to several days	Usually not necessary; Vomiting and/or diarrhea in 40-72 h
Treatment	Food elimination; symptoms clear within hours in patients with acute FPIES and in 3-10 d in patients with chronic FPIES; 80% respond to hydrolysate; soy formula can be introduced under supervision; rechallenge in 12-24 mo	Food elimination from the maternal diet or hypoallergenic formula, about 10% might need elemental formula Food reintroduction after 12 mo	Food elimination, symptoms clear in 1-3 wk, rechallenge and biopsy in 1-2 y
Natural history	Varies by population, CM tends to resolve by age 3-5 y; rice-induced FPIES, 50% outgrow by age 5 y	Majority resolve by age 12 mo	Most cases resolve in 24-36 mo

(Continued)

TABLE I. *(Continued)*

	FPIES	FPIAP	FPE
Reintroduction of food into diet	Supervised OFC in a controlled setting	Home, gradually advancing	Home, gradually advancing
Pathophysiology			
T-cell response	Inconclusive, T_H2 skewing	Unknown	Increased intestinal intraepithelial suppressor/cytotoxic CD8$^+$ T cells
B-cell response	Absent IgE, IgG$_4$, IgA responses	Unknown	Absent
Cytokine imbalance	Decreased TGF-β, increased TNF-α and IFN-γ	Unknown	Increased IFN-γ and IL-4 level in jejunal biopsy specimens

LNH, Lymphonodular hyperplasia.
*If positive, might be a risk factor for persistent disease.
†Malabsorption, steatorrhea, sugar malabsorption, and deficiency of vitamin K–dependent factors can be seen.

There are no studies that support the concept that breast-feeding does more than delay the onset of FPIES because infants asymptomatic during exclusive breast-feeding and on an unrestricted maternal diet have FPIES symptoms only after having been weaned onto milk, soy, or other proteins.

DIAGNOSIS

Diagnosis of non-IgE-GI-FAs relies on a careful and detailed history (including diet records), physical examination, and responses to trial elimination diets and oral food challenges (OFCs). Biopsy is needed for histologic confirmation of FPE, whereas it is usually not indicated in patients with FPIES presenting with acute symptoms or in patients with FPIAP.

Laboratory tests

There are no biomarkers for non-IgE-GI-FAs. Food-specific IgE antibody levels, as measured by means of skin prick tests or serum measurement, are negative in the majority of patients, although 4% to 30% of children given a diagnosis of FPIES initially have or will have food-specific IgE to the food causing FPIES over time.[27-29,31,68] Atopy patch tests with fresh foods are not recommended for routine diagnosis because of the conflicting reports on diagnostic accuracy, lack of validation by means of biopsy, lack of standardized testing materials, and interpretation of results.[2,3,57,69-72] Measurement of food-specific IgG and IgG$_4$ antibody levels for the diagnosis of non-IgE-GI-FAs is not recommended.[2,69] Increased intestinal permeability and fecal eosinophil-derived neurotoxin have been identified as potential biomarkers in small studies of young children with non-IgE-GI-FAs but need to be further validated.[73,74]

The laboratory abnormalities reported in patients with non-IgE-GI-FAs are nondiagnostic but provide supporting evidence for clinical manifestations (Table I). Increased white blood counts with neutrophilia and eosinophilia, thrombocytosis, metabolic acidosis, and methemoglobinemia can be seen after an acute FPIES reaction. Iron deficiency anemia and mild hypoalbuminemia can be seen in patients with FPIAP. Malabsorption, anemia, hypoalbuminemia, and hypoproteinemia are common in patients with FPE.

Elimination diet

A trial elimination diet is suggested to determine whether chronic gastrointestinal symptoms are responsive to dietary manipulation. Elimination of the offending food results in significant improvement of emesis and diarrhea within a few hours in patients with acute and within days in patients with chronic FPIES and resolution of visible blood in the stool within a few days in patients with FPIAP. In patients with FPE, symptoms resolve usually within 1 to 4 weeks; full mucosal repair with normalization of disaccharidase activity might take several months.[33,34,38,40,75]

OFCs

Supervised open OFCs are recommended for the diagnosis of FPIES because of the potential for severe reactions and the need for intravenous hydration.[76] OFCs might not be necessary for the initial diagnosis if the child presents with recurrent symptoms of typical FPIES (≥2 reactions with classic symptoms in a 6-month period) and is well when the offending food is eliminated from the diet.[2,69] Subsequent OFCs are warranted to determine whether FPIES has resolved. Physician-supervised OFCs in patients with FPIES are considered higher-risk procedures, with up to 50% of reactions being treated with intravenous fluids.[76-78] Although there is only one report of challenge-proved FPIES to scallop in an adult, the symptoms were severe and required vigorous intravenous fluid resuscitation.[59] Although in the Israeli population–based study all reactions during OFCs were managed with oral rehydration, it is advisable to have intravenous access available in case of severe reactions in both children and adults (Table III).[2-4,9,27,59,69,79-82] Recent reports of the successful use of intravenous and intramuscular ondansetron for the treatment of reactions during OFCs suggest that antiemetic treatment can be used; these reports need to be validated by larger studies, and the role of ondansetron in managing FPIES should be better defined.[79,80]

The original criteria for interpretation of OFC results were proposed by Powell[34] based on her experience with young infants. OFC results are considered positive if at least 3 typical symptoms, laboratory findings, or both are present. Criteria include (1) emesis (onset at 1-3 hours), diarrhea (onset at 2-10 hours; mean, 5 hours), or both; (2) increased neutrophil count (>3500 cells/mL increase from baseline); (3) fecal frank or occult blood; (4) fecal leukocytes; and (5) fecal eosinophils. Recent studies reported that diarrhea is uncommon during diagnostic OFCs, and the criteria need to be revised to focus on emesis, lethargy, and/or pallor.[29,31,50,83,84] An international expert panel was convened in 2014 as the American Academy of Allergy, Asthma & Immunology Work Group and will provide consensus guidelines for the diagnosis of FPIES, including revised criteria for OFC interpretation.

In patients with FPIAP and FPE, reintroduction of the suspected food after 4 to 8 weeks of elimination can be performed

TABLE II. Association between non-IgE-GI-FAs and gastroesophageal reflux disease, colicky behavior, constipation, and irritable bowel syndrome

Disorder	Evidence for association with food allergy
Gastroesophageal reflux disease	A subset of infants can have CM allergy, especially those with severe and persistent regurgitation, FTT, and eczema.[18-21] Feeding with CM causes gastric dysrhythmia, delayed gastric emptying, prolonged gastric distension, and increased reflux episodes.[11,12]
Colic	A subgroup of infants with colic can have intolerance to CM formula; infants with intolerance usually have associated clinical features (eg, bloody stool, vomiting, and eczema).[22-25]
Constipation	Ten prospective clinical trials reported that a CM protein–free diet has a beneficial effect on constipation, with a success rate of 28% to 78%. The hypothetic pathogenic mechanism lies in increased anal pressure at rest, probably caused by allergic inflammation of the internal sphincter area because of mucosal eosinophil and mast cell infiltration.[13,14] Children responding to CM elimination from the diet were more likely to have coexistent allergic rhinitis, dermatitis, or bronchospasm. They were also more likely to have anal fissures and perianal erythema or eczema at baseline.[26]
IBS	Among 920 adult patients with IBS who underwent dietary elimination of CM and wheat and subsequent double-blind placebo-controlled challenges, 70 were given a diagnosis of nonceliac wheat sensitivity, and 206 were given a diagnosis of hypersensitivity to wheat and CM.[16] Patients with wheat and/or CM hypersensitivity had higher frequency of anemia, weight loss, self-reported wheat intolerance, coexistent atopy, and history of food allergy in infancy compared with the control subjects with IBS without food hypersensitivity. In duodenal biopsy specimens patients with wheat hypersensitivity had increased numbers of $CD3^+$ cells/100 enterocytes and increased eosinophil counts per 10 high-power fields. In the colon they had frequent lymphoid nodules, infiltration with IELs, eosinophil infiltration in the lamina propria, and intraepithelial eosinophil infiltration compared with control subjects with IBS.
	CLE was used for real-time visualization of structural/functional changes in the intestinal mucosa after food challenge in adults with IBS and suspected food hypersensitivity. CLE showed a real-time response to food antigens in 22 of 36 patients; no responses were observed in 14 of 36 patients (CLE^-) or any of the control subjects with Barrett esophagus. Baseline IEL numbers were significantly higher in CLE^+ than CLE^- subjects ($P = .004$); numbers increased significantly after food challenge ($P = .0008$). Within 5 minutes of exposure of CLE^+ patients to food antigens, IEL numbers increased, epithelial leaks/gaps formed, and intervillous spaces widened. Epithelial leaks and intervillous spaces also increased significantly in CLE^+ patients versus baseline values (both $P < .001$). The concordance of IELs measured by using CLE and conventional histology was 70.6%; they did not correlate ($P = .89$, $r^2 = 0.027$). Symptom scores improved more than 50% in CLE^+ patients after a 4-week exclusion diet and increased to 74% at 12 months; symptoms continued in CLE^- patients.[17]

CLE, Confocal laser endomicroscopy; *IBS,* irritable bowel syndrome.

usually at home and documented with a symptom diary. In questionable reactions with the absence of visible blood, stool samples can be tested for occult blood.[69] Testing for food-specific IgE is not routinely recommended for patients with FPIAP and FPE, unless these are associated features, such as atopic dermatitis or immediate allergic symptoms to food ingestion. However, if food-specific IgE is detected by using skin prick or serum tests or the history suggests associated vomiting, physician-supervised OFCs might be necessary to safely reintroduce the suspected food.[69]

Differential diagnosis

Differential diagnosis of non-IgE-GI-FAs is extensive and includes infections (bacterial, viral, and parasitic), Hirschprung disease, gastroesophageal reflux disease, idiopathic pyloric hypertrophy, volvulus, malrotation, ileus, inflammatory bowel disease, primary immunodeficiency disorders, autoimmune enteropathy, celiac disease, and coagulation disorders. Anaphylaxis, and in particular isolated immediate gastrointestinal IgE-mediated reactions, can be confused with acute FPIES. The distinguishing features favoring FPIES diagnosis include typical delayed onset of repetitive projectile emesis, pallor and lethargy, lack of respiratory and cutaneous allergic features, and no evidence of IgE sensitization to the offending food. There is also a significant phenotypic overlap between non-IgE-GI-FAs and primary eosinophilic gastrointestinal disorders (EGIDs). Primary EGIDs represent a spectrum of inflammatory gastrointestinal disorders in which eosinophils infiltrate the gut in the

absence of known causes for such tissue eosinophilia. EGIDs can be classified as eosinophilic esophagitis, eosinophilic gastroenteritis, and EC. Chronic FPIES differs from EGIDs because the appearance of acute symptoms of severe emesis after a period of avoidance of the offending food is diagnostic of FPIES but not seen in patients with EGIDs. Because biopsies are not usually performed in patients with FPIES, there is no known histologic basis for distinguishing between chronic FPIES and EGIDs. Infantile FPE triggers are limited to a few major foods, whereas EGIDs are triggered by a wide range of food allergens. In biopsy samples FPE is characterized by villous atrophy, lymphonodular hyperplasia, and increased IEL numbers with a paucity of eosinophils. In contrast, EGIDs are characterized by extensive eosinophilic inflammation and mast cell infiltration. EC has a bimodal distribution; its infantile form is synonymous with FPIAP. EC has a more severe and chronic relapsing course in young adults and is rarely associated with food allergy. In adults with EC, an intense eosinophilic infiltration in the colon can be segmental or diffuse and might affect several intestinal layers.[44]

Neurologic, cardiac, necrotizing enterocolitis, and metabolic disorders, such as lysinuric protein intolerance, trimethylaminuria, and hereditary fructose intolerance, should be considered in the differential diagnosis of FPIES, particularly when associated with multiple food triggers.[77-88] It is important to exclude celiac disease in all children with chronic gastrointestinal symptoms while on a gluten-containing diet. Before a child is started on an elimination diet including wheat, celiac-specific antibody (tissue transglutaminase IgA and total IgA) levels should be determined, and if positive, a referral for a full gastroenterologic

TABLE III. Controversies in FPIES management: frequently asked questions

Strictness of dietary food avoidance	It is usually not necessary to avoid products with precautionary labeling (eg, "can contain traces of" of "run on the same line"); only an exceptionally sensitive subject might need this degree of avoidance.[82]
Including baked milk and/or egg in the diet of children with milk- or egg-induced FPIES	Standard management is that of strict avoidance.[2-4,69] A subset of children can tolerate baked milk or egg diet[81]; tolerance should be preferably established under a physician's supervision.
Timing and setting of the reintroduction of the offending food	In one approach reintroduction of the offending food is recommended within 12-18 mo after the most recent reaction; it is done under a physician's supervision.[9]
Timing and setting of the introduction of the new foods	Varies by food group (Table IV).
Need for securing the peripheral intravenous access before the food challenge	Considering that approximately 50% of challenges are treated with intravenous fluids with about 15% risk of shock/hypotension, it is generally advisable to secure an intravenous access before onset of the food challenge, particularly in patients with a history of severe reactions to the challenge food or anticipated difficult intravenous access, such as infants.[2,9,27,69] For the challenges to the potentially cross-reactive foods, intravenous lines might not be needed.
Role of ondansetron in managing acute FPIES reactions	Small case series reported the effectiveness of intravenous and intramuscular ondansetron for managing acute FPIES in young children during challenge.[79,80] Ondansetron in generally well tolerated; however, it has the potential to prolong the QT interval and is contraindicated in patients with heart defects or a history of arrhythmia. The utility of ondansetron for managing FPIES reactions remains to be determined.
Role of intravenous steroids in managing acute FPIES reactions	Based on the presumed inflammatory pathophysiology of FPIES, a single dose of intravenous methylprednisone can be administered for a severe acute reaction.
Role of epinephrine autoinjector in managing acute FPIES reactions	Epinephrine does not appear to stop emesis in patients with acute FPIES but might be necessary to manage hypotension.[59] Epinephrine autoinjectors are not routinely prescribed for patients with FPIES, unless they have evidence of IgE sensitization to FPIES food and/or another food trigger that indicates risk of an immediate reaction.
Administration of vaccines containing the offending foods (eg, influenza, MMR, and DTaP)	There are no reports of adverse FPIES reactions to trace amounts of food proteins found in some vaccines. It is recommended that these vaccines be administered per the standard protocol.

evaluation is warranted.[10] If symptoms do not resolve with a strict elimination diet, the child should be evaluated for other underlying diseases, particular very early-onset inflammatory bowel disease and monogenic immunodeficiency disorders.[89]

Role of endoscopy and biopsy

Given the typical constellation of clinical symptoms and strict criteria for a positive OFC result, endoscopic examination is not required in patients with suspected acute FPIES[90] but might be required for persistent and severe chronic manifestations unresponsive to dietary manipulation to exclude other gastrointestinal tract pathology.[69] The diagnosis of FPIAP and FPE is conclusively confirmed by histologic findings in combination with the usual clinical manifestations. The finding of lymphonodular hyperplasia in the duodenal bulb and colon with or without erosions is a characteristic, but not pathognomonic, feature of noninfantile FPE, as is the finding of increased IEL numbers (>25/100 epithelial cells) in the absence of celiac disease.[16,17,91]

MANAGEMENT

Management of non-IgE-GI-FAs involves elimination of the offending foods, nutritional support to avoid deficiencies, and in case of FPIES, providing an emergency treatment plan for acute reactions.[69,92,93] In patients with FPIES, there are many areas of controversy in which evidence is lacking and management is empiric (Table III). Dietary elimination includes the trigger foods, as well as potentially delaying introduction of new foods that are recognized as risks for children with FPIES.[2,9,92] Closely related and potentially cross-reactive foods from the same group, such as fish, should be introduced with caution under a physician's supervision (Table IV).[5,9,94] Although extensively heated milk and egg proteins in baked products are tolerated by the majority of children with IgE-mediated food allergy and perhaps a subset of those with eosinophilic esophagitis, there are currently no convincing data supporting tolerance to baked milk or egg in patients with FPIES.[81,95-99] Infants with CM/soy-induced FPIES can be breast-fed unless maternal ingestion of an allergen triggers FPIES reactions in the infant or an extensively hydrolyzed formula can be used. Ten percent to 20% might require an amino acid–based formula.[29,51] In infants with CM-induced FPIES, introduction of soy formula can be considered after age 6 months, when a large proportion of energy intake is from supplementary foods.[5,27,31,50,94] In infants goat's milk or other animal milks should not be used because of high homology to CM with a high risk of cross-reactivity and nutritional insufficiency.[5,92] Infants with chronic FPIES usually improve within 3 to 10 days of switching to a hypoallergenic formula, although in severe cases partial parenteral nutrition might be necessary.[33,34]

In exclusively breast-fed infants with FPIAP, elimination of the offending food from the mother's diet usually results in gradual resolution of symptoms with continued breast-feeding.[40] Rarely, an extensively hydrolyzed or amino acid–based formula might be

TABLE IV. Empiric recommendations for dietary management of FPIES (modified from Jarvinen and Nowak-Węgrzyn[9])

Age	Milk/soy-induced FPIES	Solid food–induced FPIES	Milk/soy- and solid food–induced FPIES
0-6 mo			
Avoid CM/soy*	X		X
Preferably exclusive breast-feeding† or extensively hydrolyzed formula‡; soy introduction in case of milk FPIES can be considered, although soy formula is not preferred[5,94]; OFC or home introduction at the discretion of the treating physician	X		X
Introduce yellow vegetables fruits or vegetables, which are unlikely to cause FPIES (eg, carrot and squash), followed by others, as tolerated	X	X	X
Avoid grains,§ legumes, poultry		X‖	X
6-12 mo			
Consider CM introduction in case of soy-induced FPIES; OFC or home introduction at discretion of the treating physician	X		X
Consider soy introduction in case of CM-induced FPIES; OFC or home introduction at discretion of the treating physician	X		X
Consider introduction of grains, legumes, or poultry if not tried; OFC or home introduction at discretion of the treating physician	X	X	X
>12 mo			
Avoid trigger foods, OFC with reactive food every 12-18 mo at discretion of the treating physician	X	X	X
Exclusive breast-feeding,† extensively hydrolyzed formula,‡ or consider soy introduction in case of CM-induced FPIES; OFC or home introduction at discretion of the treating physician	X		X
Consider introduction of CM or soy if not tried previously; OFC or home introduction at discretion of the treating physician	X	X	X
Consider introduction of grains, legumes, or poultry if not tried previously; OFC or home introduction at discretion of the treating physician		X‖	X‖
Consider OFC with individual fish in case of FPIES to another fish or avoid all fish		X	

No controlled trials have been performed to determine the optimal timing of food introduction in infants and toddlers with FPIES.

*In infants with milk-induced FPIES, soy formula introduction can be considered at the discretion of the treating physician.

†No maternal elimination diet is recommended unless reactions to food initially occurred through breast milk.

‡If not tolerated, an amino acid–based formula should be initiated.

§Including oat, rice, wheat, barley, and rye.

‖OFCs might be necessary to introduce new solid foods to children with multiple food–induced FPIES, especially those who are exclusively breast-fed.

necessary for resolution of bleeding, typically within 48 to 72 hours. A randomized controlled trial did not show any benefit of a probiotic over placebo in addition to maternal dietary elimination in patients with FPIAP.[100] In patients with FPE, elimination of the food leads to resolution of clinical symptoms within 1 to 3 weeks. Infants with severe initial manifestations might require partial parenteral nutrition for days or weeks.[45]

NATURAL HISTORY

FPIES can occur at any age.[29,59] FPIES to CM or soy begins in early infancy within the first 3 months of life, usually within days and up to 4 weeks after the introduction of infant formula. In an Israeli population–based birth cohort, the median onset of CM-induced FPIES onset was 30 days, and all cases presented before 6 months of age.[27] Delayed introduction of direct feeding with CM or soy in breast-fed infants might result in a later onset.[28,29,48,51] The onset of FPIES triggered by solids is usually later because they are typically introduced into the diet at between 4 and 7 months of age.[28,29] In the United States seafood-induced FPIES is reported with an onset in older children or adults, whereas in Italy fish is one of the common solid foods causing FPIES in the first years of life.[50] In general, FPIES in childhood resolves with age depending on the food and population studied[6] and has no long-lasting sequelae.[101] In the Israeli population–based cohort 90% of CM-induced FPIES resolved by age

3 years.[27] In a retrospective US study 35% resolved by age 2 years, 70% by age 3 years, and 85% by age 5 years.[28] The resolution of solid food–induced FPIES might take longer; about 50% of children outgrow rice- or oat-induced FPIES by age 4 to 5 years.[6,28,29] Fish and egg allergy can also resolve at an older age.[57] The oldest reported patient with CM-induced FPIES persisting since infancy is now 23 years old.[6,29] Patients with FPIES who have food-specific IgE antibodies appear to have a more protracted course.[5,13] In contrast, in a mixed-design US study, an overall median age at resolution of CM-induced FPIES was 13 years, whereas the median age for patients with undetectable CM-specific IgE was 5 years.[29] It is prudent to include prick skin tests, measurement of serum food-specific IgE levels, or both in both the initial and follow-up evaluations, especially in those with CM-induced FPIES, to identify patients at risk for persistent FPIES and immediate allergic reactions. FPIES in adults might begin after a period of the food being tolerated in the diet or represent persistence from childhood. The natural history of adult FPIES is not well understood; however, FPIES to shellfish appears to be a long-lasting condition.[102]

Infantile FPIAP is a benign transient condition that typically starts in the first few months of life and resolves within a few months up to 3 years of age. Up to 20% of breast-fed infants have spontaneous resolution of bleeding without changes in the maternal diet.[41,103] A case series from a single tertiary medical center in Italy reported 16 children aged 2 to 14 years (mean,

7.5 years) with new onset of FPIAP presenting as isolated rectal bleeding.[42] FPIAP accounted for 18% of rectal bleeding in children, as confirmed by means of endoscopy and biopsy. CM was identified as an allergen in all of these children, and in 2 subjects egg and wheat also caused symptoms on rechallenge. Three children had detectable serum IgE levels against CM.

Infantile FPE presents with protracted diarrhea in the first year of life, typically the first 1 to 2 months, within weeks after introduction of CM formula. FPE resolves clinically in the majority of children by age 1 to 2 years. Intestinal enteropathy was also reported in older children with delayed-type allergic reactions to CM, as well as in children with multiple food allergies.[104-106] The clinical manifestations included abdominal pain and chronic diarrhea after ingestion of dairy products, self-diagnosed lactose intolerance, a history of CM allergy in infancy (20%), atopic dermatitis (27%), and a positive double-blind challenge result to milk, eliciting gastrointestinal symptoms. The biopsy findings showed normal villous architecture and pronounced lymphonodular hyperplasia in the duodenal bulb.[104]

CHANGING TRENDS IN PREVALENCE OF NON-IgE-GI-FA

In the only population-based study to date, the prevalence of CM-induced FPIES in a birth cohort of Israeli infants younger than 12 months was estimated at 0.34% compared with 0.5% of IgE-mediated CM allergy. It is impossible to extrapolate this estimate to other patient populations; however, the Israeli findings suggest that FPIES might account for a substantial proportion of the CM allergy in infants.

The exact prevalence of FPIAP is unknown; the estimated prevalence ranges from 0.16% to 64% of infants with isolated rectal bleeding.[39,41,64] Although elimination of CM from the infant's diet was associated with resolution of rectal bleeding, subsequent reintroduction resulted in recurrence of bleeding in only a subgroup, suggesting that isolated rectal bleeding is a benign and self-limiting condition in most infants.[91,107] Anecdotally, FPIAP might be more common in countries with an overall lower prevalence of food allergy, such as Greece and Brazil.

The reported incidence of FPE peaked in the 1960s in Finland, with the disappearance of severe jejunal damage caused by CM in the past 30 years. Infant feeding practices have been implicated as a cause of the changing prevalence of FPE, with the highest incidence of classic severe FPE attributed to feeding with infant formulas high in unprocessed protein.[46,108,109] Intestinal enteropathy was reported in older children with delayed-type allergic reactions to CM and in patients with multiple food allergy; it remains to be established whether these older children represent a milder phenotype or a different disease.[104-106] Non-IgE-FA is becoming increasingly identified as a culprit in a subset of adults with irritable bowel syndrome, which is predominantly due to CM and wheat.[15,17]

NON-IgE-GI-FAS AND ATOPY

Overall, there is an increased prevalence of atopic conditions among children with non-IgE-GI-FAs; however, specific IgE to the offending food is uncommon (Table I). The majority of patients have no evidence of systemic food-specific IgE antibody positivity against the offending food, but local food-specific IgE

antibodies have been detected in duodenal mucosal tissue.[110] Between 4% and 30% of children with FPIES initially have or will have food-specific IgE to the FPIES food over time.[27-29,31,68] Those children appear to have delayed resolution of FPIES.[29,48,77] Most of the children who have food-specific IgE antibodies retain the FPIES phenotype; however, up to 35% of such children with CM-induced FPIES might experience symptoms of typical IgE-mediated food allergy to the food that previously induced an FPIES reaction.[29] Conversely, development of FPIES was documented in a rare young infant with IgE-mediated multiple food allergy,[111] pointing to potential common pathways predisposing to both cell- and IgE-mediated food allergic disorders. Alternatively, avoidance of FPIES-inducing foods might promote IgE sensitization through alternative exposures, such as through the skin. Considering relatively low concordance between skin prick test and serologic test in young infants, detection of food-specific IgE might require utilization of both methods.[112,113]

PATHOPHYSIOLOGY

The mechanisms underlying non-IgE-GI-FAs remain poorly characterized, with the best evidence supporting the involvement of food allergen–specific suppressor CD8 T cells in patients with FPE (Table I). Local production of food-specific IgE antibodies and absent systemic food-specific IgE suggests that local mucosal IgE might be involved.[110] FPIES is often considered T-cell mediated, but few studies have investigated T cells in patients with FPIES. There is some evidence of T-cell proliferation on stimulation with food antigens; however, the stimulation index is not consistently different from that in nonallergic control subjects.[114] Increased intestinal IFN-γ levels are associated with villous injury. In patients with FPIES, imbalance between intestinal TNF-α levels and decreased expression of TGF-β has been found.[115] T-cell activation by food allergens might mediate local intestinal inflammation through release of proinflammatory cytokines, such as TNF-α and IFN-γ, causing increased intestinal permeability and fluid shift.[101,115] TGF-β was not detected in supernatants of PBMC cultures stimulated with casein, suggesting a deficient response in children with milk-induced FPIES.[116] Humoral responses are poorly characterized in patients with FPIES, but IgE, IgA, and IgG$_4$ antibody responses to casein are generally suppressed.[116,117] Recent small case series reported successful treatment with intravenous ondansetron during FPIES OFCs.[79,80] Ondansetron is a serotonin 5-HT$_3$ receptor antagonist that reduces peripheral and central vagus nerve activity and is used mainly to treat nausea and vomiting after chemotherapy. The effectiveness of ondansetron suggests the potential role for serotonin in the pathophysiology of acute FPIES reactions and raises questions about the proposed T cell–mediated mechanisms. The pathophysiology of FPIAP remains largely unknown.

CONCLUSIONS

Although the majority of infantile non-IgE-GI-FAs have a favorable prognosis, in a subset of affected patients, the manifestations are severe and lead to shock in an acute form of FPIES or to FTT in a chronic form of FPIES and in patients with FPE. Onset in older children and adults can occur, mimicking inflammatory bowel disease; the natural history of the late-onset non-IgE-GI-FAs remains largely unknown. There is an urgent

need to better characterize the pathophysiology of non-IgE-GI-FAs. Without this knowledge, the identification of biomarkers and development of new treatment strategies will not be possible. In particular, the prevalence of FPIES needs to be conclusively determined to support research funding for studying this disorder.

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