

REVIEW ARTICLE

Non-IgE Mediated Food Allergy

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Abstract: Food allergies, defined as an immune response to food proteins, affect as many as 8% of young children and 2% of adults in western countries, and their prevalence appears to be rising like all allergic diseases. In addition to well-recognized urticaria and anaphylaxis triggered by IgE antibody-mediated immune responses, there is an increasing recognition of cell-mediated disorders, such as eosinophilic esophagitis and food protein-induced enterocolitis. Non-IgE-Mediated gastrointestinal food allergies are a heterogeneous group of food allergies in which there is an immune reaction against food but the primary pathogenesis is not a production of IgE and activation of mast cells and basophils.

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Those diseases tend to affect mainly the gastrointestinal tract and can present as acute (FPIES) or chronic reaction, such as Eosinophilic Esophagitis (EoE), Food Protein-Induced Allergic Proctocolitis (FPIAP). The role of food allergy in Non-EoE gastrointestinal Eosinophilic disorders (Non-EoE EGID) is poorly understood.

In some diseases like EoE, T cell seems to play a major role in initiating the immunological reaction against food, however, in FPIES and FPIAP, the mechanism of sensitization is not clear.

Diagnosis requires food challenges and/or endoscopies in most of the patients, as there are no validated biomarkers that can be used for monitoring or diagnosis of Non-IgE mediated food allergies.

The treatment of Non-IgE food allergy is dependent on diet (FPIES, and EoE) and/or use of drugs (*i.e.* steroids, PPI) in EoE and Non-EoE EGID.

Non-IgE mediated food allergies are being investigated.

Keywords: Food Allergy, IgE, non-IgE.

1. INTRODUCTION

Reactions to foods have been reported for more than two thousand years [1], however, in the last decade, there has been a steady increase in the diagnosis of food allergies (FA) due to an increase in atopic conditions as well as to increase public awareness. Recent estimates suggest that one in the four adults have FA in the western world, however, FA which is diagnosed by testing, such as oral food challenge (OFC) has a much lower prevalence, closer to 8% in young children and less than 4% in adults. It is difficult to estimate FA in the general population because FA is poorly understood and people have adverse reactions to various foods. In the present paper, we will review the definition, prevalence, clinical presentation and management of the emerging

gastrointestinal Non-IgE mediated FA that has different pathogenesis and clinical manifestation compared to the classical FA. The most common Non-IgE mediated FA is present as delayed reactions to foods and can be chronic in nature like Eosinophilic Esophagitis (EoE), Non-EoE Eosinophilic Gastrointestinal Diseases (Non-EoE EGID), Food Protein-Induced Proctocolitis (FPIAP) or acute such as Food Protein-Induced Enterocolitis (FPIES) (Fig. 1).

2. DEFINITION

Adverse food reactions are defined as an abnormal response related to the ingestion of a food. They can be classified as food intolerance or food allergy based on the pathophysiological mechanism of the reaction [2]. Food intolerance are the adverse responses to a food, that are due to the inherent properties of the food (*i.e.* toxic contaminant, pharmacologic active component such as caffeine, alcohol) or abnormal response of the host (*i.e.* lack of enzymes such as lactase in lactose intolerance or metabolic disorders, food aversion due to psychological issues). Food intolerance reactions tend to be dose-dependent and are not consistently re-

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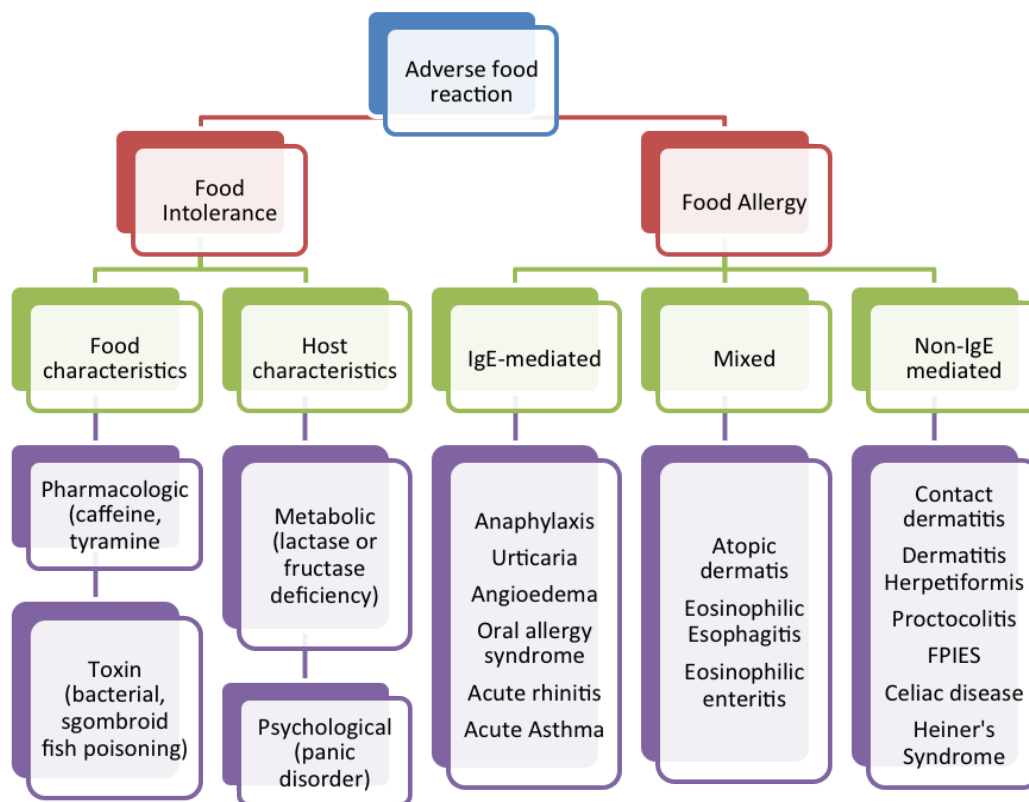


Fig. (1). Classification of adverse reactions to foods. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

produced. The vast majority of food allergic reactions reported by the general population are food intolerances [2].

Food allergic reactions are pathological immunologic responses to food that occurs in a susceptible host. These reactions are reproducible each time the food is ingested². Based on the immunological mechanism involved, food allergies may be further classified in a) IgE-mediated, which are mediated by antibodies belonging to the Immunoglobulin E (IgE) and are the best known and well-characterized food allergy reactions; b) Non-IgE, when the specific IgE to foods are not important and the cell compartment of the immune system is responsible for food allergy; c) mixed IgE cell mediated when both IgE and immune cells are involved in the reaction [1, 3-5].

The most common food allergies in the United States and the western world are the IgE mediated food allergies, which have the highest prevalence in children below 3 years of age (6-8%) [2]. Recent studies report a significant increase in food allergy and food induced-anaphylaxis, with FA being the leading cause of anaphylaxis which is treated in hospital emergency departments in Western Europe and the United States [6, 7]. The most common foods involved in IgE mediated food allergy are milk, egg, peanuts, tree nuts, seafood, soy and wheat. Treatment for IgE mediated food allergies includes avoidance of the allergens, availability of rescue medications such as self-injectable epinephrine and oral immunotherapy. IgE-mediated classic food allergic reactions are immediate, reproducible, and are caused by food-specific IgE, which can readily be detected to confirm the Food allergy diagnosis [2]. IgE binds to IgE high-affinity receptors

(FcεRI) on basophils and mast cells, and upon exposure of the food, the specific food antigen gets recognized by 2 or more specific IgE bound to the FcεRI with consequent crosslink of the receptor and activation of mast-cells to release histamine and other mediators that cause vasodilation and related hives, angioedema, low blood pressure and or smooth muscle constriction with consequent bronchospasm, diarrhea and vomiting [8].

Non-IgE mediated food allergies (Non-IgE-FA) have been increasing worldwide. The most common Non-IgE-FA are Eosinophilic Esophagitis (EoE), Non-EoE eosinophilic gastrointestinal disorders (Non-EoE-EGID), Food protein-induced enterocolitis (FPIES) and Food Protein induced Allergic Proctocolitis (FPIAP). EoE, Non-EoE-EGID, FPIAP are chronic in nature whereas FPIES is an acute disease.

The Non-IgE-FA are immunologic reactions to food and occur in the absence of demonstrable food-specific IgE antibody in the skin or serum, therefore, it can have several different pathogenetic mechanisms [9]. T cells may play a central role in EoE, however, the pathogenesis of FPIES and FPIAP is still less clear [10, 11].

3. EOSINOPHILIC ESOPHAGITIS (EoE)

EoE is a clinical-pathologic disease characterized by symptoms of esophageal dysfunction and eosinophilia affected the esophagus. EoE is as prevalent as Crohn's disease in the US with the most recent estimate at 56.7/100,000 [12, 13]. FA appears to play a role in over 90% of children and

adults with EoE, as an elemental diet is able to induce clinicopathological remission in the majority of patients [14-17].

In younger patients, EoE symptoms consist of a failure to thrive, feeding difficulties, gagging, vomiting, food refusal and appear to be related to inflammatory induced gastroesophageal dysfunction, whereas adolescents and adults develop dysphagia and food impaction due to reversible and irreversible fibrotic changes [10].

Diagnosis is based on esophagoduodenoscopy (EGD) and the finding in at least of 1 biopsy positive of 15 eos/hpf [18-20]. Macroscopically, EGD can be normal or show signs of inflammation or fibrosis, such as Exudates, Rings, Erythema, Furrows, Stricture, which can be graded in the EREFS grading system [21]. Microscopically, besides eosinophilia, ancillary signs are the organization of eosinophils in abscesses, lymphocytosis, hypertrophy of the basilar membrane and fibrosis [22, 23]. The disease leads to the development of patches to with normal areas of mucosa mixed with inflamed ones therefore, at least 3 biopsies should be performed in different parts of the esophagus, (*i.e.* Distal, mid and proximal) even if the esophagus looks normal macroscopically. Indeed, false-negative biopsy rate is reduced when more biopsies are performed [25, 26]. EGD is the only available follow up tool to assess the efficacy of treatment. Serial EGDs are often necessary for proper EoE management because there are no available biomarkers or pathognomonic elements that can replace EGD for clinicopathologic diagnosis and monitoring [27].

The individuals affected by EoE are mostly Caucasian, males and have a high rate of atopic co-morbidities (*i.e.* allergic rhinitis, asthma, IgE mediated food allergy and/or eczema) [28]. Other family members are often affected as genetics play a larger role in EoE compared to other atopic diseases [29]. For example, having a sibling affected by asthma doubles the chance of developing the same disease compared to the general population, but having a sibling affected by EoE increases the chances by about 40 times [30]. Identical twins have almost 800 times higher risk than the general population. It is therefore not surprising that many Single-nucleotide Polymorphisms (SNP) (-TGF- β [31-33], CCL-26 (Eotaxin 3) [34]; Toll-like receptor 3 (TLR3) [35]; thymic stromal lymphopoietin (TSLP) at 5q22, Calpain 14 (CAPN14) on chr2p23.1 and c11orf30/EMSY on chr11q13.5 [36-39] and genetic defects, such as the risk of connective tissue disorders such as Marfan's syndrome, hypermobile Ehlers Danlos' Syndrome [40], autosomal dominant Hyper-IgE Syndrome, AD-HIES) [41]; defects in PTEN, tumor suppressor lipid phosphatase and tensin homolog and a defect in the epithelial protease inhibitor SPINK5 [42, 43]; dehydrogenase E1 and transketolase domain-containing 1 (DHTKD1) in DHTKD1 homolog oxoglutarate dehydrogenase-like (OGDHL) [44].

However, the reason why multiple family members are affected by EoE might be because of common environmental risk factors. Fraternal twins have 5-10 times higher risk of developing EoE compared to siblings and only 40% of identical twins develop the disease suggesting that environmental factors may play a role. This also explains the rapid rise of disease in many western countries. Jensen *et al.* [45] found a positive association between EoE and several early-life fac-

tors such as maternal fever, preterm labor, cesarean delivery, antibiotic and acid suppressant use in infancy. The authors observed an inverse association between having a furry pet in infancy and EoE. The same data have been shown independently by other groups [46, 47]. Environmentrisk gene interaction has been examined in one study and there was an association between breast-feeding and SNP rs6736278 on CAPN14 and NICU admission and SNP rs17815905 on LOC283710/KLF13 [45].

Food allergens, mainly milk and wheat, but also egg, legumes, meats and soy have played a central role in EoE [10], probably by activating Th2 cells [48]. Recent advances in research have shown that a dysfunctional epithelium may play a central role in inducing a local and possibly systemic Th2 response against food and environmental allergens in genetically predisposed individuals [10, 49]. In patients who have active EoE, esophageal biopsy specimens have been consistently found to have greater number of T cells, invariant natural killer cells (iNKTs), basophils and mast cells and increased expression of the Th2 prototypical cytokines such as IL-5, IL-4, and IL-13 [50, 51].

Eosinophils are infiltrating cells in EoE biopsies and are able to secrete some Th2 cytokines, they appear to be the result of an initial Th2 inflammation but they do not initiate inflammation. Anti-IL-5 trials in both adults and children are able to reduce eosinophils from esophageal biopsies of EoE, but it does not reduce symptoms or other inflammatory changes in the tissue [10].

Similarly, despite the high rate of atopic diseases and IgE-mediated FA, some evidence suggests that IgE doesn't play a central role in EoE pathogenesis [52]. Indeed measurement of specific IgE to foods *via* a skin prick test or serum is not useful to establish the real food triggers in EoE [53, 54]. Oral immunotherapy, which is used to induce desensitization in IgE-mediated food allergy, can cause EoE in approximately 2-5% of desensitized patients, indicating a non-IgE mechanism in EoE pathogenesis [55, 56]. Similarly, patients that overcame IgE-FA can develop EoE once food dysmotility reintroduced in the diet [57]. Other evidence such as the ability of mice to develop EoE like disease in the absence of IgE, the lack of efficacy in clinical trials with anti-IgE suggests that IgE are not central in EoE pathogenesis [52, 58]. Another feature common to other atopic chronic diseases such as asthma, AD, and EoE is the remodeling, the by-product of chronic inflammation [10, 59]. Food impaction is due to inflammation-induced dysmotility or reversible or irreversible fibrosis, and it is the most common symptom of EoE in teenagers and adults [60, 61]. In patients who have untreated EoE, the development of strictures is a concern as a longer duration of EoE leads to the development of irreversible fibrotic strictures [60].

In order to prevent long-lasting fibrosis and for the treatment of symptoms, there are three main clinically-accepted treatment strategies for EoE: Proton Pump Inhibitors (PPIs), Dietary elimination and corticosteroid treatment. Esophageal Dilation is an option in patients with irreversible fibrosis [62].

PPIs are now considered the first drug to be used in the management of EoE based on the most recent guidelines [63,

Table 1. 95% predictive values for prick skin test and specific IgE.

Food	Specific IgE (kU/L)	Wheal Size
Egg	7 (>2 yr) [141]	13 mm [142]
Egg	2 (<2 yr) [143]	6 mm [143]
Egg	17.5 (not previous exposed to eggs) [144]	5 mm [144]
Peanut	15 [145]	8 mm [145]
Peanut	15 [141]	8 mm [146]
Milk	32 [141]	12.5 mm [142]
Milk	None found [147]	6 mm [146]
Soy, Wheat	None [141, 147]	

64]. Many practitioners consider PPIs as a first-line therapy in EoE as they are easy to administer and have a very favorable risk-benefit ratio. Patients with EoE responsive to PPIs should be treated indefinitely with PPI as mono-therapy [63]. A therapy with dietary exclusion or steroid should be performed only on those patients whose EoE doesn't respond to PPI [63]. In a meta-analysis of 32 studies on PPI treatment in EoE, 50.5% (95% CI 42.2%-58.7%) patients had histologic improvement (to <15 eosinophils/hpf) with significant differences among different studies [65]. The dosage effective in EoE treatment is on the higher side with most physicians using 1-2 mg/kg in children and 40 mg of omeprazole (or equivalent dosages for other PPIs) once or twice a day. The mechanism of action of PPIs in EoE is not clear. PPIs are well-established inhibitors of gastric parietal H⁺/K⁺-ATPase and this effect may reduce acidic injury to the esophagus and cause epithelial healing. However, PPI show anti-cytokine effects at the level of the esophageal epithelium [66], by directly inhibiting epithelial STAT6, a key transcription factor for the secretion of pro-inflammatory chemokines (*i.e.* Eo-taxon-3) and cytokines (*i.e.* Th2 cytokine) [67] (Table 1).

As in all atopic diseases, steroids, both oral and topical are very effective in inducing EoE remission. Oral steroids can treat the disease clinically and histologically, however, they carry significant side effects if used long term and given the chronicity and life long duration of EoE, they are not recommended for long term treatment [68]. Systemic corticosteroids can, however, be used for emergency cases, such as severe dysphagia, hospitalization, and weight loss [27].

Topical corticosteroids are effective in inducing EoE remission, although steroid resistance (as demonstrated by the lack of histological responsiveness and the failure to modify local esophageal gene expression) has been reported [69]. In Europe, oro-dispersible tablets of 1 mg Budesonide (Jorveza®) are approved for the treatment of EoE in adults. In the US, there are no topical steroids approved for EoE, therefore, steroids used for asthma, such as fluticasone or budesonide are the most common off label prescribed drugs. Patients are instructed to spray fluticasone from a metered dose without a spacer in the back of their mouth and swallow (not inhale) at the dose of 110 mcg X 2 puffs twice daily for children year < 8 years of age and 220 mcg X 2 puffs twice

daily for children year > 8 years of age. No food or drink is allowed 30 minutes after the medication is administered.

Oral viscous budesonide has also been shown to be effective. Children under the age of 10 received 1 mg daily and those who were 10 or over received 2 mg/day. Viscous budesonide is obtained by mixing 1 mg Pulmicort Respule™ (0.5mg or 1 mg budesonide/2 mL intended for nebulized administration) with 10 g (10 packets) of sucralose (Splenda™) to create a volume of approximately 8mL [70, 71]. No food or drink is allowed 30 minutes after the medication is administered.

In a prospective randomized trial [26] in children and adults, the efficacy of Fluticasone by metered-dose inhaler in inducing histological and clinical remission ranges from 50 to 90% as reported by different authors [69, 72-74]. Esophageal Candida overgrowth is a major side effect and is seen in approximately 15% of patients. Randomized control study in children and adults for the use of Oral viscous budesonide indicates 70-80% of responders [70, 71, 75]. A recent randomized trial to compare Fluticasone and viscous Budesonide for EoE treatments showed that viscous budesonide provided a significantly higher level of esophageal exposure to the therapeutic agent, which correlated with lower eosinophil counts [76]. Moreover, there is some evidence that budesonide can reverse esophageal fibrosis [77]. Additional studies have documented their short-term safety, except for local fungal infections [27]. Oral dispersible tablets appear to have similar efficacy to viscous budesonide and are more favorable to patients [78].

Based on such studies, topical corticosteroid therapy can be considered in all children and adults affected by EoE for both initial therapy and maintenance therapy. Currently, there are many unanswered question in topical steroids chronic use. In particular, there is no consensus regarding dosage, formulation, frequency and how to obtain remission using minimal steroid dosage. Long term side effects are an important concern, no study has been conducted regarding bone health in either adults or children for longer than 1 year. Moderate high dose of topical steroids like the one used to treat EoE, is associated with significant reduction in growth in children [79, 80]. Adrenal suppression, for example, has been reported in some children using topical steroids

for EoE, especially if they were using inhaled steroids for asthma and allergic rhinitis at the same time [81].

FA has been shown globally to be the most common trigger of EoE, as numerous studies in both adults and children have demonstrated how dietary restriction therapies have been successfully used for EoE treatment [52-54, 68, 82-86]. Elemental diets using amino-acid based formula as the sole source of nutrition are able to induce clinical and histological remission in the vast majority of patients with EoE [54, 68, 87]. This strategy is associated with a significant reduction in quality of life, tube feeding and it is extremely difficult to adhere to for longterm [88]. As such, single and multi-food elimination diets have been described in multiple clinical trials and observational studies were effective in inducing disease remission in 60-80% of the patients [52-54, 68, 82-86]. Various dietary strategies have been tried with comparable efficacies, with the more restrictive being able to induce a more rapid and frequent remission [88]. Examples of common diet used in EoE management are: 6-food (milk, wheat, egg, soy, peanut/treenut, fish/shellfish), 4-food (milk, wheat, egg, soy) ; to 2-food elimination (milk, wheat) or 1-food (milk) elimination diets with a recent prospective study showing benefit in 2-food elimination (milk, wheat) with step-wise additional restriction if clinically necessary compared to more restrictive approaches [52-54, 68, 82-86]. If more restrictive diets are chosen, once remission is achieved, it is important to do a sequential single food reintroduction followed by EGD in order to identify the trigger to find the least restrictive effective diet as those are more likely to be followed successfully long term [88]. Unfortunately at the moment, the diet is largely empirical as traditional allergy testing measurements of specific IgE to food via skin prick test, serum evaluation and atopy patch test have been shown to be less effective than the empiric method to find EoE food trigger [63, 89]. This is probably due to the fact that the role of IgE in food-induced EoE is minimal, if any [52] and to the lack of standardization of food atopy patch tests [89]. This empiric dietary approach is very undesirable as patients have to wait a long time and undergo multiple endoscopies before finding the allergen trigger [88]. Therefore, the development of allergen testing for food allergens with high specificity and sensitivity for use in EoE is a priority for many researchers working in the field.

Recently, a specific CD154 induction in vitro of peripheral blood T cells to milk in patients with milk induced EoE, suggesting that this test could be used in the future to predict specific FA in patients with EoE, however further prospective study will be needed to confirm the clinical applicability of the test [48].

In the future, more targeted therapy for EoE is going to be available as several novel treatments are under investigation. Antibodies that target only specific aspects of Th2 inflammation, such as anti-IgE and anti-IL5 have been tried with limited success [90-94]. On the other hand, antibodies which were able to block more broadly Th2 inflammation like anti chemoattractant receptor-homologous molecule on Th2 cells (CRTH2) (a prostaglandin D (2) (PGD (2)) receptor) [95], the anti-IL-4 anti-IL-13 (dupilumab) or anti-IL-13 (RPC4046) have been shown to be more promising in small

clinical trials [95-97]. Antibodies targeting Th2 pathway are very desirable as many patients with EoE have a number of atopic disorders including asthma or atopic dermatitis which are amenable to management with these biologic therapies and therefore, it remains important to understand their effects on the disease process in EoE.

4. Non-EoE-EGID

Eosinophilic Gastroenteritis (EGE), Eosinophilic Gastritis (EG), Eosinophilic Colitis (EC) are a group of very rare, ill-defined diseases characterized by eosinophilia limited to the gastrointestinal tract (esophagus, stomach, duodenum, ileus, colon) [98-100]. Differently from EoE, Non-EoE-EGID are rarely responsive to dietary restriction with consistent success only in a minority of cases reported for those diseases limited to the stomach. Therefore, the role of food allergy in such diseases is less clear.

EGE are characterized by the involvement of multiple locations, whereas in EG and EC, eosinophils are found only in the stomach/duodenum or colon. Eosinophilic ileitis exists but they are poorly characterized as biopsies of the ileum are rarely obtained [31, 101].

The diagnosis of Non-EoE-EGID has based primarily on clinic pathological criteria, but the exact number of eosinophils considered pathologic has not been universally established, indeed differently from the esophagus in normal individuals eosinophils are commonly found in the lower gastrointestinal tract [98-100]. In a recent pediatric study, the authors defined as pathological > 50 eos/hpf in stomach or colon, 30/hpf for duodenum and ileum based on the fact that normal levels are between 10 to 50 eos/hpf (with the distal colon and stomach being the organ where the highest level of eosinophils is found in normal individuals and lower levels in duodenum, ileum and proximal colon) with a gradual distribution [102]. The eosinophilic infiltration can be limited to the superficial layer of the GI mucosa (mucosal EGE, EG, EC), they can involve only the serosal epithelium (serosal EGE, EG, EC) or can be deep and involve the muscular layer (mucularis EGE, EG, EC).

The type of inflammation responsible for EGE, EG and EC appears to be similar. It is not clear if EGE, EG and EC are different diseases or a spectrum of the same common pathological process however, they appear to be on a different spectrum than EoE [103]. A recent study, for example, showed that EoE and EG are different diseases as EG is different from EoE and it is appeared to be a systemic disorder associated with high levels of blood and gastrointestinal tract eosinophilia, Th2 immunity, and a conserved gastric transcriptome signature, with only 7% of patients with EG having a transcriptome that overlapped with EoE [103].

In one of the largest published studies on 42 patients, Dellon et al. [104] found that only a minority of patients with EGE responded to treatment (35%; 15/42). Among those who responded about 47% responded to diet, 80% to steroids, and 7% mast cell stabilizer or anti-leukotrienes. In another study [101], 40% of EGE patients had spontaneous remission and the rest responded poorly to any treatment [101]. The value of the diets, both elemental and elimination ones is the object of some debate, and recent meta-analysis

on the use of diet in EGE shows no efficacy in the majority of cases [105].

The oral steroids are the most effective treatment both in the short term and in the long term [101, 104, 106]. The use of the topical steroid budesonide used in capsule has had some sporadic success [101, 104, 106-111]. Patients with suspected predominantly ileal disease can use the budesonide granules in capsules for optimal ileal activity. These capsules controlled release budesonide in the ileum with very minimal gastric delivery [112]. If stomach is affected opening the capsule and drink them intact and after crashing them mixed with liquid can help the diseases. The starting dose for swallowed budesonide is typically 9-27 mg once daily [112]. Case reports show that occasionally PPI and mast cell stabilizers are effective in EGE treatment [101, 104, 106, 113, 114]. However, it is hard to tell as patients can have spontaneous remission and the effects in case reports maybe due to medication or spontaneous remission.

In both pediatric and adult patients with EG diet (both elemental and SFED) have been reported to be more effective [102, 115]. However, diet often is effective after several days and most patients are treated initially with systemic steroids (0.5-1 mg/kg/day 5-14 days), which differently from EGE are very effective in inducing remissions. Once symptoms are controlled, steroids are typically tapered over a few weeks (2-4). Once remission is achieved, long term therapy can be done with diet or with the use of topical or swallowed steroids (Crashed granules from budesonide capsules as above described) [111].

Recently, advances in biologics targeting cytokines and cells responsible for eosinophilic inflammation are being used in clinical trials to treat Non-EoE EGIDs. Antibodies specific Anti-IL-5 (mepolizumab, reslizumab, benralizumab), anti-IL-13 (QAX576, RPC4046), anti-IL-4/IL-13 (Dupilumab), anti-integrin responsible for transmigration of lymphocytes (Vedolizumab), anti Eotaxin 1-2-3 (GW766994), or able to induce apoptosis of Eosinophils such as anti-Siglec-8 (AK002) have been shown to reduce eosinophilic infiltrations and are currently being tried in several non-EoE-EGID cohorts [116].

5. FOOD PROTEIN INDUCED ENTEROCOLITIS (FPIES)

Initially described in the late '70s and early '80s, food protein-induced enterocolitis syndrome (FPIES) [117, 118], FPIES has been increasingly recognized as an important food allergy in infants and young children and the first international consensus guidelines were published in 2017 to improve diagnosis and management of FPIES [119]. Recent limited epidemiological studies show that FPIES is not as rare as previously thought, with an estimated prevalence between 0.34 to 0.7% in infancy [120, 121, 122]. Typically FPIES manifest acutely 1 to 4 hours (usually 2 hours) after food ingestion and is characterized by profuse, repetitive vomiting, lethargy and pallor [119]. A minority of patients (20-50%) will develop diarrhea several hours later [120, 123-128]. Recently, a form of chronic FPIES has been described in young infants due to soy or milk intake. In those infants symptoms manifests as chronic diarrhea, intermittent vomiting, failure to thrive, hypo-albuminemia and anemia. If the

offending food is removed, symptoms improve rapidly within 72 hours, however, upon reintroduction classical FPIES with life threatening reaction ensues [129-132].

The most common food reported as trigger of FPIES are milk, rice followed by soy, oat, egg, poultry [119, 127]. It appears that the most common food allergens in FPIES differ within different geographical regions with milk being the most common foods in US and Israel and rice in Australia [119, 127]. Similarly, soy is a common trigger in the US, but rare in Australia and Israel where soy based formula are less used [119, 127]. However, every food including those rarely considered allergenic (*i.e.* sweet potatoes, squash, banana and avocado) have been described as culprits [119, 127, 133]. Most patients are allergic to only 1-2 foods but multiple food allergies are not rare [119, 127, 133]. Typically, patients outgrow the disease by age 3 [119]. However, long lasting diseases into elementary school age have been described especially among patients with multiple food triggers and those that develop IgE antibodies to FPIES food triggers [119, 134]. The natural history for more rare food triggers is largely unknown.

The pathogenesis of FPIES is still not completely understood. Monocytes and lymphocytes have been shown to have a pan-activation during acute reactions [11]. However, the cell ultimately responsible of antigen recognition and reaction initiation is unknown and therefore no biomarker or in vitro testing are currently available for diagnosis of FPIES or its food allergy trigger [119].

Acute FPIES reactions are treated with the use of IV fluids, ondasetron IV or IM may help to reduce severity based on limited studies. Epinephrine is used only IV in an intensive care setting to support blood pressure in case of prolonged reduced blood pressure irrespective to fluid resuscitation. IV steroids may also be helpful in prolonged reactions associated with diarrhea [119, 135].

The disease is currently treated long with diet, avoiding the known triggers, and its diagnosis is largely empirical based on history and open food challenges in protected clinical setting [119]. Skin prick tests, measurement of specific IgE in the blood and atopy patch tests are unreliable to predict food allergy triggers as IgE specific to food are absent in the vast majority of patients at diagnosis and Atopy patch test have poor sensitivity and specificity [119].

Food challenges are indicated only if history is not consistent with suspected clinical triggers, or to assess the achieved tolerance [119, 135]. Food challenges to trigger foods may be dangerous and result in protracted vomiting and low blood pressure that may need vaso-pressure support, therefore, should be done only in a protected clinical environment and when necessary [136].

6. FOOD PROTEIN-INDUCED ALLERGIC PROCTOCOLITIS (FPIAP)

A form of Food protein Induced Allergic Proctocolitis (FPIAP) is a very common food allergy in infancy. Infants, bottle fed or breast fed, may present with bloody stools in the absence of any other symptoms. Removal of the products causing allergy, typically milk and or soy, from the diet either using hypoallergenic formulas or by restricting the diet

in breastfed babies, induces a rapid remission in a few days [137]. Diets are largely empiric as skin prick test and atopy patch tests are not sensitive or specific in predicting triggers of FPIAP. Oral food challenges following a restricted diet are necessary to establish diet [138, 139]. If left untreated, the major risk of FPIAP is anemia, so severely restricted diet in breastfeeding moms are not indicated. Indeed is extremely rare that foods other than milk and soy are implicated; therefore, if there is not a prompt response to milk elimination at least a month should be waited before further restricting maternal diet [140]. FPIAP is, therefore, very different from chronic FPIES and the 2 forms should not be confused

CONCLUSION

Non-IgE-Mediated gastrointestinal food allergies are a heterogeneous group of food allergies in which there is an immune reaction against food but the primary pathogenesis is not a production of IgE and activation of mast cells and basophils.

Those diseases tend to affect mainly the gastrointestinal tract and can present acutely (FPIES) or as chronic delayed reactions, such as EoE, FPIAP. The role of food allergy in Non-EoE EGID is poorly defined.

In EoE, T cell seems to play a major role in initiating the immunological reaction against food, however, in FPIES and FPIAP, the mechanism of sensitization is less clear.

Diagnosis requires food challenges and or endoscopies in most of the patients. None of the Non-IgE mediated food allergies have validated biomarkers.

Treatment of Non-IgE FA relies on diet (FPIES, and EoE) or the use of steroids and PPI in EoE and Non-EoE EGID

Non-IgE mediated food allergies are an object of intense investigation.

LIST OF ABBREVIATIONS

FA	=	Food Allergies
TH2-T	=	Helper Cells Type 2
FPIES	=	Food Protein-Induced Enterocolitis
FPIAP	=	Food Protein Induced Allergic Proctocolitis
EoE	=	Eosinophilic Esophagitis
EGID	=	Eosinophilic Gastrointestinal Diseases
OFC	=	Oral Food Challenge

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