Non–Immunoglobulin E–Mediated Food Allergies

Distinguishing the Nuances

Eva D. Weston, RDN, LD, NBC-HWC
Esther Myers, PhD, RDN, LD, FAND

In food allergy, there is an unfortunate misconception that all allergies are equally dangerous. This third article on food allergies focuses on non–immunoglobulin E–mediated food allergy, which classically presents in infancy or early childhood and predominantly involves the gastrointestinal tract. Most non–immunoglobulin E–mediated food allergies have a good prognosis, with the majority outgrown in childhood, although a minority of cases do persist into adulthood. Nutr Today 2024;59(2):52–59

In food allergy (FA), there is an unfortunate misconception that all allergies are equally dangerous.[1] It is suggested in the literature that incorrect diagnosis may unnecessarily add risk and burden to a patient and family by impacting both mental and physical health.[2] All food allergy is defined as an immune response that is consistent and reproducible upon every exposure. In contrast, food intolerance is largely gastrointestinal in nature and does not involve the immune system. Within food allergies, there are 2 major categories, immunoglobulin E (IgE)–mediated and non–IgE-mediated, as well as a category that is "mixed." The onset of reaction in a non–IgE-mediated FA (non-IgE FA) immune response is often delayed several hours or days as opposed to IgE-mediated FA where the immune response is immediate, defined as within minutes to 2 hours.

This article focuses on non-IgE FA. Non-IgE FA classically presents in infancy or early childhood and predominantly involves the gastrointestinal tract. The specific challenges of non-IgE FA will be addressed: diagnosing non-IgE FA with very few tests or procedures available for a definitive diagnosis, many common signs and symptoms, differing times between exposure and signs and symptoms, potentially unintended consequences of using an elimination diet to both diagnose and treat non-IgE FA, and the importance of a reintroduction plan with elimination diets. This article includes celiac disease because it falls under the category of both a non-IgE FA and an autoimmune disease. The majority of non-IgE FAs have a good prognosis and are outgrown in childhood. Exceptions such as celiac disease and a minority of non-IgE FA persist into adulthood.

Non–IgE-mediated FA is a reproducible allergic immune response that does not elicit anaphylaxis caused by the IgE-mediated food allergy–specific cascade of reactions.

RECOGNIZING NON–IGE-MEDIATED FOOD ALLERGY

Non-IgE FAs are often diagnosed based on discerning reproducible reactions that occur upon exposure to a food, which then resolve when the food is avoided via an elimination diet, and signs and symptoms return when the allergen is reintroduced. Most non-IgE-FA are diagnosed based primarily on clinical history with supporting lab work. For example, Elevated levels of celiac disease antibody in blood and genetic tests for human leukocyte antigen (HLA-DQ2 and HLADQ8) are used to confirm celiac disease or risk, and biopsies can be used to support diagnosis in both celiac disease and FPE. Relatively little is known about non-IgE FA pathophysiology, so the definition for these disorders is established through expert opinion and consensus.[3] A patient's medical history consistent with non-IgE FA presentation, typically gastrointestinal reactions, is the key factor

Eva D. Weston, RDN, LD, NBC-HWC, began working in clinical dietetics in 2008 and is a clinical, private practice dietitian at Weston Nutrition & Wellness, where she specializes in food allergies and intolerances. She is a Food Allergy Research and Education–trained Pediatric Food Allergy dietitian.

Esther Myers, PhD, RDN, LD, FAND, is an internationally known lecturer and author with more than 20 years of experience in creating evidence-based nutrition care practice guidelines and led the development of the Evidence Analysis Library for the Academy of Nutrition and Dietetics.

The authors have no conflicts of interest to disclose.

Correspondence: Eva D. Weston, RDN, LD, NBC-HWC, Weston Nutrition & Wellness, Houston, TX (eva@westonrd.com).

DOI: 10.1097/NT.0000000000000675

when considering FA diagnosis. A non-IgE FA reaction is typically delayed several hours or days after exposure to an offending allergen, and symptoms such as altered bowel habits, reflux, constipation, colic, and vomiting are often present in otherwise healthy infants.[4] With the absence of test results that definitively diagnose most non-IgE FAs, there is strong reliance on clinical history and elimination diets as a tool for diagnosis (Fig. 1).

Celiac disease is an immune-mediated response to gluten that is classified as both a non–IgE-mediated food allergy and an autoimmune disorder.

ELIMINATION DIETS: AS A DIAGNOSTIC AND DISEASE MANAGEMENT TOOL IN NON–IGE-MEDIATED FA

Following a detailed clinical history, elimination diets are the key to diagnosing as well as managing non-IgE FA. Important determinants for healthcare professionals to consider prior to proceeding with an elimination diet are included in Table 1.

Elimination Diets in Diagnosis

Elimination diets utilized for diagnosis or management of FA may lead to growth stunting and other nutritional deficiencies, particularly if the food eliminated is of key nutritional importance for pediatric patients, for example, cow's milk.[5,6] However, the impact for both of these parameters improves if the diet is adequately supplemented following the recommendations of a physician or dietitian.[5,7–9]

TABLE 1 Considerations in Proceeding With an Elimination Diet

What is the risk of eating it? (Will symptoms worsen, or should we watch and wait?)
What is the benefit of eating it? (Is it of significant nutritional or developmental value?)
What is the risk of avoiding it? (Is this person sensitized to the allergen, and could they go on to develop an IgE-mediated food allergy?)
What is the benefit of avoiding it? (Will it significantly improve symptoms?)
And a very important step of the plan: If we eliminate the potential allergen, what is the plan for the reintroduction challenge?

Abbreviation: IgE, immunoglobulin E.

Regular follow-ups with their physician should be part of the management plan for all patients on an elimination diet. Consistent anthropometric data support early detection in patients who begin to exhibit signs and symptoms of poor growth.[10,11]

In addition to considering the potential long-term nutritional growth implications impacted by using an elimination diet, the need for strict avoidance in relation to the potential development of IgE-mediated FA should be part of the shared decision-making process. Strict avoidance of the allergen may not be necessary, as in the case of patients who tolerate baked milk or egg.[11] Risk of developing an IgE-mediated allergy following an elimination diet is not well defined, but has been reported in the literature as a

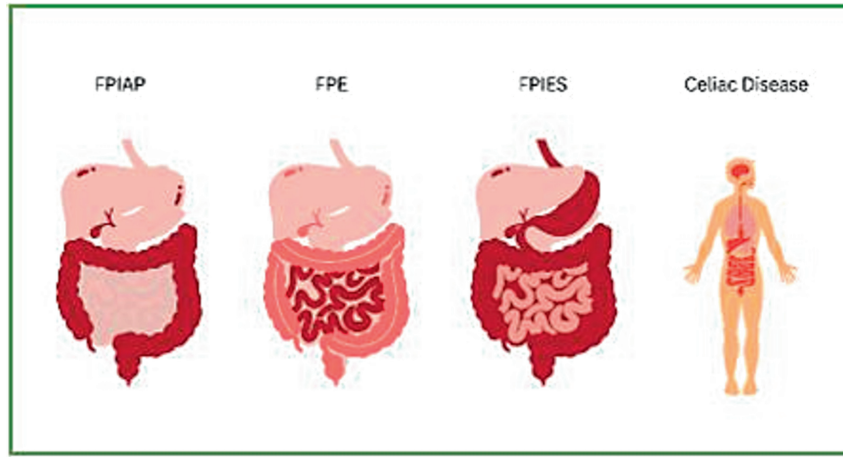

FIGURE 1. Body organs affected in different non–IgE-mediated Food Allergies. FPIAP affects the colon. Celiac disease is both a non–IgE-mediated food allergy and an autoimmune disease that classically impacts the small intestine, but all body systems may be affected. FPE predominantly impacts the small intestine. FPIES can impact the entire GI tract. Abbreviations: FPIAP: food protein–induced allergic proctocolitis; FPIES, food protein–induced enterocolitis syndrome; GI, gastrointestinal.

clinical consideration.[2,12] It is possible that those sensitized, (defined as a positive skin prick test or serum specific IgE) and those previously tolerant to a food may develop a new-onset IgE-mediated FA when reintroducing an allergen after a period of elimination.[13] Utilizing a shared decision-making process to determine the best individualized course of action, including having a risk-benefit conversation, ideally will take place with the patient or caregiver.[11] Working with a registered dietitian as part of a multidisciplinary team can improve growth parameters and nutritional biomarkers for patients on an elimination diet.[5] A patient-specific approach to elimination diets will consider individual diagnosis and circumstances. See the excellent resource provided in Table 2, entitled "A Patient-Specific Approach to Develop an Exclusion Diet to Manage Food Allergy in Infants and Children"[11] and other resources for patient-specific support (Fig. 2).

TABLE 2 Resources for Healthcare Professionals

Literature
Health Professional's Guide to Nutrition Management of Food Allergies 2023
Diagnosis and Management of Non-IgE Gastrointestinal Allergies in Breastfed Infants—An EAACI Position Paper 2019
Dietary Management of Food Allergy Durban et al 2021
A Patient-Specific Approach to Develop an Exclusion Diet to Manage Food Allergy in Infant and Children (Venter et al 2017)
Non–IgE-Mediated Gastrointestinal Food Allergies in Children: An Update (2020)
Feeding Difficulties in Children With Non–IgE-Mediated Food Allergic Gastrointestinal Disorders (Chehade et al 2019)
International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome: Executive Summary—Workgroup Report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology 2017
Food Protein-Induced Allergic Proctocolitis in Infants: Literature Review and Proposal of a Management Protocol (Mennini et al 2020)
Non–IgE-Mediated Food Allergy Courses
Food Allergy Research and Education Food Allergy Academy[a]
Nutrition Masterclass Infant GI series 2023

Abbreviation: IgE, immunoglobulin E.

[a] Free registration, browse the courses available, several are specific to non–IgE-mediated food allergy.

Elimination diets in diagnosis or management ideally have food allergen reintroduction planned when initiated.

Dietary Support in Managing Non-IgE Food Allergy

The primary management plan for patients with these diagnoses involves complete elimination/avoidance of the food trigger(s) while also supporting growth and development, quality of life, and advancing complementary foods in the pediatric population.[7] Although food triggers may vary, the most common food triggers for the different allergies are included in the Management column in Table 3. Ideally, a registered dietitian nutritionist specialist with a clear understanding of FA management should be involved prior to beginning elimination diets to provide patient-specific support, including which foods to avoid and to what degree of avoidance, as well as alternatives to meet nutritional needs.[11] Elimination diets utilized for the management of non-IgE FA need to be managed well to reduce the risk for nutritional deficiencies, potentially prevent new onset of IgE-mediated FA and increase the quality of life of patients and their caregivers. Health-related quality-of-life determinants have both objective and subjective factors; however, some studies suggest that quality of life may be lower for those with non-IgE FA when compared with IgE-mediated FA, sickle cell anemia, and intestinal failure.[4,15,25] Lower quality of life in all FA diagnosis is often associated with a greater number of foods eliminated and the severity of the disease.[15]

Most non-IgE FAs are diagnosed in early childhood, and this directly impacts the development of a healthy relationship with food as well as feeding skills. Symptoms common to many of the non-IgE diagnoses, such as abdominal pain, vomiting, diarrhea, and chronic inflammation, can result in children associating food with pain or discomfort, which may lead to a fear of eating, limited appetite, food refusal, and/or parental fear of feeding.[25] Working with food allergies is a nuanced area of practice. For example, for patients with food protein–induced enterocolitis syndrome there are geographical differences in age of tolerance development as well as the prevalence of common food triggers. The reason for these differences is unknown, but one theory is related to geographical feeding practices.[7] Patients with food protein–induced allergic proctocolitis are typically told to eliminate the trigger until 12 months of age; however, healthcare professionals may consider IgE-mediated allergy prevention guidelines and evaluate earlier reintroduction challenge on a case-by-case basis.[26]

Healthcare Teams Support Food Allergy Patients and Caregivers

Optimal management approaches, usually developed through collaboration of multidisciplinary health professionals educated and experienced in food allergies, focus on

FIGURE 2. Finding a food allergy registered dietitian nutritionist.

TABLE 3 Overview of Non-IgE Food Allergy.

Name	Description	Presentation	Diagnose	Management	Prognosis	Resources
Food protein–induced enterocolitis syndrome (FPIES)[2,4,7,14–16]	Uncommon[a] diagnosis, awareness amongst physicians in low. Two types: acute and chronic, often reflect type of exposure to food trigger. Chronic: seen in patients fed food repetitively, as in milk or soy formula. Rare occurrence in exclusively breastfed infants. Acute: seen when the food is eliminated then accidental exposure occurs, or when introducing food for the first time. Atypical: FPIES non-IgE diagnosis plus an IgE sensitization to the food allergen, which is either coexisting atopic disease or sensitization that may result in an IgE-mediated food allergy after elimination.	Early presentation in 3–6 mo infants, later presentation with introduction of complementary foods in 4–7 mo infants. Key signs/symptoms: • Delayed vomiting, typically 1–4 h after ingestion, with or without diarrhea. Medical emergency: Risk for hypotension or metabolic acidosis related to dehydration in severe cases. Vomiting may accompany lethargy and pallor.	A convincing clinical history consistent with FPIES diagnosis criterion.[d] Elimination of the suspected allergen followed by resolution of symptoms. Evaluation for necessity of an oral food challenge (OFC) to confirm diagnosis. OFC: Utilize a shared decision-making process with patient/ caregiver, reviewing the risk/benefit ratio as FPIES OFC's are: • not always necessary. • Performed to determine food trigger or establish tolerance (typically 12-18 mo after last reaction). • Require a medically appropriate setting, one with prolonged observation and fluid resuscitation available. • Suggested to be done at regular intervals to determine tolerance and if necessary, possible prevention of IgE-mediated food allergy development.	*Avoidance of food triggers.* Most common triggers: cow's milk, soy, rice, oat, wheat, meat, fish, sweet potato, banana, avocado The threshold dose for reaction is not established, but at this time it is not a standard practice to eliminate foods based on contact exposure or precautionary allergen labeling (PAL) statements. Periodic OFC to determine tolerance development.	FPIES is often outgrown prior to 5 y of age, although a small percentage of FPIES persists to adulthood. Note: Adult onset FPIES has been more recently recognized, with seafood as the primary trigger.	• FPIES Foundation Emergency Care Plan • International FPIES Association
Food protein–induced enteropathy (FPE)[3,4,10,15]	• Uncommon[a] diagnosis specifically impacts the small intestine, most often chronic gastrointestinal symptoms concurrent with chronic ingestion of food trigger, possible to have acute onset of symptoms (<12 h) after ingestion. May be initially confused with celiac disease.	• Typically presents in infants in the first few weeks/ months of life or before 12 mo in formula-fed infants. May occur in older children. • Key symptoms: • protracted diarrhea/ steatorrhea and failure to thrive related to malabsorption. • Recurrent vomiting may also occur.	• Elimination of food trigger supports resolution of symptoms in 1–3 wk. • Small bowel biopsy confirmed villous injury, inflammation, crypt hyperplasia. • Fecal fat increase seen in 80% of patients. • Lab assays may indicate malabsorption of nutrients.	• Avoid food triggers. • Most common food triggers: • Primarily: Cow's milk, soy (often in formula.) • Secondary: Egg, wheat, rice, poultry, fish • Patients with significant mucosal damage may also develop *lactose intolerance*.	• Typically resolves by 1–3 y; however, the small bowel villus recovery may take longer.	• FPE Case Study
Food protein–induced allergic proctocolitis (FPIAP)[15,17,18]	Common[a] disease of infancy, impacts the large intestine, seen in both breastfed and formula-fed infants.	Typically presents in infants in the first few weeks/months of life. Key symptoms: Blood or mucous in the stool of an otherwise healthy infant.	Option 1: In patients with non-severe symptoms <1mo "watch and wait" for spontaneous resolution of symptoms. Option 2: Maternal or infant elimination diet of the suspected allergen for 2–4 wk, accompanied by resolution of symptoms (3 d to 3 wk) and recurrence of signs and symptoms on reintroduction challenge.	Elimination diet with periodic tolerance development challenge. Most common food triggers: Cow's milk, soy, egg, wheat Infants may continue breastfeeding or utilize exclusively hydrolyzed formula (EHF). Amino Acid formulas are utilized when improvement is not seen on EHF.	Typically resolves by 1–2 y of age.	

(continues)

TABLE 3 Overview of Non-IgE Food Allergy., Continued

Name	Description	Presentation	Diagnose	Management	Prognosis	Resources
Celiac disease (CD)[13,19–23]	Common diagnosis,[b] both a non–IgE-mediated food allergy and an autoimmune disease. An immune system reaction to gluten which produces antibodies that damage the lining of the small intestine. Occurs in genetically predisposed individuals carrying the HLA- DQ2 or HLA-DQ8 genes. First-degree relatives of CD patients carry a 1:10 risk of development. May be symptomatic: further divided into *classical* presentation (GI s/s after gluten exposure with malabsorption issue) or *nonclassical* presentation (nonspecific findings, eg, abdominal distention/pain, migraine, chronic fatigue, unexplained infertility, etc) Asymptomatic—no symptoms reported even on detailed questioning.	May present at any age once gluten is introduced in the diet. May present immediate or delayed reaction following ingestion, and reaction may resolve within hours or days. GI symptoms: *Primary:* weight loss, diarrhea, steatorrhea *Secondary:* Constipation, bloating, altered bowel habits Extraintestinal symptoms: *Primary:* dermatitis herpetiformis, Osteoporosis, anemia, celiac hepatitis, recurrent miscarriage *Secondary*: vary widely and may impact any body system/ tissue as well as mental health.	Screening suggested for those with symptoms. Higher risk for patients with other autoimmune disease and those with a first-degree relative diagnosed with CD. Clinical: History consistent with symptomatic CD. Elimination of gluten containing foods including wheat, barley, or rye with resolution of symptoms. Labs: • tTG - IgA • EMA • DGP-IgG • HLA CD is a patchy disease and multiple biopsies are central for diagnosis. In select patients diagnosis may be based on clinical s/s and specific (+) serology. See special consideration[c]	Strict gluten elimination diet (food and medicine) required. Gluten is a protein found in wheat, barley, and rye. Poor gluten-free diet adherence or late celiac disease diagnosis has been associated with: enteropathy-associated T-cell lymphoma.	CD is a lifelong diagnosis. There is currently no treatment; however, research is ongoing to find effective therapies for symptom control and inflammation reversal.	Celiac Disease Foundation Beyond Celiac

Abbreviations: DGP-IgG, deaminated gliadin peptides–immunoglobulin G; EMA, endomysial antibody; HLA, human leukocyte antigen haplotype; IgE, immunoglobulin E; s/s, signs and symptoms; tTG-IgA, tissue transglutaminase–immunoglobulin A; .

[a] The prevalence of non–IgE-mediated food allergy, outside of celiac disease, is not well established and is thought to be higher than reports in the literature based on misdiagnosis/ not recognized symptoms.[4,24] Descriptions of the table "uncommon" and "common" are based on verbiage used in current literature. Of note, FPE is the least common of these diagnoses and is thought to be declining in recent decades.[13]

[b] Celiac disease is a common diagnosis in those genetically predisposed and affects 1 in 133 people in the United States.

[c] Special consideration: To produce elevated laboratory assays and tests for evidence of small bowel injury are performed while the patient is on a "normal" gluten-containing diet. Patients on a gluten-free diet (GFD) prior to evaluation may be tested for HLA genes prior to gluten challenges of 3 g gluten/d for 2 to 6 weeks.[23]

[d] FPIES diagnostic criterion:[6] Acute FPIES (meets major and >3 minor criterion with one episode) Major criterion: vomiting 1-4 hours after ingestion of suspected allergen and absence of classic IgE-mediated skin or respiratory symptoms; Minor criterion: 1. A second (or more) episode of repetitive vomiting after eating the same suspect food 2. Repetitive vomiting episode 1-4h after eating a different food 3. Extreme lethargy 4. Marked pallor 5. Need for emergency department visit 6. Need for IV fluid support 7. Diarrhea in 24 hours 8. Hypotension 9. Hypothermia Chronic FPIES: *Severe presentation*: regular ingestion of the food trigger (e.g. formula) results in intermittent or progressive vomiting and diarrhea (occasionally with blood), sometimes with dehydration or metabolic acidosis. *Milder presentation*: lower doses of the problem food lead to intermittent vomiting or diarrhea, usually with poor weight gain/failure to thrive but without dehydration or severe metabolic acidosis.

minimizing the risks associated with elimination diets, for example, impaired grown, negative changes in nutritional biomarkers, and feeding difficulties.[8,11,25,27]

Many non-IgE FA diagnoses happen in early childhood; therefore, the intervention therapy is often complex and involves not only food acceptance and the development of feeding skills by the child, but also the feeding approach by the caregiver. Healthcare team members, such as allergists, gastroenterologist, FA-trained dietitians and mental health specialists, and speech language pathologists who specialize in feeding therapy, as well as primary care pediatricians and physicians, may be considered as part of the multidisciplinary approach.

Non-IgE food allergies include multiple separate distinct diagnoses that often have overlapping signs and symptoms. Working with an experienced healthcare professional can support the nuanced diagnosis and management of each disease.

Each of these non-IgE FA diagnoses involves the gastrointestinal tract and may have overlapping signs and symptoms. Figure 1 shows the body systems impacted by the different diagnosis. Non-IgE FA diagnosis is obtained through a detailed clinical history,which will elucidatewhich diagnosismay be considered andwhich allergensmay be suspected. Elimination dietswill further clarify allergen triggers. Once the allergen(s) has been identified, management of these diagnoses is elimination; however, the length of time before a reintroduction challenge varies with each diagnosis. Celiac disease is also the only diagnosis that will require immediate lifelong allergen elimination, although a small percentage of FPIES diagnosis will carry on through adulthood.[14] The prognosis for most non-IgE FA allergies is resolution at varying points in childhood.

CONCLUSION

Food allergy is an immune response that may be either an IgE-mediated immediate reaction, a non–IgE-mediated delayed reaction, or a combination of both. Non–IgE-mediated FA is a reproducible allergic immune response that does not involve the IgE-mediated FA-specific cascade of reactions that may potentially elicit anaphylaxis. Despite the contrast to IgE-mediated food allergies where the threat of anaphylaxis is constantly looming, non–IgE-mediated food allergies can have a significant impact on both physical and mental health.[15] It is particularly challenging to diagnose the specific non–IgE-mediated FA because gastrointestinal symptoms may overlap between multiple different diagnoses. A detailed clinical history and an elimination diet are often the key to diagnosis. Including a plan for reintroduction when the elimination diet is started is a critical part of ensuring that the elimination diet does not cause long-term nutritional concerns.

Celiac disease is the one exception where there are tests that can confirm the diagnosis; however, it is a lifelong disease and management challenge. There are potential risks when utilizing elimination diets, making it advisable for healthcare professionals to consider patient-specific needs. When applicable, it is ideal to implement shared decision-making as part of the non–IgE-mediated FA management plan. Healthcare professionals who are experienced in FA can best support both patient and family/caregiver needs for those living with non–IgE-mediated FA.

Acknowledgments

The authors express their appreciation to the following subject matter expert, Charlene Kennedy, RDN, of Nutrition Masterclass, who reviewed the manuscript.

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This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 1.5 contact hours. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia, Georgia, West Virginia, New Mexico, South Carolina, and Florida, CE Broker #50-1223. Your certificate is valid in all states.

Payment: The registration fee for this test is $17.95.

Disclosure Statement: The author and planners have disclosed no potential relevant financial relationships or otherwise.