Non–IgE-mediated gastrointestinal food allergy

Anna Nowak-Węgrzyn, MD,[a] Yitzhak Katz, MD,[b] Sam Soheil Mehr, MBBS, BMedSci, FRCPA, FRACP,[c] and Sibylle Koletzko, MD[d] *New York, NY, Tel Aviv, Israel, Westmead, Australia, and Munich, Germany*

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 Clin Immunol 2015;135:1114-24.)

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

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 understanding of non-IgE-GI-FAs is lack of access to target gastrointestinal 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

From [a]the Jaffe Food Allergy Institute, Division of Pediatric Allergy, Mount Sinai School of Medicine, New York; [b]the Allergy and Immunology Institute, Assaf Harofeh Medical Center, Department of Pediatrics, Sackler Faculty of Medicine, Tel Aviv University; [c]the Department of Allergy and Immunology, Children's Hospital at Westmead; and [d]the Division of Gastroenterology and Hepatology, Dr von Hauner Children's Hospital, Ludwig-Maximilians-Universität Munich.

Disclosure of potential conflict of interest: A. Nowak-Węgrzyn has received compensation for board membership from Merck, consultancy fees from Nestlé, and payment for delivering lectures from Thermo Fisher Scientific; she receives royalties from UpToDate, and has received compensation for travel and other meeting-related expenses from Nestlé and Thermo Fisher; her institution has received or has grants pending from the National Institutes of Health, FARE, and Nutricia. S. Koletzko has received compensation for board membership from MSD, Nestlé, Danone, Merck, and Nutricia; she has received consultancy fees from Boehringer Ingelheim, MSA, Merck, AbbVie, and Danone; her institution has received or has grants pending from Nestlé, Mead Johnson, Thermo Fisher, EuroImmun, INOVA, R-Biopharm, and Schär; she has received payment for delivering lectures from Centocor, MSD, Danone, Merck, Vifor, Nestlé, EuroImmun, Thermo Fisher, AbbVie, Schär, Hipp, and Falk; she has received compensation for travel and other meeting-related expenses from MSD. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication November 3, 2014; revised March 25, 2015; accepted for publication March 25, 2015.

Corresponding author: Anna Nowak-Węgrzyn, MD, Department of Pediatrics, Box 1198, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029. E-mail: anna.nowak-wegrzyn@mssm.edu.

0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2015.03.025

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.

REFERENCES

1. Wuthrich B. History of food allergy. Chem Immunol Allergy 2014;100:109-19.
2. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. J Allergy Clin Immunol 2010;126:1105-18.
3. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Brindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy 2014;69:1008-25.
4. Fiocchi A, Brozek J, Schunemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines. Pediatr Allergy Immunol 2010; 21(suppl 21):1-125.
5. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. J Pediatr Gastroenterol Nutr 2012;55:221-9.
6. Katz Y, Goldberg MR. Natural history of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014;14:229-39.
7. Mehr S, Frith K, Campbell DE. Epidemiology of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014;14:208-16.
8. Schultz F, Westcott-Chavez A. Food protein-induced enterocolitis syndrome from the parent perspective. Curr Opin Allergy Clin Immunol 2014;14:263-7.
9. Jarvinen K, Nowak-Wegrzyn A. Food protein-induced enterocolitis syndrome: current management strategies. J Allergy Clin Immunol Pract 2013;1:317.
10. Husby S, Koletzko S, Korponay-Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012; 54:136-60.
11. Borrelli O, Mancini V, Thapar N, Giorgio V, Elawad M, Hill S, et al. Cow's milk challenge increases weakly acidic reflux in children with cow's milk allergy and gastroesophageal reflux disease. J Pediatr 2012;161:476-81.e1.
12. Ravelli AM, Tobanelli P, Volpi S, Ugazio AG. Vomiting and gastric motility in infants with cow's milk allergy. J Pediatr Gastroenterol Nutr 2001;32:59-64.
13. Borrelli O, Barbara G, Di Nardo G, Cremon C, Lucarelli S, Frediani T, et al. Neuroimmune interaction and anorectal motility in children with food allergy-related chronic constipation. Am J Gastroenterol 2009;104:454-63.
14. Turunen S, Karttunen TJ, Kokkonen J. Lymphoid nodular hyperplasia and cow's milk hypersensitivity in children with chronic constipation. J Pediatr 2004;145: 606-11.
15. Carroccio A, Mansueto P, Iacono G, Soresi M, D'Alcamo A, Cavataio F, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. Am J Gastroenterol 2012;107:1898-907.
16. Carroccio A, Mansueto P, D'Alcamo A, Iacono G. Non-celiac wheat sensitivity as an allergic condition: personal experience and narrative review. Am J Gastroenterol 2013;108:1845-53.
17. Fritscher-Ravens A, Schuppan D, Ellrichmann M, Schoch S, Rocken C, Brasch J, et al. Confocal endomicroscopy reveals food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. Gastroenterology 2014;147:1012-20.e4.
18. Vandenplas Y. Management of paediatric GERD. Nat Rev Gastroenterol Hepatol 2014;11:147-57.
19. Lightdale JR, Gremse DA. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics 2013;131:e1684-95.
20. Nielsen RG, Bindslev-Jensen C, Kruse-Andersen S, Husby S. Severe gastroesophageal reflux disease and cow milk hypersensitivity in infants and children: disease association and evaluation of a new challenge procedure. J Pediatr Gastroenterol Nutr 2004;39:383-91.
21. Hill DJ, Heine RG, Cameron DJ, Catto-Smith AG, Chow CW, Francis DE, et al. Role of food protein intolerance in infants with persistent distress attributed to reflux esophagitis. J Pediatr 2000;136:641-7.
22. Hill DJ, Roy N, Heine RG, Hosking CS, Francis DE, Brown J, et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. Pediatrics 2005;116:e709-15.
23. Iacovou M, Ralston RA, Muir J, Walker KZ, Truby H. Dietary management of infantile colic: a systematic review. Matern Child Health J 2012;16:1319-31.
24. Dobson D, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database Syst Rev 2012;12: CD004796.
25. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J Paediatr Child Health 2012;48:128-37.
26. Miceli Sopo S, Arena R, Greco M, Bergamini M, Monaco S. Constipation and cow's milk allergy: a review of the literature. Int Arch Allergy Immunol 2014; 164:40-5.
27. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. J Allergy Clin Immunol 2011;127: 647-53.
28. Ruffner MRK, Barni S, Cianferoni A, BrownWhitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insigts from review f a large referral population. J Allergy Clin Immunol Pract 2013;1:343-9.
29. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. J Allergy Clin Immunol 2014;134:382-9.
30. Ludman S, Harmon M, Whiting D, du Toit G. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. Ann Allergy Asthma Immunology 2014;113:290-4.
31. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. Pediatrics 2009;123:e459-64.
32. Burks AW, Jones SM, Boyce JA, Sicherer SH, Wood RA, Assa'ad A, et al. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. Pediatrics 2011;128:955-65.
33. Powell GK. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance. J Pediatr 1976;88:840-4.
34. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. J Pediatr 1978;93:553-60.
35. Flinterman AE, Knulst AC, Meijer Y, Bruijnzeel-Koomen CA, Pasmans SG. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. Allergy 2006;61:370-4.
36. Jenkins HR, Pincott JR, Soothill JF, Milla PJ, Harries JT. Food allergy: the major cause of infantile colitis. Arch Dis Child 1984;59:326-9.
37. Goldman H, Proujansky R. Allergic proctitis and gastroenteritis in children. Clinical and mucosal biopsy features in 53 cases. Am J Surg Pathol 1986;10: 75-86.
38. Lake AM, Whitington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. J Pediatr 1982;101:906-10.
39. Elizur A, Cohen M, Goldberg MR, Rajuan N, Cohen A, Leshno M, et al. Cow's milk associated rectal bleeding: a population based prospective study. Pediatr Allergy Immunol 2012;23:766-70.
40. Lake AM. Food-induced eosinophilic proctocolitis. J Pediatr Gastroenterol Nutr 2000;30(suppl):S58-60.
41. Xanthakos SA, Schwimmer JB, Melin-Aldana H, Rothenberg ME, Witte DP, Cohen MB. Prevalence and outcome of allergic colitis in healthy infants with rectal bleeding: a prospective cohort study. J Pediatr Gastroenterol Nutr 2005; 41:16-22.
42. Ravelli A, Villanacci V, Chiappa S, Bolognini S, Manenti S, Fuoti M. Dietary protein-induced proctocolitis in childhood. Am J Gastroenterol 2008;103: 2605-12.
43. Carroccio A, Mansueto P, Morfino G, D'Alcamo A, Di Paola V, Iacono G, et al. Oligo-antigenic diet in the treatment of chronic anal fissures. Evidence for a relationship between food hypersensitivity and anal fissures. Am J Gastroenterol 2013;108:825-32.
44. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). J Allergy Clin Immunol 2004;113:11-28.
45. Kuitunen P, Visakorpi JK, Savilahti E, Pelkonen P. Malabsorption syndrome with cow's milk intolerance. Clinical findings and course in 54 cases. Arch Dis Child 1975;50:351-6.
46. Saarinen K, Juntunen-Backman K, Jarvenpaa AL, Kuitunen P, Lope L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: a prospective study of 6209 infants. J Allergy Clin Immunol 1999;104: 457-61.
47. Iyngkaran N, Robinson NJ, Sumithran E, Lam SK, Putchucheary SD, Yadav M. Cow's milk protein-sensitive enteropathy. An important factor in prolonging diarrhoea in acute infective enteritis in early infancy. Arch Dis Child 1978;53: 150-3.
48. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. J Pediatr 1998;133:214-9.
49. Burks AW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. Pediatr Allergy Immunol 1994;5:40-5.

50. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. Clin Exp Allergy 2012;42:1257-65.
51. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. Pediatrics 2003;111:829-35.
52. Borchers SD, Li BU, Friedman RA, McClung HJ. Rice-induced anaphylactoid reaction. J Pediatr Gastroenterol Nutr 1992;15:321-4.
53. Cavataio F, Carroccio A, Montalto G, Iacono G. Isolated rice intolerance: clinical and immunologic characteristics in four infants. J Pediatr 1996;128:558-60.
54. Vandenplas Y, Edelman R, Sacre L. Chicken-induced anaphylactoid reaction and colitis. J Pediatr Gastroenterol Nutr 1994;19:240-1.
55. Mehr SS, Kakakios AM, Kemp AS. Rice: a common and severe cause of food protein-induced enterocolitis syndrome. Arch Dis Child 2009;94:220-3.
56. Levy Y, Danon YL. Food protein-induced enterocolitis syndrome—not only due to cow's milk and soy. Pediatr Allergy Immunol 2003;14:325-9.
57. Zapatero Remon L, Alonso Lebrero E, Martin Fernandez E, Martinez Molero MI. Food-protein-induced enterocolitis syndrome caused by fish. Allergol Immunopathol (Madr) 2005;33:312-6.
58. Hwang JB, Kang KJ, Kang YN, Kim AS. Probiotic gastrointestinal allergic reaction caused by *Saccharomyces boulardii*. Ann Allergy Asthma Immunol 2009;103:87-8.
59. Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. J Allergy Clin Immunol 2012;130:1199-200.
60. Arik Yilmaz E, Cavkaytar O, Uysal Soyer O, Sackesen C. Egg yolk: An unusual trigger of food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2014;25:296-7.
61. Hsu P, Mehr S. Egg: a frequent trigger of food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2013;131:241-2.
62. Caubet JC, Nowak-Wegrzyn A. Food protein-induced enterocolitis to hen's egg. J Allergy Clin Immunol 2011;128:1386-8.
63. Hayashi D, Aoki T, Shibata R, Ichikawa K. [Case of food protein-induced enterocolitis syndrome caused by short-neck clam ingestion]. Arerugi 2010;59:1628-33.
64. Arvola T, Ruuska T, Keranen J, Hyoty H, Salminen S, Isolauri E. Rectal bleeding in infancy: clinical, allergological, and microbiological examination. Pediatrics 2006;117:e760-8.
65. Monti G, Castagno E, Liguori SA, Lupica MM, Tarasco V, Viola S, et al. Food protein-induced enterocolitis syndrome by cow's milk proteins passed through breast milk. J Allergy Clin Immunol 2011;127:679-80.
66. Tan J, Campbell D, Mehr S. Food protein-induced enterocolitis syndrome in an exclusively breast-fed infant-an uncommon entity. J Allergy Clin Immunol 2012;129:873, author reply 873-4.
67. Nomura I, Morita H, Hosokawa S, Hoshina H, Fukuie T, Watanabe M, et al. Four distinct subtypes of non-IgE-mediated gastrointestinal food allergies in neonates and infants, distinguished by their initial symptoms. J Allergy Clin Immunol 2011;127:685-8, e1-8.
68. Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. Curr Allergy Asthma Rep 2012;12:297-303.
69. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update—2014. J Allergy Clin Immunol 2014;134:1016-25.e43.
70. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2006;17:351-5.
71. Lucarelli S, Di Nardo G, Lastrucci G, D'Alfonso Y, Marcheggiano A, Federici, T, et al. Allergic proctocolitis refractory to maternal hypoallergenic diet in exclusively breast-fed infants: a clinical observation. BMC Gastroenterol 2011;11:82.
72. Jarvinen KM, Caubet JC, Sickles L, Ford LS, Sampson HA, Nowak-Wegrzyn A. Poor utility of atopy patch test in predicting tolerance development in food protein-induced enterocolitis syndrome. Ann Allergy Asthma Immunol 2012;109:221-2.
73. Kalach N, Kapel N, Waligora-Dupriet AJ, Castelain MC, Cousin MO, Sauvage C, et al. Intestinal permeability and fecal eosinophil-derived neurotoxin are the best diagnosis tools for digestive non-IgE-mediated cow's milk allergy in toddlers. Clin Chem Lab Med 2013;51:351-61.
74. Wada T, Toma T, Muraoka M, Matsuda Y, Yachie A. Elevation of fecal eosinophil-derived neurotoxin in infants with food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2014;25:617-9.
75. Savilahti E. Food-induced malabsorption syndromes. J Pediatr Gastroenterol Nutr 2000;30(suppl):S61-6.
76. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, Bock SA, Sicherer SH, Teuber SS. Work Group report: oral food challenge testing. J Allergy Clin Immunol 2009;123(suppl):S365-83.
77. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. J Allergy Clin Immunol 2005;115:149-56.
78. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol 2010;126(suppl):S1-58.
79. Holbrook T, Keet CA, Frischmeyer-Guerrerio PA, Wood RA. Use of ondansetron for food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2013;132:1219-20.
80. Miceli Sopo S, Battista A, Greco M, Monaco S. Ondansetron for food protein-induced enterocolitis syndrome. Int Arch Allergy Immunol 2014;164:137-9.
81. Miceli Sopo S, Buonsenso D, Monaco S, Crocco S, Longo G, Calvani M. Food protein-induced enterocolitis syndrome (FPIES) and well cooked foods: a working hypothesis. Allergol Immunopathol (Madr) 2013;41:346-8.
82. Mane SK, Hollister ME, Bahna SL. Food protein-induced enterocolitis syndrome to trivial oral mucosal contact. Eur J Pediatr 2014;173:1545-7.
83. Hwang JB, Sohn SM, Kim AS. Prospective follow-up oral food challenge in food protein-induced enterocolitis syndrome. Arch Dis Child 2009;94:425-8.
84. Serafini S, Nowak-Wegrzyn A, Eigenmann PA, Caubet JC. A case of food protein-induced enterocolitis syndrome to mushrooms challenging currently used diagnostic criteria. J Allergy Clin Immunol Pract 2015;3:135-7.
85. Maines E, Comberiati P, Piacentini GL, Boner AL, Peroni DG. Lysinuric protein intolerance can be misdiagnosed as food protein-induced enterocolitis syndrome. Pediatr Allergy Immunol 2013;24:509-10.
86. Fiocchi A, Claps A, Dahdah L, Brindisi G, Dionisi-Vici C, Martelli A. Differential diagnosis of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014;14:246-54.
87. Fiocchi A, Dionisi-Vici C, Cotugno G, Koch P, Dahdah L. Fruit-induced FPIES masquerading as hereditary fructose intolerance. Pediatrics 2014;134:e602-5.
88. Miller NB, Beigelman A, Utterson E, Shinawi M. Transient massive trimethylaminuria associated with food protein-induced enterocolitis syndrome. JIMD Rep 2014;12:11-5.
89. Uhlig HH, Schwerd T, Koletzko S, Shah N, Kammermeier J, Elkadri A, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. Gastroenterology 2014;147:990-1007.e3.
90. Gryboski JD. Gastrointestinal milk allergy in infants. Pediatrics 1967;40:354-62.
91. Molnar K, Pinter P, Gyorffy H, Cseh A, Muller KE, Arato A, et al. Characteristics of allergic colitis in breast-fed infants in the absence of cow's milk allergy. World J Gastroenterol 2013;19:3824-30.
92. Sopo SM, Iacono ID, Greco M, Monti G. Clinical management of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014;14:240-5.
93. Venter C, Groetch M. Nutritional management of food protein-induced enterocolitis syndrome. Curr Opin Allergy Clin Immunol 2014;14:255-62.
94. Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91.
95. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol 2008;122:342-7.
96. Ford LS, Bloom KA, Nowak-Wegrzyn AH, Shreffler WG, Masilamani M, Sampson HA. Basophil reactivity, wheal size, and immunoglobulin levels distinguish degrees of cow's milk tolerance. J Allergy Clin Immunol 2013;131:180-6, e1-3.
97. Kim JS, Nowak-Wegrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. J Allergy Clin Immunol 2011;128:125-31.
98. Lemon-Mule H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol 2008;122:977-83.
99. Leung J, Hundal NV, Katz AJ, Shreffler WG, Yuan Q, Butterworth CA, et al. Tolerance of baked milk in patients with cow's milk-mediated eosinophilic esophagitis. J Allergy Clin Immunol 2013;132:1215-6.e1.
100. Szajewska H, Gawronska A, Wos H, Banaszkiewicz A, Grzybowska-Chlebowczyk U. Lack of effect of Lactobacillus GG in breast-fed infants with rectal bleeding: a pilot double-blind randomized controlled trial. J Pediatr Gastroenterol Nutr 2007;45:247-51.

101. Caubet JC, Nowak-Wegrzyn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. Exp Rev Clin Immunol 2011;7:317-27.
102. Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. J Allergy Clin Immunol Pract 2014;2:355-7.e1.
103. Maloney J, Nowak-Wegrzyn A. Educational clinical case series for pediatric allergy and immunology: allergic proctocolitis, food protein-induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestations of non-IgE-mediated cow's milk allergy. Pediatr Allergy Immunol 2007;18:360-7.
104. Kokkonen J, Haapalahti M, Laurila K, Karttunen TJ, Maki M. Cow's milk protein-sensitive enteropathy at school age. J Pediatr 2001;139:797-803.
105. Veres G, Westerholm-Ormio M, Kokkonen J, Arato A, Savilahti E. Cytokines and adhesion molecules in duodenal mucosa of children with delayed-type food allergy. J Pediatr Gastroenterol Nutr 2003;37:27-34.
106. Latcham F, Merino F, Lang A, Garvey J, Thomson MA, Walker-Smith JA, et al. A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy. J Pediatr 2003;143:39-47.
107. Pumberger W, Pomberger G, Geissler W. Proctocolitis in breast fed infants: a contribution to differential diagnosis of haematochezia in early childhood. Postgrad Med J 2001;77:252-4.
108. Verkasalo M, Kuitunen P, Savilahti E, Tiilikainen A. Changing pattern of cow's milk intolerance. An analysis of the occurrence and clinical course in the 60s and mid-70s. Acta Paediatr Scand 1981;70:289-95.
109. Vitoria JC, Sojo A, Rodriguez-Soriano J. Changing pattern of cow's milk protein intolerance. Acta Paediatr Scand 1990;79:566-7.
110. Lin XP, Magnusson J, Ahlstedt S, Dahlman-Hoglund A, Hanson LL, Magnusson O, et al. Local allergic reaction in food-hypersensitive adults despite a lack of systemic food-specific IgE. J Allergy Clin Immunol 2002;109:879-87.
111. Banzato C, Piacentini GL, Comberiati P, Mazzei F, Boner AL, Peroni DG. Unusual shift from IgE-mediated milk allergy to food protein-induced enterocolitis syndrome. Eur Ann Allergy Clin Immunol 2013;45:209-11.
112. Mehl A, Niggemann B, Keil T, Wahn U, Beyer K. Skin prick test and specific serum IgE in the diagnostic evaluation of suspected cow's milk and hen's egg allergy in children: does one replace the other? Clin Exp Allergy 2012;42:1266-72.
113. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. N Engl J Med 2015;372:803-13.
114. Morita H, Nomura I, Orihara K, Yoshida K, Akasawa A, Tachimoto H, et al. Antigen-specific T-cell responses in patients with non-IgE-mediated gastrointestinal food allergy are predominantly skewed to T(H)2. J Allergy Clin Immunol 2013;131:590-2, e1-6.
115. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-α in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. J Allergy Clin Immunol 2002;109:150-4.
116. Konstantinou GN, Ramon B, Grishin A, Caubet JC, Bardina L, Sicherer SH, et al. The role of casein-specific IgA and TGF-beta in children with food protein-induced enterocolitis syndrome to milk. Pediatr Allergy Immunol 2014;25:651-6.
117. Shek LP, Bardina L, Castro R, Sampson HA, Beyer K. Humoral and cellular responses to cow milk proteins in patients with milk-induced IgE-mediated and non-IgE-mediated disorders. Allergy 2005;60:912-9.