REVIEW ARTICLE

Non-IgE-mediated gastrointestinal food allergies in children

Jean-Christoph Caubet[1,2], Hania Szajewska[3], Raanan Shamir[4] & Anna Nowak-Węgrzyn[1]

[1]Division of Allergy and Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, Jaffe Food Allergy Institute, New York, NY, USA; [2]Department of Child and Adolescent, Medical School of the University of Geneva, University Hospitals of Geneva, Geneva, Switzerland; [3]Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland; [4]Sackler Faculty of Medicine, Schneider Children's Medical Center of Israel, Institute for Gastroenterology, Nutrition and Liver Diseases, Tel-Aviv University, Tel-Aviv, Israel

To cite this article: Caubet J-C, Szajewska H, Shamir R, Nowak-Węgrzyn A. Non-IgE-mediated gastrointestinal food allergies in children. *Pediatr Allergy Immunol* 2017: **28**: 6–17.

Keywords
food allergy; gastrointestinal food allergy; food protein-induced enterocolitis syndrome; food protein-induced enterocolitis syndrome; allergic proctocolitis; food protein-induced allergic proctocolitis; food protein-induced enteropathy; food protein-induced enteropathy; celiac disease; irritable bowel syndrome; fermentable oligosaccharides, disaccharides, monosaccharides and polyols; gastroesophageal reflux; gastroesophageal reflux; gastroesophageal reflux disease; gastroesophageal reflux disease; constipation

Correspondence
Jean-Christoph Caubet, Pediatric Allergology Unit, Geneva University Hospitals, 6 Rue Willy Donzé, 1205 Geneva, Switzerland
E-mail: jeanchristoph.caubet@gmail.com

Accepted for publication 14 September 2016

DOI:10.1111/pai.12659

Abstract

Non-IgE-mediated gastrointestinal food allergic disorders (non-IgE-GI-FA) including food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPE), and food protein-induced allergic proctocolitis (FPIAP) are relatively uncommon in infants and young children, but are likely under-diagnosed. Non-IgE-GI-FA have a favorable prognosis, with majority resolving by age 3–5 years. Diagnosis relies on the recognition of symptoms pattern in FPIAP and FPIES and biopsy in FPE. Further studies are needed for a better understanding of the pathomechanism, which will lead eventually to the development of diagnostic tests and treatments. Limited evidence supports the role of food allergens in subsets of constipation, gastroesophageal reflux disease, irritable bowel syndrome, and colic. The immunologic pathomechanism is not fully understood and empiric prolonged avoidance of food allergens should be limited to minimize nutrient deficiency and feeding disorders/food aversions in infants.

Disorders involving the gastrointestinal tract constitute one of the main causes of pediatric consultations, and a subset of these disorders has been attributed to immunologic reactions to foods. In contrast to IgE-mediated reactions, non-IgE-mediated gastrointestinal food allergic disorders (non-IgE-GI-FA) are characterized by subacute and/or chronic symptoms and classically include food protein-induced enterocolitis syndrome (FPIES), food protein-induced allergic proctocolitis (FPIAP), food protein-induced enteropathy (FPE), celiac disease, and cow milk (CM)-induced iron deficiency anemia (1–3). In this review, pathomechanism, clinical characteristics, diagnosis, and management of classical non-IgE-GI-FA will be discussed.

In addition, food allergens are suggested to play a role in a subset of children with gastroesophageal reflux disease (GERD), colic, and constipation (4–21). According to the current classification, an allergy is by definition an immune-mediated adverse food reaction (22). Although a specific

Abbreviations
non-IgE-GI-FA, non-IgE-mediated gastrointestinal food allergic disorders; FPIES, food protein-induced enterocolitis syndrome; FPE, food protein-induced enteropathy; FPIAP, food protein-induced allergic proctocolitis; CM, cow milk; IBS, irritable bowel syndrome; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides and polyols; FTT, failure to thrive; IgE, immunoglobulin E.

immunologic mechanism has not been clearly demonstrated in these functional disorders, symptoms improvement after food elimination diet and recurrence on re-exposure have been demonstrated in a subgroup of children, implying a role for food allergy in these conditions. Similarly, non-celiac gluten sensitivity has been described, where gastrointestinal and extra-intestinal symptoms respond to a gluten-free diet (23). Although these disorders are not classified as the non-IgE–GI-FA and do not strictly fulfill the current criteria for food allergy, we will review and discuss the possible role of food allergens in GERD, colic, IBS, and constipation, as it constitutes a major issue in clinical practice for pediatricians and allergists.

Classical non-IgE-mediated gastrointestinal food allergies

Non-IgE-GI-FA can affect any part of the gastrointestinal tract and ranges from benign proctitis to severe enterocolitis and enteropathy (Table 1) (1). The prevalence of non-IgE-GI-FA remains largely unknown. An Israeli study reported 0.34% prevalence of CM-FPIES compared with 0.5% of IgE-mediated CM-allergy in a population-based birth cohort (24). FPIAP prevalence estimates range widely from 0.16% to 64% of isolated rectal bleeding in infants. (25–27). Prevalence of FPE is not clearly defined. In the seventies, in Finland, a prevalence of 3 patients per year has been reported, with a gradual decrease since then (28).

Clinical manifestations

Although non-IgE-GI-FA have overlapping clinical features, they can be distinguished by gastrointestinal symptoms that differ in regard to temporal relationship to food ingestion, severity, and natural history (Table 1). FPIAP represents the milder end of the spectrum, characterized by intermittent bloody stools in otherwise healthy, thriving infants (1, 25, 29–31). Symptoms usually start gradually at 2–8 weeks of age, although presentation as early as first week has been described (32). Moderate-to-severe bloody stools can also be seen in chronic-FPIES, but are usually associated with chronic diarrhea and/or vomiting when the patient is continuously ingesting the offending food. In the most severe form of FPIES, nutritional deficiencies and failure to thrive (FTT) are observed. Acute-FPIES is characterized by profuse vomiting, pallor, and/or lethargy occurring 1–4 h after food ingestion (3). Diarrhea may follow within 5–10 h after ingestion, particularly in young infants with a more severe phenotype (i.e., less than 30% of children older than 1 year) (24, 33, 34). The acute-FPIES can be the initial presentation of FPIES or may occur if the food is reintroduced after a period of exclusion in patients with chronic-FPIES (i.e., acute-on-chronic form of FPIES). While occurring usually in infants, FPIES has been described in older children and even in adults, usually caused by fish or shellfish (35). Chronic-FPIES shares clinical features with FPE, characterized by malabsorption, FTT, anemia, diarrhea, and vomiting, occurring usually prior 9 months of age (36–40). However, in FPE, chronic diarrhea is the most prominent feature and does not lead to severe dehydration or metabolic de-arrangements that are seen in chronic-FPIES.

Table 1 Clinical characteristics of non-IgE-mediated gastrointestinal food allergies

	FPIES	FPIAP	FPE
Typical age of onset	Days to 1 year	Days to 6 months	2–24 months
Symptoms			
Emesis	Prominent	No	Intermittent
Diarrhea	Severe	No	Moderate
Bloody stools	Severe	Moderate	Rare
Edema	Acute, severe	No	Moderate
Shock	15–20%	No	No
Failure to thrive	Moderate	No	Moderate
Allergy evaluation			
Food prick skin test	Negative*	Negative	Negative
Serum food-specific IgE	Negative*	Negative	Negative
Total IgE	Normal	Normal	Normal
Peripheral blood eosinophilia	No	Occasional	No
Biopsy findings			
Villous injury	Patchy, variable	No	Variable, crypt length
Colitis	Prominent	Focal	No
Mucosal erosions	Occasional	Occasional, linear	No
Lymph nodular hyperplasia	No	Common	No
Eosinophils	Prominent	Prominent	Few
Food challenge	Vomiting in 4–6 h; diarrhea in 5–8 h	Rectal bleeding in 6–72 h	Vomiting, diarrhea, or both in 40–72 h

FPIES, food protein-induced enterocolitis syndrome; FPIAP, food protein-induced allergic proctocolitis; FPE, food protein-induced enteropathy.
*Positive prick test and/or specific IgE may be present at initial diagnosis or at follow-up (atypical FPIES).

Foods involved

While infants suffering from FPIAP may react to CM, soy, egg, and/or wheat in maternal diet through breast milk, CM- or soy-based infant formula can also cause FPIAP (26, 31, 41–43). In less than 10% of the cases, extensively hydrolyzed formulas may lead to FPIAP symptoms. Older children and adults with allergic colitis to CM, egg, and wheat have been rarely described (44, 45). In FPE, CM is the most common isolated trigger, while egg, soy, and wheat may cause FPE in children with multiple food allergies (36, 46).

In contrast to FPIAP, acute- and chronic-FPIES are rarely described in exclusively breastfed infants (47, 48). CM, soy, and rice are the most common triggers of FPIES in the USA;

rice is the most frequently incriminated food in Australia (33, 34). In addition to grains (rice, oat, barley, wheat), variety of other solid foods have been reported as triggers, including white and sweet potatoes, egg, chicken, vegetables, fruits, mushrooms, shellfish, fish, nuts, and peanut (33–35, 49–61). Solid-FPIES typically occurs later than CM/soy-FPIES, probably reflecting the timing of introduction of solids into the infants' diet (34, 51). The majority of FPIES patients react to a single food (65–80%), usually CM or soy (3). However, patients with CM- and/or soy-FPIES may react to solids. In reports from the USA, up to 50% of patients with CM/soy-FPIES react to both foods (49, 62, 63) and around one-third of patients with CM and/or soy-FPIES react to solids (64). Sixty-five percent of patients with solid-FPIES are previously diagnosed with CM/soy-FPIES (51). The majority of children with solid-FPIES react to multiple foods. Particularly those with FPIES to rice, oat, or barley often experience symptoms with other grains (34, 51). However, patients with multiple foods-FPIES are less common in Japan, Australia, and Italy (24, 33, 50). These differences may reflect country-specific dietary habits. This hypothesis is supported by recent data showing that early introduction of CM or soy formula is a risk factor for development of CM/soy-FPIES and that solid-FPIES occurs at a later age. (34). These differences might also be explained by different phenotypes of disease identified from unselected population-based birth cohort vs. tertiary center with more severe cases and or genetic predisposition (24, 34).

Pathogenesis

The pathogenesis of non-IgE-GI-FA is poorly understood, mainly due to the fact that endoscopy and biopsies are not routinely performed. These diseases with overlapping clinical features share eosinophils dominated inflammation and more work needs to be done to determine whether they are pathophysiologically distinct or represent a spectrum of the same disease process.

Among non-IgE-GI-FA, FPIES has been most actively investigated. Several studies have suggested a key role of T cells, with the secretion of pro-inflammatory cytokines that may influence intestinal permeability (65–76). However, the role of T cells has been questioned in several studies and further studies are needed (62, 65, 70–74, 77). Antigen-specific $CD4^+CD25^+$ regulatory T cells may be involved in the pathomechanism of tolerance acquisition in FPIES, particularly by the secretion of TGF-β and IL-10 (73, 76). Neuroendocrine pathways may play a role in the FPIES pathogenesis (78), based on efficacy of ondansetron, a serotonin $5\text{-}HT_3$ receptor antagonist, in managing acute-FPIES reaction (78–80). Although neutrophilia and thrombocytosis are classically found in FPIES patients, the role of these cells in the pathomechanism is not clear (33, 63, 81–83).

A paucity of humoral responses in FPIES has been found (47, 67, 70, 84–86). Although specific IgEs to the causal food are typically not detected in FPIES, a subset of children may have detectable specific IgE to the incriminated food either at presentation or during follow-up (atypical FPIES) (24, 34, 62, 64). These patients tend to experience a more prolonged course and, in some cases, progression to IgE-mediated allergy (51, 64). In one study, up to 35% of patients with CM-FPIES and positive CM-IgE progressed to the IgE-mediated CM-allergy phenotype (34). In addition, high rates of atopic diseases have been found in FPIES patients (34, 51). A recent report described a patient with a shift from IgE-mediated CM-allergy to CM-FPIES (87).

Histological findings similar to those found in patients with celiac disease have been found in endoscopic biopsies from patients with FPE, particularly damage to the villous architecture (88). Eosinophils and CM-specific T-helper 2 lymphocytes have been incriminated (67, 89). Localized production of IgE in the mucosa of the small intestine and absence of systemic food-specific IgE suggested that local IgE might be involved (90). Pathomechanism of FPIAP remains largely unknown due to lack of data, probably due to benign nature of the disease. Eosinophils above 10/hpf and increased intra-epithelial $CD8^+$ lymphocytes are typically found (41, 91).

Diagnosis

Diagnosis of non-IgE-GI-FA is based on the recognition of a symptom pattern. Differential diagnosis is broad, as described in Table 2. Lack of definitive diagnostic tests contributes to frequently delayed diagnosis (33). In addition, distinction between the various disorders currently classified as non-IgE-GI-FA is difficult due to a large overlap (60). Biopsies are rarely performed in patients with FPIES or FPIAP, but may be useful to confirm the diagnosis of FPE.

Specific diagnostic criteria for these disorders have been proposed and are summarized in Table 3. A trial of elimination diet is part of the diagnostic criteria of non-IgE-GI-FA to determine whether gastrointestinal symptoms are responsive to dietary elimination. One approach would consist of avoidance of a wide variety of foods (or rarely an elemental diet), followed by sequential reintroduction of foods ('top-down approach'). In another approach, one or few foods are removed initially, followed by an expanded elimination diet according to the clinical response ('bottom-up approach') (92). The choice of the approach is predominantly based on the severity of the initial symptoms, particularly FTT and/or dehydration (92). The timing of symptom resolution varies between few hours for acute-FPIES to several weeks for FPE (28, 31, 41, 81, 82).

The OFC remains the gold standard to confirm the diagnosis after resolution of the symptoms under an elimination diet or to assess tolerance acquisition. In FPIAP and FPE, reintroduction of the suspected food after 4–8 weeks of elimination can be performed usually at home and documented with a symptom diary. Of note, Ravelli et al. (44) found that CM allergy was involved in only 18% of cases of rectal bleeding as confirmed by means of endoscopy and biopsy. To reduce the number of false-positive diagnosis of FPIAP that is associated with significant medical cost and parental anxiety, an accurate diagnosis based on re-challenge following a trial of an elimination diet is recommended in those children (93). In FPIES, physician-supervised OFC needs to be performed in an appropriate monitored setting. The decision to secure IV access

Table 2 Differential diagnosis of non-IgE-mediated gastrointestinal food allergies

FPIES	FPIAP	FPE
Infections	Infections	Infections
Viral gastroenteritis	Viral gastroenteritis	Viral gastroenteritis
Sepsis	Bacterial enteritis (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*)	Sepsis
Bacterial enteritis (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*)	Parasites	Bacterial enteritis (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*)
Parasites		Parasites
Allergic disorders	Allergic disorders	Allergic disorders
Other non-IgE-mediated gastrointestinal food allergy disorders (FPE and eosinophilic gastrointestinal disorders)	Other non-IgE-mediated gastrointestinal food allergy disorders (i.e., mainly FPIES)	Other non-IgE-mediated gastrointestinal food allergy disorders (i.e., mainly chronic FPIES)
Acute IgE mediated allergy (anaphylaxis)		Eosinophilic gastroenteropathy
Gastrointestinal disorders	Gastrointestinal disorders	Gastrointestinal disorders
Gastroesophageal reflux disease	Anal fissure	Celiac disease
Hirschsprung disease		Autoimmune enteropathy
Intussusception		Protein losing gastroenteropathy
Volvulus		Pancreatic insufficiency
Pyloric stenosis		Primary immunodeficiency
Celiac disease		Lymphangiectasia
Meckel's diverticulum		Inherited epithelial defects (e.g., microvillus inclusion disease)
Necrotizing enterocolitis		
Others	Others	Others
Neurologic disorders (i.e., seizure, encephalopathy, or bleeding)	Swallowed maternal blood	Neurologic disorders (i.e., seizure, encephalopathy, or bleeding)
Heart defects (i.e., congenital heart disease, cardiomyopathy, or arrhythmia)		Intoxication
Congenital methemoglobinemia		Metabolic disorders
Intoxication		
Metabolic disorders		

FPIES, food protein-induced enterocolitis syndrome; FPIAP, food protein-induced allergic proctocolitis; FPE, food protein-induced enteropathy.

is based on clinician judgment and is usually recommended for patients with severe initial reactions or in patients in whom emergency vascular access may be difficult, such as young infants (3). Criteria for positive OFC in FPIES have been initially proposed by Powell in 1986 and recently modified (Table 3) (34, 94, 95). It has been proposed to emphasize clinical manifestations (emesis, pallor, and lethargy) and blood testing (leukocytosis with left shift and thrombocytosis) over stool analysis, as only 30% of patients have lower digestive symptoms during an acute-FPIES reaction (24, 33, 34). OFC is not required to confirm FPIES diagnosis in patients with two or more typical reactions over a 6-month period (95).

Four to 30% of FPIES patients develop specific IgE to the incriminated food over time (24, 33, 34, 62, 96). Thus, skin tests and/or specific IgE are recommended before OFC to adapt the protocol (i.e., gradual increase of the administered doses). The diagnostic value of patch tests is controversial; due to the lack of validation, patch tests are not recommended for routine diagnosis (1, 2, 57, 69, 77). Neither patch test nor specific IgE/prick test is useful in the diagnosis of FPIAP and FPE (1, 2).

Management and natural history

The management of non-IgE-GI-FA is empiric due to limited evidence and remains controversial in many areas. Elimination of the offending food constitutes the cornerstone of the management. In FPIES, breastfeeding can be continued unless maternal ingestion of a non-identified allergen triggers acute- or chronic-FPIES. Extensively hydrolyzed formula is usually well tolerated, although up to 20% patients may need an amino acid-based formula (34, 51). It is usually not necessary to avoid products with precautionary labeling 'contain traces of'.(3, 97). In FPIAP, elimination of food from the maternal diet is usually sufficient. Identification of the causing factor may be difficult occasionally. An extensively hydrolyzed or amino acid-based formula might be necessary if breastfeeding is not an option or if blood in stools becomes severe. Involvement of dietitian in the management of FPIES is important, especially in patients reacting to multiple foods (3, 92).

In addition to food avoidance, treatment of acute-FPIES is usually mainly based on aggressive fluid resuscitation (e.g., 10–20 ml/kg boluses of normal saline), empiric administration of a

Table 3 Currently used diagnostic criteria of non-IgE-mediated gastrointestinal food allergies

FPIES*	FPIAP†	FPE†
1. Less than 2 years of age at first presentation (frequent feature but not mandatory)	1. Small amount of rectal bleeding in an otherwise healthy infant	1. Less than 9 months of age at initial diagnosis
2. Exposure to the incriminated food elicits repetitive and projectile vomiting, pallor, lethargy within 2–4 h. The symptoms last a few hours, usually resolve within 6 h Diarrhea may be present, much less frequently and later (5–10 h).	2. Disappearance of the symptoms after all antigens are removed from diet	2. Repeated exposure to causative food elicits gastro-intestinal symptoms without alternative cause, predominantly vomiting and failure to thrive
3. Absence of symptoms that may suggest an IgE-mediated reaction	3. Exclusion of other cause of rectal bleeding	3. Confirmation of the diagnosis by small bowel biopsy in a symptomatic child, showing villous injury, crypts hyperplasia, and inflammation
4. Avoidance of the offending protein from the diet results in resolution of symptoms		4. Removal of causative food results in resolution of symptoms within several weeks, although the complete healing of villus injury may take several months
5. Re-exposure or oral food challenge elicits typical symptoms within 2−4 h. Two typical episodes are needed to establish the definitive diagnosis without the need to perform an oral food challenge.		

FPIES, food protein-induced enterocolitis syndrome; FPIAP, food protein-induced allergic proctocolitis; FPE, food protein-induced enteropathy.
*Modified Powell's diagnostic criteria (Sopo et al., 2013).
†There is no defined diagnostic criteria in the literature. Those are criteria generally used to diagnose FPIAP or FPE in clinical practice.

single dose of intravenous methylprednisolone (1 mg/kg, with a maximum of 60–80 mg). Intravenous and intramuscular ondansetron has been reported efficacious in treatment of acute-FPIES reaction during an OFC in small case series from the USA and Italy (79, 80).

Another common dilemma in the management of patients with non-IgE-GI-FA concerns introduction of new foods due to potential cross-reactivity and/or development of multiple food allergies during a period of vulnerability. The risk is higher in patients developing symptoms during the first few months of life, and in this case breastfeeding or hypoallergenic formula until one year of age may be advisable. In CM-FPIES occurring after the first month of life, soy formula can be proposed as an alternative, although a physician-supervised OFC is generally recommended for introduction (3). Regarding solid-FPIES, it remains unclear whether delaying introduction of other foods, particularly grains, could prevent development of multiple food-FPIES. Avoidance of foods from the same category (e.g., grains, poultry, or legumes) or those often associated with multiple food-FPIES can be considered, and it is left at the discretion of the treating physician, considering both risk and benefit of delayed food introduction (92). In patients with FPIAP and FPE, food diversification can be performed following usual recommendations, without any restrictions.

Most of the non-IgE-GI-FA are transient and resolve in early childhood. Thus, the majority of FPIAP patients achieve tolerance before 1 year of age (98). It has been shown that up to 20% of breastfed infants have spontaneous resolution of bleeding without changes in the maternal diet (26, 99). Infantile FPE resolves usually by age 1–2 years (38, 100). The natural course of FPIES has been investigated in several studies (24, 33, 34, 51, 57, 62, 101, 102), but there are major methodological differences between the studies making comparison difficult. The age of resolution differs by the food implicated, the sequence of food introduction as well as the characteristics of the population studied, particularly the atopic status. For example, CM-FPIES was reported to resolve in 20% by age 3 years in a US cohort, 90% by age 3 years in an Israeli cohort, and 64% by age 10 months in a Korean cohort (24, 34, 51, 102). Similar data are available for soy-FPIES (33, 34, 51, 102). Less robust data regard resolution of solid foods-FPIES, which tends to occur at a later age than CM/soy-FPIES (i.e., resolution by 5 years of age in only 65.5%, 50%, and 0% of patients with FPIES to grains, meat, and fish/shellfish, respectively) (34). It is generally recommended to perform an OFC every 12–18 months to assess tolerance acquisition (3). Timing of the OFC can be modified by the patient's history, food-IgE positivity, dietary, and/or social importance of the food and is ultimately best left at the discretion of the treating physician.

Celiac disease

Celiac disease is an immune-mediated systemic disorder elicited by the consumption of gluten and related prolamines in genetically susceptible individuals. The disease is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, celiac disease-specific antibodies, HLA-DQ2 or HLA-DQ8 haplotypes, and enteropathy (5). The factors leading to the breakdown of tolerance to gluten are not known. As the majority of individuals with a genetic predisposition do not develop celiac disease, and the concordance

between monozygotic twins is 75%, additional environmental as well as genetic factors may play a role (103). The prevalence of celiac disease in the general population varies considerably. It does not exist in populations lacking the HLA-DQ2 or HLA-DQ8 haplotypes, and the prevalence ranges from <0.25% to >1% (104), but may be as high as 3% (105, 106).

Although celiac disease is mainly an enteropathy elicited by the consumption of gluten, other clinical manifestations (i.e., FTT, diarrhea, abdominal distention, muscle wasting, anorexia, and irritability) are commonly seen (5, 107). However, currently, non-classic and asymptomatic presentations (positive serology without symptoms) are common.

In 2012, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition updated their guidelines for the diagnosis of celiac disease (5). Two groups of patients were identified with different diagnostic approaches. In symptomatic children, in whom antibodies to tissue transglutaminase type 2 (IgA-TG2) are high (>10 times the upper limit of normal), endomysial antibodies (EMA) are present in a separately obtained blood sample, HLA-DQ2 or HLA-DQ8 is positive, and a duodenal biopsy is optional. This is a change from previous guidelines in Europe recommending duodenal biopsy in all cases. Also, the diagnostic algorithm requires the absence of IgA deficiency. In cases of IgA deficiency, testing for deamidated gliadin peptide IgG antibodies is carried out. In asymptomatic children at increased risk for celiac disease, the diagnosis is based on positive serology and duodenal biopsy findings. The typical histopathologic findings include increased intra-epithelial lymphocytes, crypt hyperplasia, and reduced villous height up to complete villous atrophy. The diagnostic procedure must be performed in subjects currently consuming a gluten-containing diet, as eliminating gluten from the diet prior to testing may result in low-to-normal serology and inconclusive histopathology. Furthermore, serology must be carried out with a linear kit with established performance, and the biopsy specimen should be evaluated only with proper orientation of the sample and the evaluation made by a pathologist familiar with the pitfalls of the evaluation procedure (5). The only currently available treatment is a lifelong gluten-free diet, that is, dietary exclusion of wheat, rye, and barley (108).

The role of food allergy in other common infantile gastrointestinal disorders

Gastroesophageal reflux disease (GERD), colic, irritable bowel syndrome (IBS), and constipation are among the most common pediatric ailments, and food allergy may play a role in their pathogenesis (109). Symptoms of these disorders are classical manifestations of digestive motility dysfunction that may be due to food allergen-induced mediators (7, 109–112). Thus, a direct interaction between the enteric nervous system and inflammatory cells (i.e., mast cells, eosinophils) and pro-inflammatory cytokines secretion has been suggested (8, 109, 113–117). Stimulation of afferent nerve circuits via the brainstem during allergic reaction may influence sphincter tone and trigger gastrointestinal symptoms (118). Further studies are needed for a better understanding of the underlying pathomechanism by which food play a role in these diseases, such as increased intestinal permeability, induction of inflammation and changes in gut microbiota to name a few.

Gastroesophageal reflux disease

GER is the physiologic phenomenon of gastric contents moving into the esophagus that may cause symptoms such as intermittent vomiting, effortless spitting up, coughing, crying, and/or food refusal (14). GER disease (GERD) is GER that is associated with complications, including esophagitis, FTT, esophageal peptic strictures, Barrett's esophagus, pulmonary diseases, or even apparent life-threatening events (119–121). GER pathomechanism is multifactorial; the predominant mechanism is attributed to transient lower esophageal sphincter relaxation. The vast majority of patients with GER do not require treatment and symptoms resolve around 12 months of age (122). The role of food allergens, particularly CM, in the pathophysiology of GER has been long entertained (16, 123–126). Based on CM-free diet and OFC, Iacono et al. (123) found that CM may play a role in 41% of infantile GERD. CM-allergy may be more relevant in a subset of infants with severe and persistent regurgitations, food aversion, and FTT (127–129), as well as associated atopic dermatitis. Distinction between infantile eosinophilic esophagitis (EoE) and GERD may be particularly difficult and requires endoscopy and esophageal biopsies (13). Classic GER/GERD are typically characterized by eosinophils below 5/hpf (130), while the diagnosis of EoE requires more than 15 eosinophils/hpf with other distinctive features. The existence of PPI-responsive esophageal eosinophilia leads to more confusion and controversy regarding the distinction of EoE from GERD (131). It has been suggested that feeding with CM causes gastric dysrhythmia, delayed gastric emptying, prolonged gastric distension, and increased reflux episodes (6, 7). There is no convincing evidence supporting immunologically mediated mechanism for GERD; the clinical response to hydrolysates in infants with GER may be due to an effect of more rapid gastric emptying with an extensive hydrolysate than with native proteins (13, 132).

Colic

Infantile colic is characterized by unexplained inconsolable crying episodes during the early weeks of life (133, 134). Although the term colic suggests involvement of the gastrointestinal tract, the etiology of infantile colic is likely multifactorial (109). Several gastrointestinal factors have been incriminated; particularly intestinal immaturity, hypermotility secondary to a presumed autonomic imbalance and alterations in fecal microbiome (135). Faulty feeding techniques (i.e., underfeeding, overfeeding, and/or swallowing air) may also contribute to colic development (135). Food allergens may be relevant in a subset of patients with severe colic (132) and those with atopic dermatitis. Systematic reviews confirmed the benefit of hypoallergenic hydrolyzed or soy formula as well as low-allergenic maternal diet in exclusively breastfed colicky infants (17, 18, 20, 132, 136–143). However, these studies have

methodological limitations and the fact that colic is a transient disorder resolving within few weeks, renders investigations of the effect of restrictive diet particularly difficult (144). Considering that spontaneous improvement of colic usually occurs by 3 months of age, the duration of a proper diagnostic elimination diet would exceed the duration of symptoms in the majority of the affected infants (20, 132, 144). In addition, rapid maturation of the gut within the first months of life constitutes a significant bias for long-term studies (145).

Irritable bowel syndrome

IBS is a common functional disorder, characterized by abdominal pain, discomfort, and altered bowel habits (146). Adverse food reactions may play an important role in IBS, as up to 71% of patients report symptoms improvement with exclusion diet and exacerbations following food ingestion (147, 148). Although different foods have been incriminated (147), major interest has recently focused on wheat (149–154). Well-conducted studies demonstrated that patients with IBS-like symptoms but negative key criteria for celiac disease (CD) or IgE-mediated wheat allergy, experienced symptom improvement following wheat elimination and recurrence upon reintroduction of wheat (149–154). 'Non-celiac wheat (or gluten) sensitivity' is the term proposed to describe these patients (155). There is a reasonable overlap between non-celiac wheat (or gluten) sensitivity and IBS, and the current classification probably needs revision (148). Although gluten has been initially incriminated, the effect of wheat-free diet may also be due to other wheat components, that is, gliadin, amylase-trypsin inhibitors (ATI), or poorly absorbed short-chain carbohydrates (146, 148, 149).

The role of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) has been explored (156–159). In addition to wheat, these short-chain, poorly absorbed carbohydrates are found in a large variety of foods including some fruits and vegetables, onion, sorbitol, and some dairy products (146). While FODMAPs do not cause gastrointestinal symptoms in healthy adults aside from increased flatulence, FODMAPs are important IBS symptom triggers (160, 161). Thus, FODMAPs' effect is probably a consequence of underlying abnormalities in gut physiology leading to increased motility and gas production. The role of FODMAPs in functional abdominal pain and IBS in children is poorly studied. A randomized clinical trial showed improvement in gastrointestinal symptoms and decreased breath hydrogen production in children on a low FODMAPs diet (162–164). Additional pediatric studies are necessary before a low FODMAPs diet can be recommended in children with IBS.

Based on data showing an increased prevalence of atopic diseases among patients with IBS and improvement of symptoms after treatment with cromoglycate, food allergies were suggested to play a role in the IBS pathogenesis (165–167). Localized IgE-mediated reaction limited to the intestinal mucosa could be responsible for the symptoms (168). However, further studies are needed to investigate the exact role of food allergy in IBS patients.

Constipation

Up to 30% of children are affected by constipation, with an estimated of 3–5 percent of all pediatric office visits (169). The role of diet in the pathogenesis is well known; ingestion of large amounts of highly processed foods at the expense of fiber is one of the leading causes of constipation (170–172). Cereal grains may increase stool consistency and may trigger constipation (173). The role of CM in constipation is controversial (174). Transition from breast milk to CM-formula is often associated with mild constipation, and CM-formula has been associated with greater stool hardness (132, 175). Beneficial effect of CM-free diet was found in 28% to 78% of children with chronic constipation in prospective clinical trials (8, 9, 176–184). Patients with chronic constipation responding to CM-free diet are more likely to be atopic (8, 9). Inflammation of the rectal mucosa and anal fissures suggests that a non-IgE-mediated mechanism similar to FPIAP or FPIES may be involved (21, 176). Allergic inflammation may lead to increased anal pressure at rest and predispose to fecal retention (180). However, the potential effect of CM could also be explained by non-specific mechanisms that lead to change in stool consistency (9, 185).

Diagnosis and management of potentially food related GI disorders (GERD, colic, IBS, constipation, and non-celiac wheat sensitivity)

As for other non-IgE-GI-FA, no biomarkers are available to confirm the involvement of foods in these disorders, and the diagnosis is based on elimination diet followed by food reintroduction. Elimination of the potentially incriminated food (mainly CM) should be implemented for at least 2–4 weeks, and the diagnosis needs to be confirmed by subsequent food reintroduction to avoid unnecessary dietary restrictions for the mother or the child.

Elimination diets are associated with the risk of nutrient deficiency with major consequences, particularly in infants and the FODMAPs-free diet as FODMAPs are ubiquitous in foods essential to a well-balanced diet (186). Involvement of a dietitian is of major importance, especially in severe cases and a periodic reevaluation of the benefits of diet is warranted. In most cases, reintroduction of the incriminated food can be performed at home, without the need for a physician-supervised OFC. However, skin prick test and/or specific IgE have been shown to be positive in subset of patients. Thus, it is recommended to perform those tests before food reintroduction, and if positive, an OFC should be performed with an adapted protocol (3).

Conclusions

Non-IgE-GI-FA including FPIES, FPE, and FPIAP are relatively common in infants and young children, but are likely under-diagnosed. Further studies are needed for a better understanding of the pathomechanism, which will lead eventually to the development of diagnostic tests and treatment modalities. Limited evidence supports the role of food allergens

in subsets of constipation, GERD, IBS, and colic, but the immunologic pathomechanism is not fully understood. From a clinical point of view, the potential side effects of a long-term elimination diet should be taken into account, particularly to avoid nutrient deficiency and feeding disorders/food aversions in infants.

References

1. Boyce JA, Assa'ad A, Burks AW, 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**: S1–58.
2. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014: **69**: 1008–25.
3. Nowak-Wegrzyn A, Katz Y, Mehr SS, Koletzko S. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin Immunol* 2015: **135**: 1114–24.
4. Fiocchi A, Brozek J, Schunemann H, 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. Husby S, Koletzko S, Korponay-Szabo IR, 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.
6. Borrelli O, Mancini V, Thapar N, 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.
7. 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.
8. Borrelli O, Barbara G, Di Nardo G, et al. Neuroimmune interaction and anorectal motility in children with food allergy-related chronic constipation. *Am J Gastroenterol* 2009: **104**: 454–63.
9. 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.
10. Carroccio A, Mansueto P, Iacono G, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol* 2012: **107**: 1898–906; quiz 907.
11. 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**: 1845–52; quiz 53.
12. Fritscher-Ravens A, Schuppan D, Ellrichmann M, et al. Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. *Gastroenterology* 2014: **147**: 1012–20 e4.
13. Vandenplas Y. Management of paediatric GERD. *Nat Rev Gastroenterol Hepatol* 2014: **11**: 147–57.
14. Lightdale JR, Gremse DA. Gastroesophageal reflux: management guidance for the pediatrician. *Pediatrics* 2013: **131**: e1684–95.
15. 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.
16. Hill DJ, Heine RG, Cameron DJ, et al. Role of food protein intolerance in infants with persistent distress attributed to reflux esophagitis. *J Pediatr* 2000: **136**: 641–7.
17. Hill DJ, Roy N, Heine RG, et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics* 2005: **116**: e709–15.
18. 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.
19. Dobson D, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. *Cochrane Database Syst Rev* 2012: **12**: CD004796.
20. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. *J Paediatr Child Health* 2012: **48**: 128–37.
21. 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.
22. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004: **113**: 832–6.
23. Meijer CR, Shamir R, Mearin ML. Coeliac disease and noncoeliac gluten sensitivity. *J Pediatr Gastroenterol Nutr* 2015: **60**: 429–32.
24. 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 e1–3.
25. Elizur A, Cohen M, Goldberg MR, et al. Cow's milk associated rectal bleeding: a population based prospective study. *Pediatr Allergy Immunol* 2012: **23**: 766–70.
26. 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.
27. 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.
28. Savilahti E. Food-induced malabsorption syndromes. *J Pediatr Gastroenterol Nutr* 2000: **30** (Suppl): S61–6.
29. 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.
30. 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.
31. Lake AM, Whitington PF, Hamilton SR. Dietary protein-induced colitis in breast-fed infants. *J Pediatr* 1982: **101**: 906–10.
32. Odze RD, Bines J, Leichtner AM, Goldman H, Antonioli DA. Allergic proctocolitis in infants: a prospective clinicopathologic biopsy study. *Hum Pathol* 1993: **24**: 668–74.
33. Mehr S, Kakakios A, Frith K, Kemp AS. Food protein-induced enterocolitis syndrome: 16-year experience. *Pediatrics* 2009: **123**: e459–64.
34. Caubet JC, Ford LS, Sickles L, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol* 2014: **134**: 382–9.
35. 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.
36. 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.
37. Iyngkaran N, Yadav M, Boey CG, Lam KL. Severity and extent of upper small bowel mucosal damage in cow's milk protein-sensitive enteropathy. *J Pediatr Gastroenterol Nutr* 1988: **7**: 667–74.
38. Walker-Smith JA. Cow milk-sensitive enteropathy: predisposing factors and treatment. *J Pediatr* 1992: **121**: S111–5.
39. Iyngkaran N, Robinson MJ, Sumithran E, Lam SK, Puthucheary SD, Yadav M. Cows' milk protein-sensitive enteropathy. An important factor in prolonging diarrhoea of acute infective enteritis in early infancy. *Arch Dis Child* 1978: **53**: 150–3.
40. Yssing M, Jensen H, Jarnum S. Dietary treatment of protein-losing enteropathy. *Acta Paediatr Scand* 1967: **56**: 173–81.
41. Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr* 2000: **30** (Suppl): S58–60.
42. Lake AM. Chronic abdominal pain in childhood: diagnosis and management. *Am Fam Physician* 1999: **59**: 1823–30.
43. Lucarelli S, Di Nardo G, Lastrucci G, et al. Allergic proctocolitis refractory to maternal hypoallergenic diet in exclusively breast-fed infants: a clinical observation. *BMC Gastroenterol* 2011: **11**: 82.
44. 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.
45. Carroccio A, Mansueto P, Morfino 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.
46. Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, 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. Monti G, Castagno E, Liguori SA, et al. Food protein-induced enterocolitis syndrome by cow's milk proteins passed through breast milk. *J Allergy Clin Immunol* 2011: **127**: 679–80.
48. 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 73–4.
49. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998: **133**: 214–9.
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* 2005: **33**: 312–6.
58. 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.
59. Hsu P, Mehr S. Egg: a frequent trigger of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2013: **131**: 241–2.
60. Caubet JC, Nowak-Wegrzyn A. Food protein-induced enterocolitis to hen's egg. *J Allergy Clin Immunol* 2011: **128**: 1386–8.
61. 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.
62. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013: **1**: 343–9.
63. 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.
64. Sicherer SH. Food protein-induced enterocolitis syndrome: case presentations and management lessons. *J Allergy Clin Immunol* 2005: **115**: 149–56.
65. Benlounes N, Dupont C, Candalh C, et al. The threshold for immune cell reactivity to milk antigens decreases in cow's milk allergy with intestinal symptoms. *J Allergy Clin Immunol* 1996: **98**: 781–9.
66. Benlounes N, Candalh C, Matarazzo P, Dupont C, Heyman M. The time-course of milk antigen-induced TNF-alpha secretion differs according to the clinical symptoms in children with cow's milk allergy. *J Allergy Clin Immunol* 1999: **104**: 863–9.
67. Chung HL, Hwang JB, Kwon YD, Park MH, Shin WJ, Park JB. Deposition of eosinophil-granule major basic protein and expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in the mucosa of the small intestine in infants with cow's milk-sensitive enteropathy. *J Allergy Clin Immunol* 1999: **103**: 1195–201.
68. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor beta1, transforming growth factor type I and II receptors, and TNF-alpha in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2002: **109**: 150–4.
69. 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.
70. 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.
71. Van Sickle GJ, Powell GK, McDonald PJ, Goldblum RM. Milk- and soy protein-induced enterocolitis: evidence for lymphocyte sensitization to specific food proteins. *Gastroenterology* 1985: **88**: 1915–21.
72. Heyman M, Darmon N, Dupont C, et al. Mononuclear cells from infants allergic to cow's milk secrete tumor necrosis factor alpha, altering intestinal function. *Gastroenterology* 1994: **106**: 1514–23.
73. Karlsson MR, Rugtveit J, Brandtzaeg P. Allergen-responsive CD4+CD25+ regulatory T cells in children who have outgrown cow's milk allergy. *J Exp Med* 2004: **199**: 1679–88.
74. Hoffman KM, Ho DG, Sampson HA. Evaluation of the usefulness of lymphocyte

proliferation assays in the diagnosis of allergy to cow's milk. *J Allergy Clin Immunol* 1997: **99**: 360–6.
75. Scaparrotta A, Di Pillo S, Consilvio NP, et al. Usefulness of atopy patch test on a child with milk protein-induced enterocolitis syndrome: a case report. *Int J Immunopathol Pharmacol* 2013: **26**: 795–800.
76. Mori F, Barni S, Cianferoni A, Pucci N, de Martino M, Novembre E. Cytokine expression in CD3+ cells in an infant with food protein-induced enterocolitis syndrome (FPIES): case report. *Clin Dev Immunol* 2009: **2009**: 679381.
77. 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.
78. Berin MC. Immunopathophysiology of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2015: **135**: 1108–13.
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. Powell GK. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance. *J Pediatr* 1976: **88**: 840–4.
82. Powell GK. Milk- and soy-induced enterocolitis of infancy. Clinical features and standardization of challenge. *J Pediatr* 1978: **93**: 553–60.
83. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. *Pediatrics* 1998: **102**: e6.
84. Fontaine JL, Navarro J. Small intestinal biopsy in cows milk protein allergy in infancy. *Arch Dis Child* 1975: **50**: 357–62.
85. McDonald PJ, Goldblum RM, Van Sickle GJ, Powell GK. Food protein-induced enterocolitis: altered antibody response to ingested antigen. *Pediatr Res* 1984: **18**: 751–5.
86. Konstantinou GN, Bencharitiwong R, Grishin A, 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.
87. 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.
88. Iyngkaran N, Abdin Z, Davis K, et al. Acquired carbohydrate intolerance and cow milk protein-sensitive enteropathy in young infants. *J Pediatr* 1979: **95**: 373–8.
89. Beyer K, Castro R, Birnbaum A, Benkov K, Pittman N, Sampson HA. Human milk-specific mucosal lymphocytes of the gastrointestinal tract display a TH2 cytokine profile. *J Allergy Clin Immunol* 2002: **109**: 707–13.
90. Lin XP, Magnusson J, Ahlstedt S, 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.
91. Ormala T, Rintala R, Savilahti E. T cells of the colonic mucosa in patients with infantile colitis. *J Pediatr Gastroenterol Nutr* 2001: **33**: 133–8.
92. Meyer RSC, Shah N. A review on the diagnosis and management of food-induced gastrointestinal allergies. *Curr Allergy Clin Immunol* 2012: **25**: 10–7.
93. Hwang JB, Hong J. Food protein-induced proctocolitis: is this allergic disorder a reality or a phantom in neonates? *Korean J Pediatr* 2013: **56**: 514–8.
94. Powell GK. Food protein-induced enterocolitis of infancy: differential diagnosis and management. *Compr Ther* 1986: **12**: 28–37.
95. Serafini S, Bergmann MM, 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.
96. 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.
97. Mane SK, Hollister ME, Bahna SL. Food protein-induced enterocolitis syndrome to trivial oral mucosal contact. *Eur J Pediatr* 2014: **173**: 1545–7.
98. Kaya A, Toyran M, Civelek E, Misirlioglu E, Kirsaclioglu C, Kocabas CN. Characteristics and prognosis of allergic proctocolitis in infants. *J Pediatr Gastroenterol Nutr* 2015: **61**: 69–73.
99. 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.
100. Sicherer SH. Clinical aspects of gastrointestinal food allergy in childhood. *Pediatrics* 2003: **111**: 1609–16.
101. Katz Y, Goldberg MR. Natural history of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014: **14**: 229–39.
102. 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.
103. Marild K, Ludvigsson JF, Stordal K. Current evidence on whether perinatal risk factors influence coeliac disease is circumstantial. *Acta Paediatr* 2016: **105**: 366–75.
104. Ludvigsson JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut* 2014: **63**: 1210–28.
105. Mustalahti K, Catassi C, Reunanen A, et al. The prevalence of celiac disease in Europe: results of a centralized, international mass screening project. *Ann Med* 2010: **42**: 587–95.
106. Myleus A, Ivarsson A, Webb C, et al. Celiac disease revealed in 3% of Swedish 12-year-olds born during an epidemic. *J Pediatr Gastroenterol Nutr* 2009: **49**: 170–6.
107. Mozer-Glassberg Y, Zevit N, Rosenbach Y, Hartman C, Morgenstern S, Shamir R. Follow-up of children with celiac disease - lost in translation? *Digestion* 2011: **83**: 283–7.
108. Hill ID, Fasano A, Guandalini S, et al. NASPGHAN clinical report on the diagnosis and treatment of gluten-related disorders. *J Pediatr Gastroenterol Nutr* 2016: **63**: 156–65.
109. Heine RG. Allergic gastrointestinal motility disorders in infancy and early childhood. *Pediatr Allergy Immunol* 2008: **19**: 383–91.
110. Fargeas MJ, Theodourou V, Fioramonti J, Bueno L. Relationship between mast cell degranulation and jejunal myoelectric alterations in intestinal anaphylaxis in rats. *Gastroenterology* 1992: **102**: 157–62.
111. Fargeas MJ, Fioramonti J, Bueno L. Central action of interleukin 1 beta on intestinal motility in rats: mediation by two mechanisms. *Gastroenterology* 1993: **104**: 377–83.
112. Heine RG. Pathophysiology, diagnosis and treatment of food protein-induced gastrointestinal diseases. *Curr Opin Allergy Clin Immunol* 2004: **4**: 221–9.
113. Zangen T, Ciarla C, Zangen S, et al. Gastrointestinal motility and sensory

abnormalities may contribute to food refusal in medically fragile toddlers. *J Pediatr Gastroenterol Nutr* 2003: **37**: 287–93.
114. Ito A, Hagiyama M, Oonuma J, Murakami Y, Yokozaki H, Takaki M. Involvement of the SgIGSF/Necl-2 adhesion molecule in degranulation of mesenteric mast cells. *J Neuroimmunol* 2007: **184**: 209–13.
115. Rothenberg ME, Cohen MB. An eosinophil hypothesis for functional dyspepsia. *Clin Gastroenterol Hepatol* 2007: **5**: 1147–8.
116. Wood JD. Histamine, mast cells, and the enteric nervous system in the irritable bowel syndrome, enteritis, and food allergies. *Gut* 2006: **55**: 445–7.
117. Schappi MG, Borrelli O, Knafelz D, et al. Mast cell-nerve interactions in children with functional dyspepsia. *J Pediatr Gastroenterol Nutr* 2008: **47**: 472–80.
118. Shaker R. Gastroesophageal reflux disease: beyond mucosal injury. *J Clin Gastroenterol* 2007: **41** (Suppl 2): S160–2.
119. Shay S. Esophageal impedance monitoring: the ups and downs of a new test. *Am J Gastroenterol* 2004: **99**: 1020–2.
120. Sherman PM, Hassall E, Fagundes-Neto U, et al. A global, evidence-based consensus on the definition of gastroesophageal reflux disease in the pediatric population. *Am J Gastroenterol* 2009: **104**: 1278–95; quiz 96.
121. Zevit N, Shamir R. 3.12 Regurgitation and gastroesophageal reflux. *World Rev Nutr Diet* 2015: **113**: 203–8.
122. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009: **49**: 498–547.
123. Iacono G, Carroccio A, Cavataio F, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996: **97**: 822–7.
124. Cavataio F, Carroccio A, Iacono G. Milk-induced reflux in infants less than one year of age. *J Pediatr Gastroenterol Nutr* 2000: **30** (Suppl): S36–44.
125. Kamer B, Chilarski A, Lange A, Piaseczna-Piotrowska A. Gastroesophageal reflux in infants with food allergy. *Med Sci Monit* 2000: **6**: 348–52.
126. Milocco C, Torre G, Ventura A. Gastro-oesophageal reflux and cows' milk protein allergy. *Arch Dis Child* 1997: **77**: 183–4.
127. Wu YP, Franciosi JP, Rothenberg ME, Hommel KA. Behavioral feeding problems and parenting stress in eosinophilic gastrointestinal disorders in children. *Pediatr Allergy Immunol* 2012: **23**: 730–5.
128. Mathisen B, Worrall L, Masel J, Wall C, Shepherd RW. Feeding problems in infants with gastro-oesophageal reflux disease: a controlled study. *J Paediatr Child Health* 1999: **35**: 163–9.
129. Mukkada VA, Haas A, Maune NC, et al. Feeding dysfunction in children with eosinophilic gastrointestinal diseases. *Pediatrics* 2010: **126**: e672–7.
130. Liacouras CA, Furuta GT, Hirano I, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allergy Clin Immunol* 2011: **128**: 3–20 e6; quiz 21–2.
131. Kia L, Hirano I. Distinguishing GERD from eosinophilic oesophagitis: concepts and controversies. *Nat Rev Gastroenterol Hepatol* 2015: **12**: 379–86.
132. Heine RG. Gastrointestinal food allergies. *Chem Immunol Allergy* 2015: **101**: 171–80.
133. Barr RG. Colic and crying syndromes in infants. *Pediatrics* 1998: **102**: 1282–6.
134. Freedman SB, Al-Harthy N, Thull-Freedman J. The crying infant: diagnostic testing and frequency of serious underlying disease. *Pediatrics* 2009: **123**: 841–8.
135. Shamir R, St James-Roberts I, Di Lorenzo C, et al. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. *J Pediatr Gastroenterol Nutr* 2013: **57** (Suppl 1): S1–45.
136. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review. *BMJ* 1998: **316**: 1563–9.
137. Evans RW, Fergusson DM, Allardyce RA, Taylor B. Maternal diet and infantile colic in breast-fed infants. *Lancet* 1981: **1**: 1340–2.
138. Campbell JP. Dietary treatment of infant colic: a double-blind study. *J R Coll Gen Pract* 1989: **39**: 11–4.
139. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* 1982: **70**: 7–10.
140. Hill DJ, Cameron DJ, Francis DE, Gonzalez-Andaya AM, Hosking CS. Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. *J Allergy Clin Immunol* 1995: **96**: 386–94.
141. Forsyth BW. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. *J Pediatr* 1989: **115**: 521–6.
142. Lucassen PL, Assendelft WJ. Systematic review of treatments for infant colic. *Pediatrics* 2001: **108**: 1047–8.
143. Garrison MM, Christakis DA. A systematic review of treatments for infant colic. *Pediatrics* 2000: **106**: 184–90.
144. Bergmann MM, Caubet JC, McLin V, Belli DC, Schappi MG, Eigenmann PA. Common colic, gastroesophageal reflux and constipation in infants under 6 months of age do not necessitate an allergy work-up. *Pediatr Allergy Immunol* 2014: **25**: 410–2.
145. Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* 1954: **14**: 421–35.
146. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015: **313**: 949–58.
147. Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? *Am J Gastroenterol* 1998: **93**: 2184–90.
148. Mansueto P, D'Alcamo A, Seidita A, Carroccio A. Food allergy in irritable bowel syndrome: the case of non-celiac wheat sensitivity. *World J Gastroenterol* 2015: **21**: 7089–109.
149. Biesiekierski JR, Newnham ED, Irving PM, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011: **106**: 508–14; quiz 15.
150. Kaukinen K, Turjanmaa K, Maki M, et al. Intolerance to cereals is not specific for coeliac disease. *Scand J Gastroenterol* 2000: **35**: 942–6.
151. Usai P, Manca R, Cuomo R, Lai MA, Boi MF. Effect of gluten-free diet and co-morbidity of irritable bowel syndrome-type symptoms on health-related quality of life in adult coeliac patients. *Dig Liver Dis* 2007: **39**: 824–8.
152. Ellis A, Linaker BD. Non-coeliac gluten sensitivity? *Lancet* 1978: **1**: 1358–9.
153. Cooper BT, Holmes GK, Ferguson R, Thompson RA, Allan RN, Cooke WT. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology* 1980: **79**: 801–6.
154. Vazquez-Roque MI, Camilleri M, Smyrk T, et al. A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function. *Gastroenterology* 2013: **144**: 903–11 e3.
155. Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009: **104**: 1587–94.
156. Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel

syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* 2008: **6**: 765–71.
157. Ong DK, Mitchell SB, Barrett JS, et al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. *J Gastroenterol Hepatol* 2010: **25**: 1366–73.
158. Austin GL, Dalton CB, Hu Y, et al. A very low-carbohydrate diet improves symptoms and quality of life in diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2009: **7**: 706–8 e1.
159. Rao SS, Yu S, Fedewa A. Systematic review: dietary fibre and FODMAP-restricted diet in the management of constipation and irritable bowel syndrome. *Aliment Pharmacol Ther* 2015: **41**: 1256–70.
160. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology* 2014: **146**: 67–75 e5.
161. Shepherd SJ, Lomer MC, Gibson PR. Short-chain carbohydrates and functional gastrointestinal disorders. *Am J Gastroenterol* 2013: **108**: 707–17.
162. Lothe L, Ivarsson SA, Lindberg T. Motilin, vasoactive intestinal peptide and gastrin in infantile colic. *Acta Paediatr Scand* 1987: **76**: 316–20.
163. Chumpitazi BP, Cope JL, Hollister EB, et al. Randomised clinical trial: gut microbiome biomarkers are associated with clinical response to a low FODMAP diet in children with the irritable bowel syndrome. *Aliment Pharmacol Ther* 2015: **42**: 418–27.
164. Chumpitazi BTC, McMeans A, Shulman R. A low FODMAPS diet ameliorates symptoms in children with irritable bowel syndrome: a double blind, randomized crossover trial. *Gastroenterology* 2014: **146**: S144.
165. Olen O, Neuman A, Koopmann B, et al. Allergy-related diseases and recurrent abdominal pain during childhood - a birth cohort study. *Aliment Pharmacol Ther* 2014: **40**: 1349–58.
166. White AM, Stevens WH, Upton AR, O'Byrne PM, Collins SM. Airway responsiveness to inhaled methacholine in patients with irritable bowel syndrome. *Gastroenterology* 1991: **100**: 68–74.
167. Stefanini GF, Saggioro A, Alvisi V, et al. Oral cromolyn sodium in comparison with elimination diet in the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. *Scand J Gastroenterol* 1995: **30**: 535–41.
168. Bischoff SC, Mayer J, Wedemeyer J, et al. Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. *Gut* 1997: **40**: 745–53.
169. van den Berg MM, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol* 2006: **101**: 2401–9.
170. Roma E, Adamidis D, Nikolara R, Constantopoulos A, Messaritakis J. Diet and chronic constipation in children: the role of fiber. *J Pediatr Gastroenterol Nutr* 1999: **28**: 169–74.
171. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014: **58**: 258–74.
172. Loening-Baucke V. Clinical approach to fecal soiling in children. *Clin Pediatr (Phila)* 2000: **39**: 603–7.
173. Di Lorenzo C. Pediatric anorectal disorders. *Gastroenterol Clin North Am* 2001: **30**: 269–87, ix.
174. Heine RG, Elsayed S, Hosking CS, Hill DJ. Cow's milk allergy in infancy. *Curr Opin Allergy Clin Immunol* 2002: **2**: 217–25.
175. Quinlan PT, Lockton S, Irwin J, Lucas AL. The relationship between stool hardness and stool composition in breast- and formula-fed infants. *J Pediatr Gastroenterol Nutr* 1995: **20**: 81–90.
176. Iacono G, Cavataio F, Montalto G, et al. Intolerance of cow's milk and chronic constipation in children. *N Engl J Med* 1998: **339**: 1100–4.
177. Irastorza I, Ibanez B, Delgado-Sanzonetti L, Maruri N, Vitoria JC. Cow's-milk-free diet as a therapeutic option in childhood chronic constipation. *J Pediatr Gastroenterol Nutr* 2010: **51**: 171–6.
178. Iacono G, Carroccio A, Cavataio F, Montalto G, Cantarero MD, Notarbartolo A. Chronic constipation as a symptom of cow milk allergy. *J Pediatr* 1995: **126**: 34–9.
179. Daher S, Tahan S, Sole D, et al. Cow's milk protein intolerance and chronic constipation in children. *Pediatr Allergy Immunol* 2001: **12**: 339–42.
180. Iacono G, Bonventre S, Scalici C, et al. Food intolerance and chronic constipation: manometry and histology study. *Eur J Gastroenterol Hepatol* 2006: **18**: 143–50.
181. El-Hodhod MA, Younis NT, Zaitoun YA, Daoud SD. Cow's milk allergy related pediatric constipation: appropriate time of milk tolerance. *Pediatr Allergy Immunol* 2010: **21**: e407–12.
182. Syrigou EI, Pitsios C, Panagiotou I, et al. Food allergy-related paediatric constipation: the usefulness of atopy patch test. *Eur J Pediatr* 2011: **170**: 1173–8.
183. Dehghani SM, Ahmadpour B, Haghighat M, Kashef S, Imanieh MH, Soleimani M. The role of cow's milk allergy in pediatric chronic constipation: a randomized clinical trial. *Iran J Pediatr* 2012: **22**: 468–74.
184. Sopo SM, Arena R, Scala G. Functional constipation and cow's-milk allergy. *J Pediatr Gastroenterol Nutr* 2014: **59**: e34.
185. Magazzu G, Scoglio R. Gastrointestinal manifestations of cow's milk allergy. *Ann Allergy Asthma Immunol* 2002: **89**: 65–8.
186. van Tilburg MA, Felix CT. Diet and functional abdominal pain in children and adolescents. *J Pediatr Gastroenterol Nutr* 2013: **57**: 141–8.