Published in final edited form as:

Pediatr Clin North Am. 2015 December ; 62(6): 1393–1408. doi:10.1016/j.pcl.2015.07.009.

Diagnosis of Food Allergy

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Synopsis

The prevalence of food allergies has been on the rise over the last two decades. Diagnosing food allergies can be complicated as there are multiple types of food allergies that have distinct clinical and immunologic features. Food allergies are broadly classified into IgE-mediated, non-IgE-mediated or mixed food allergic reactions. This review focuses on the clinical manifestations of the different categories of food allergies and the different tests available to aid the clinician towards an accurate diagnosis.

Keywords

food allergy; IgE-mediated; non-IgE-mediated; skin prick testing; oral food challenge; component testing; elimination diets

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The authors have no relevant conflicts of interest to disclose.

Introduction

The prevalence of food allergies in children and adults has been rising over the last few decades ¹. Food allergies are due to abnormal immunologic responses following ingestion of the offending food. There are multiple food allergy entities that can be characterized based on the immunologic response. For the topic of this review, we will address the diagnosis of food allergies as divided into IgE-mediated reactions, non-IgE-mediated reactions, and mixed allergic reactions (Table 1). The most important diagnostic tool is the clinical history, which is aided by diagnostic testing such as skin and blood tests to assess for food specific IgE. When necessary, the diagnosis is confirmed with oral food challenges and elimination diets to assess for clinical symptoms related to the ingestion of an implicated food.

Diagnosing IgE-Mediated Food Allergies

Clinical History

When the clinician suspects an IgE-mediated food allergy, the medical history and physical examination can provide a good pre-test probability of an IgE-mediated allergy ^{2,3}. It is important to note the dietary history, foods involved at the time of the allergic event, timing of exposure to the onset of symptoms ⁴, route of exposure, nature and duration of symptoms, and treatments received (Table 2). Supplemental factors, such as concomitant medication use or alcohol ingestion may play a role in the reaction severity ⁵. Symptoms during an IgE-mediated allergic reaction can range from mild to severe, involving one or multiple organ systems (Table 3). A history consistent with anaphylaxis, an immediate, severe, allergic reaction involving multiple organ systems, after the ingestion of a food is highly suggestive of an IgE-mediated food allergy. The timing and events during an allergic episode, such as the timing of exercise in food-dependent, exercise induced anaphylaxis (FDEIAN), as well as the type (cooked vs raw) and amount of the suspected offending food ingested, are important parts of the history to elicit and are detailed below. Co-morbid conditions such as asthma, allergic rhinitis or atopic dermatitis might indicate an increased risk of IgE-mediated food allergy ⁶.

It is important to consider and rule out, if necessary, other diseases, triggers, and syndromes that may be mistaken for IgE-mediated food allergies. These may include allergic reactions caused by:

- Medications or insect stings (possibly around the same time of a food ingestion)
- Metabolic disorders: gluten and lactose intolerances and sensitivities
- Toxic reactions: food poisoning caused by toxins, such as histamine in scombroid poisoning
- Chemical exposures, such as chlorine or fragrant perfumes, which may cause rhinitis, skin irritation, or exacerbation of asthma
- Viral syndromes: may cause rhinorrhea and/or urticaria
- Reactions/sensitivities to food additives like sulfites, nitrites, and/or monosodium glutamate ².

- Most cases of new-onset urticaria in children are infectious in origin not involving IgE-mediated mechanisms. In addition, most cases of chronic idiopathic urticaria are related to physical factors (cold, pressure, sun exposure, etc.) rather than food ingestion ⁷.

Food Dependent Exercise Induced Anaphylaxis (FDEIAN)

FDEIAN is a disorder in which allergic symptoms occur if exercise takes place within several hours after consumption of the causative food allergen, as identified by clinical history and allergy testing ^{2,8,9}. Omega-5 gliadin, a protein component of gluten, is a major protein involved in wheat allergy causing exercise-induced anaphylaxis, although other foods have also been implicated, including egg, nuts, crustaceans, meats, fruits, and vegetables ^{10,11}. The diagnosis of FDEIAN can be made when a patient has signs and symptoms consistent with recurrent anaphylaxis upon or soon after physical exertion, and if the food allergen was consumed within two to four hours prior to the allergic event. There should also be an absence of symptoms during vigorous physical activities or food allergen ingestion alone ^{2,8,9}. The patient should demonstrate evidence of sensitization to the food allergen by skin prick or *in vitro* (specific IgE) testing ^{8,10,11}. When no allergen is found, repeating testing in six to twelve months may increase the sensitivity of identifying the culprit food allergen ¹².

Oral Allergy Syndrome (OAS)

Almost all patients with pollen-food allergy syndrome, more commonly known as OAS, have underlying allergic rhinoconjunctivitis due to respiratory sensitization to airborne pollens. OAS results from IgE sensitization to aeroallergens and cross-reactive antibodies recognizing homologous epitopes in fruits (ie, Pru p 1 in peach), vegetables (ie, Api g 1 in celery), or other plant-derived, heat-labile food proteins (ie, Ara h 8 in peanut) ^{13–16}. A local IgE-mediated response leads to an immediate sensation of oropharyngeal pruritus after food contact or ingestion, which is sometimes accompanied by angioedema of the oral mucosa and abdominal discomfort ^{13,14}. Cooking or factory processing of the food can denature the conformational integrity of the culprit proteins, resulting in significant reductions in IgE-binding avidity, which generally renders the food harmless when consumed ^{14–16}. More severe symptoms such as vomiting, diarrhea, and anaphylaxis rarely develop, and thus would be less consistent with OAS but rather more concerning for systemic reactions associated with heat-stable proteins ¹⁷.

Skin Prick Tests and Serum Tests

Diagnostic testing in suspected IgE-mediated food allergy should be guided by the clinical history. A positive skin prick test (SPT) or positive specific IgE denotes sensitization and not necessarily clinically relevant allergy. Careful patient selection for testing is advised due to the potential for false positive results, possibly resulting in unnecessary dietary restrictions. In general, the larger the SPT or specific IgE (sIgE), the more likely that the allergen is clinically relevant, though these tests are less correlative to the severity of reactions ¹⁸. Although SPTs have varying positive predictive values (PPVs), they generally have a relatively high negative predictive value (NPV). Threshold values for SPTs and sIgE have

been identified for some allergens to define the 95% positive predictive value at which patients are likely to react to a food challenge^{19,20} (Tables 4).

Skin and *in vitro* testing with commercially available, heat-labile, and easily degradable fruit and vegetable extracts often leads to false negative results. However, the prick-prick skin test, where the fruit or vegetable is pricked and then the patient's skin is pricked, is a reliable method for confirming OAS, described in the previous section^{21,22}.

The ratio of sIgE to total IgE has also been examined. Some have found that it does not add additional value compared to sIgE alone²³, while others have found that the ratio was higher for those who failed their food challenge compared to those who passed. This is particularly true for allergens that are less likely to be outgrown: peanuts, shellfish, tree nuts, and seeds²⁴.

Component resolved diagnosis (CRD) is now more widely available to investigate IgE against smaller, relevant peptides of the larger parent protein. This allows for distinction between peptides that are similar to pollens and may be heat-labile^{3,25}. Proteins that are degraded by digestion or heat are less likely to cause systemic reactions and are often implicated in OAS. In addition, non-specific lipid transfer proteins have been implicated in allergic reactions associated with supplemental factors^{11,26,27}. Using components may aid in understanding which patients might tolerate baked egg or milk food challenges^{28–30}. Some clinical pearls using component testing are listed in Table 5. It is important to note that severe reactions can still occur despite negative component testing results because all relevant peptides have not been identified.

Oral Food Challenge

The gold standard of diagnosing an IgE-mediated food allergy is the double-blind, placebo-controlled food challenge (DBPCFC). If this is not feasible or realistic, open challenges or single-blind challenges, where a placebo dose is introduced into the succession of true allergen doses, may be considered. The challenge is typically done in the office of a specialist that is well trained in treating allergic reactions and consists of ingesting multiple doses of a food, spaced out over time, to minimize the risk of severe reactions. Patients are then observed for clinical reactions, with medications to treat allergic reactions readily available in the clinic. OFCs are necessary due to the poor sensitivity and specificity of SPT and sIgE tests; 89% of children diagnosed with food allergy based on sIgEs were able to reintroduce foods into their diet following a challenge³¹.

Diagnosing Mixed IgE and Non-IgE Food Reactions

Some food allergy disorders can have both IgE-mediated and cellular-mediated pathologies (delayed Th2 responses). Mixed disorders typically manifest in the gastrointestinal (GI) tract and the skin. The relationship between food allergies and atopic dermatitis has been reviewed comprehensively elsewhere^{32–37}. This review will address mixed food allergic GI disorders. Eosinophilic gastrointestinal disorders (EGIDs) are a group of inflammatory disorders that are primarily classified by the presence of a high density of infiltrating eosinophils within the GI mucosal epithelium, muscularis and/or serosal layers. EGIDs

include eosinophilic esophagitis (EoE), eosinophilic gastroenteritis (EG), and eosinophilic colitis (EC) ³⁸. EoE is one of the most studied of the EGIDs, while less is known about EC due to its rare occurrence. Healthy esophageal tissue is normally free of eosinophils and the rest of the GI tract contains a low density of these cells ³⁹. Characteristic findings for the EGIDs are outlined in Table 6 ^{22,37–45}.

Clinical History

Eosinophilic infiltration of the GI tract can be induced by drug hypersensitivities, parasitic infections, *Helicobacter pylori* infections, and cancer, and it is important to rule out these conditions ³⁹. Additionally, gastroesophageal reflux disease (GERD) and inflammatory bowel disease (IBD) can present with symptoms similar to EGIDs ⁴⁶. Individuals who have unexplained dysphagia and/or food impaction, a history of atopy, peripheral eosinophilia, and a family history of EGIDs should be considered for EGID. The most characteristic symptoms seen in EoE in children is failure to thrive and malnutrition ⁴⁵, while adults present with dysphagia, food impaction, and heartburn ^{22,42}. The prevalence of EoE is approximately 50 out of 100,000 inhabitants in select regions of the US and Europe, and the condition appears to be more common in males than females at a 3:1 ratio ⁴¹. Several studies show that at least half of both children and adult populations with EoE and EG often suffer from other atopic conditions ^{38,42,44–49}. In one study, more than 40% of 381 children with EoE had first-degree family members with atopic or food allergies ⁵⁰.

Serum Testing

The pathogenesis of these diseases is not well understood, but epidemiologic and clinical features suggest allergic components ^{40,44}. IgE-mediated food sensitizations and elevated total and food-specific IgE's are common among patients with EoE, though they are often not correlative with the culprit food ⁴⁷. A cross-sectional study of 53 children with EoE showed that 80% had IgE sensitization to multiple food and aeroallergens, and 32% had elevated total IgE levels ⁵¹. Younger EoE patients had more sensitizations to foods, while older patients had more sensitizations to aeroallergens. In another study, 62% of 107 patients with EGIDs (EoE or EG) had sensitizations to an average of 10.5 food allergens ⁴⁴. However, food sensitizations detected by skin prick tests (SPT) and atopy patch tests (APT) generally do not correlate with clinical episodes of EoE ⁵². This is an indication that food sensitizations and elevations in IgE levels detected by conventional tests may not necessarily be able to link those foods to the EGID pathophysiology.

Endoscopic Evaluation

Along with gross endoscopic observation, histological studies of GI biopsies are an integral part of the diagnostic process. Four to five biopsies should be taken from each site, including normal and grossly abnormal appearing mucosa, as either can demonstrate eosinophilic inflammation ⁵³. Classic endoscopic and histological findings are represented in Table 6. In the case of eosinophilic esophageal findings, one must rule out GERD (a common finding includes eosinophils in the middle and distal portions of the esophagus). A trial of proton pump inhibitor (PPI) is given for six to eight weeks. EoE is considered if eosinophils remain in the middle esophagus, which is distinguished from PPI responsive EoE (PPI-REE) if eosinophils remit from the mid-esophagus. It is unclear if PPI-REE is a distinct disease from

EoE⁵⁴. Oftentimes, repeat endoscopies are necessary to assess the effectiveness of appropriate management of EoE, whether a patient is treated with topical steroids or elimination diets.

Elimination Diets

Food elimination diets have been highly effective at reversing the clinical severity of all types of EGIDs, and are thus a part of the diagnostic algorithm. A meta-analysis and systemic review of numerous studies published between 1995 and 2013 compared the efficacy of the various elimination diets in both pediatric and adult EoE patient populations⁴⁹. The majority of studies removed specific foods from the diet for a minimum of six weeks, followed by clinical, endoscopic, and histological analyses. Efficacy of the diets was defined as histological remission, denoted by a peak eosinophil count of <15 eosinophils/HPF⁴⁹. The summary findings of the elimination diets from this meta-analysis are depicted in Table 7.

The sum of these studies found that cow's milk, wheat, eggs and soy/legumes are the most common trigger foods in EoE patients^{49,55–58}. Remarkably, the elemental and milk elimination diets were capable of reducing eosinophil counts to <1 eosinophils/HPF^{48,59,60}. Similar rates of remission with elemental formulas were also observed in EG patients, while studies on elimination diets in this EGID are limited^{45,61}.

Food Challenges

Once an elimination diet has been instituted, foods are re-introduced, typically one at a time over six week intervals. Symptoms are then reviewed and endoscopy with biopsies are repeated to ascertain if histological remission persists. The gradual re-introduction of excluded foods into the diet was met with high failure rates^{50,62}. In one study with 22 adults, only 9% of patients who had remission on the Four Food Group Elimination Diet were able to add all food groups back without return of EoE⁵⁵. However, most patients only had one or two problem food groups. The post-diet remission rates were comparable in both adult and pediatric populations; however, the allergy test-directed diet appeared to be more successful in children. While these short-term elimination diets do not resolve the condition permanently, the food challenges act as a valuable tool in identifying problem foods to avoid long-term in individuals with food-related EGIDs and provide a means for symptom management. However, elimination diets may pose social, psychological and nutritional repercussions in the long-term. Alternatives to management of EGIDs include corticosteroids, both topical and systemic, leukotriene receptor antagonists, and anti-IL-5 monoclonal antibodies⁶³. Despite their effectiveness, these methods may come with serious repercussions due to their unnatural modulation of the immune system. Further investigations should focus on developing clinically-relevant and standardized methods for diagnosing these complex disorders.

Diagnosing Non-IgE-Mediated Adverse Food Reactions

A number of adverse reactions to foods in children are the result of non-IgE-mediated immunologic reactions to food proteins. By definition, the pathogenesis of these diseases

does not involve the production of food-specific IgE, and therefore their clinical presentation differs from IgE-mediated and mixed adverse food reactions. Similarly, testing strategies that involve the identification of food-specific IgE are not useful. Diagnosis often requires the demonstration of clinical improvement following the withdrawal of the implicated food and, occasionally, a recurrence of symptoms with a subsequent oral food challenge. There are many non-IgE-mediated diseases that can affect a variety of different tissues, including the gastrointestinal tract (food protein-induced allergic proctitis (FPIAP), food protein-induced enteropathy (FPE), food protein-induced enterocolitis (FPIES), celiac disease), the skin (systemic contact dermatitis), and the lungs (Heiner syndrome) ⁶⁴. Further discussion of celiac disease and extragastrointestinal adverse reactions to foods are beyond the scope of this review, but have been discussed extensively elsewhere ^{65–67}.

FPIAP, FPE, and FPIES are a spectrum of diseases can affect the entire gastrointestinal tract. They are thought to be the result of a T cell-mediated immunologic response to specific food proteins and are differentiated by the specific region of the gastrointestinal tract affected ^{68,69}.

Food Protein-Induced Allergic Proctitis (FPIAP)

FPIAP is the least severe, non-IgE-mediated disease and is a common cause of isolated rectal bleeding in otherwise healthy infants ⁷⁰. Pathogenic inflammation is primarily limited to the rectum, but rarely, it can extend further up the sigmoid colon ⁷¹. Although FPIAP has been rarely described in older children ⁷⁰, it is more commonly found in breastfed infants and typically starts within the first few months of life ^{72–74}. Infants classically present with a history of stools streaked with bright red blood and mucous. Although stools may be more frequent, frank diarrhea is uncommon, and infants otherwise appear healthy. The most common causes in breastfeeding infants are milk, soy, and egg from the maternal diet, and most patients will have symptom resolution within 72hrs of strict food elimination ⁷⁴. Typically, cow's milk should be strictly eliminated first, followed by soy and then egg if symptoms do not completely resolve within two weeks ⁷². Formula-fed infants and breastfed infants that do not respond to elimination diets should be placed on an extensively hydrolyzed or amino acid-based formula due to a high rate of sensitization to both cow's milk and soy proteins ⁷⁵.

The diagnosis of FPIAP is made based on clinical history and resolution of symptoms following food elimination; skin testing and other *in vitro* tests assessing for food-specific IgE are not recommended ^{2,64}. It may be necessary to perform a more extensive evaluation in children who continue to have symptoms despite food elimination. Colonoscopy in FPIAP generally demonstrates features of mild colitis, patchy erythema, and a loss of vascularity, and biopsies are notable for high numbers of eosinophilia in the lamina propria and muscularis mucosa ^{76–78}. After symptom resolution, home diet reintroduction is generally recommended after six to nine months of age since most children have been shown to tolerate the implicated food after this time. Some studies have even demonstrated that up to 20% of breastfed infants had spontaneous resolution of symptoms without changes in the maternal diet ⁷⁹.

Food Protein-Induced Enteropathy (FPE)

In contrast to FPIAP, FPE involves the small bowel and typically presents in the first nine months of life with protracted diarrhea that can lead to failure to thrive (FTT) in over 50% of infants^{80,81}. In many infants, symptoms usually have a gradual onset within a few weeks of introduction of the implicated food. Although the most common causal food of FPE is cow's milk, other foods such as soy, egg, rice, poultry, fish, and shellfish have been described^{81–83}. FPE can also occur after acute episodes of infectious gastroenteritis^{84,85}.

The diagnosis of FPE is made upon the presence of clinical symptoms often with confirmation by endoscopy and biopsies. Histological findings include mucosal changes in the proximal and distal small bowel with villous atrophy and cellular infiltration⁸⁰. As in other non-IgE-mediated diseases, skin testing and *in vitro* assessments for food-specific IgE are not recommended. Once a diagnosis is established, elimination of the implicated food generally leads to resolution of symptoms within one to three weeks, with severe cases sometimes requiring partial parenteral nutrition during the initial recovery period⁸¹. After one to two years, most children with FPE have been shown to tolerate reintroduction of the eliminated food without any clinical symptoms or long-term complications.

Food Protein-Induced Enterocolitis (FPIES)

FPIES is the most severe form of the food protein-induced gastrointestinal diseases, involving the entire gastrointestinal tract. It was originally described as a cause of weight loss and FTT in hospitalized infants that were regularly ingesting cow's milk and soy protein^{86,87}. Complete resolution of symptoms was shown to occur after elimination of these foods, however, upon reintroduction, patients developed profuse, repetitive vomiting one to three hours after ingestion often later associated with diarrhea, lethargy, and occasionally hypotension. Although there is no specific diagnostic test, some laboratory findings associated with an acute-phase FPIES reaction include: leukocytosis with neutrophilia (>3500 cells/mL), thrombocytosis, metabolic acidosis, methemoglobinemia, and fecal leukocytes, eosinophils, and erythrocytes^{88,89}.

Like FPE, FPIES is typically caused by direct consumption of the offending food and reactions in strictly breastfed infants are extremely rare^{90,91}. Although cow's milk and soy continue to be the most common triggers for FPIES, with up to 50% of children reacting to both, solid foods have more recently been reported and include grains (rice, oats, barley), meat (beef, chicken, turkey), eggs, vegetables, fruit, fish, shellfish, and even the probiotic *Saccharomyces boulardii*^{89,92–99}. Generally, the onset of cow's milk and soy FPIES occurs in infants and younger children, whereas solid food FPIES tends to occur in older children and even adults^{98–100}. Children with solid food FPIES are also more likely to react to more than one food^{92,98}. As in FPIAP and FPE, assessing for specific IgE to foods does not have any diagnostic benefit, however, up to 25% of patients with FPIES have been found to have measurable IgE to their causative food and these patients typically have a more protracted course as well as the potential for developing symptoms of IgE-mediated disease^{99,101}.

Diagnosis of FPIES is made on the basis of clinical symptoms, improvement after specific food elimination, and, if necessary, response to a clinician-supervised oral food

challenge^{88,89}. Once a diagnosis has been made, patients should be instructed on elimination of the implicated foods and provided with an emergency treatment plan for acute reactions¹⁰². Potentially cross-reactive foods that have not yet been introduced should also be avoided and introduced only under physician supervision^{102–104}. Although somewhat population-based, resolution of classic FPIES to milk or soy generally occurs by three to five years of age, whereas solid food FPIES tends to resolve at an older age¹⁰⁵. Currently, recommendations are to consider performing a supervised OFC to the causative food every 18 to 24 months in patients without history of a recent reaction¹⁰⁶.

Summary

The mainstay of diagnosing food allergies is the clinical history. The differential diagnosis of food allergy consists of a number of immunological and non-immunological diseases. Utilizing skin tests, blood tests, and food challenges can help narrow the differential and improve our diagnostic accuracy. Oftentimes, obtaining the correct diagnosis involves a multi-disciplinary approach. Improved diagnostic capabilities will transform food allergy diagnosis and management for patients and their care team.

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Key Points

- Food allergies consist of a group of diseases that result from immunologic, adverse reactions to foods
- Clinical history is paramount in the diagnosis of food allergy
- Skin tests and specific IgE can indicate sensitization that may not be clinically relevant
- It is important to recognize and distinguish IgE-mediated reactions, as these can be life threatening and require significant patient education
- Specialists, such as Allergists/Immunologists and Gastroenterologists play an important role in the diagnosis and management of food allergies

Table 1

Different Types of Food Allergies

IgE-mediated Reactions	Mixed Allergic Reactions	Non-IgE-mediated Reactions
Food ingestion reactions within 2 hours of ingestion	Atopic Dermatitis	Food Protein Induced Enteropathy (FPE)
“Alpha Gal” Allergy	Eosinophilic Esophagitis (EoE)	Food Protein Induced Enterocolitis (FPIES)
Oral Allergy Syndrome (OAS)	Eosinophilic Gastritis (EG)	Food Protein Induced Proctitis (FPIAP)
Food Dependent Exercise Induced Anaphylaxis (FDEIA)		Celiac Disease

Table 2**Clinical Pearls of an IgE-Mediated Food Allergy**

Offending Food	Cow's milk, egg, wheat, soy, peanut, tree nut, fish, shellfish (these 8 foods account for 90% of reactions)
Timing of Exposure to Onset of Symptoms	Minutes to hours (usually within the first two hours); however late reactions can occur with normal foods and within three to six hours after ingestion of red meat, such as beef, pork and lamb in "Alpha Gal" Allergy ⁴
Route of Exposure	Oral ingestions tend to have more severe reactions; mild skin reactions occur with cutaneous exposure
Type of Food	Oral pruritus with raw forms of fruits or vegetables, but tolerance of cooked forms, would suggest oral allergy syndrome
Nature of Symptoms	Cutaneous, gastrointestinal, and respiratory symptoms predominate
Duration of Symptoms	Less than one hour to several hours; however, late reactions and biphasic reactions can occur
Treatment of Symptoms	Responsive to antihistamines and/or epinephrine
Dietary History	Foods eaten before and after an allergic episode without reaction are typically not the culprit of an IgE-mediated food allergy (exception is Exercise Induced Anaphylaxis); note avoidance patterns
Supplemental Factors	Alcohol consumption, NSAID use, Exercise, Concurrent Illness

Table 3

Examples of Most Common Symptoms During an IgE-Mediated Allergic Reaction

Cutaneous	Gastrointestinal	Respiratory
Erythema Pruritus Urticaria Morbilliform rash Angioedema Eczematous rash (typical of late reactions)	Nausea Abdominal pain Reflux Vomiting Diarrhea	Nasal Congestion Rhinorrhea Sneezing Hoarseness Laryngeal Edema Cough Chest tightness Dyspnea Wheezing Increased work of breathing

Table 4

Predictive Values of SPT in Positive or Negative Oral Food Challenge Results

>95% Positive Predictive Value in Children		
Food	SPT (mm)	sIgE (kUA/L)
Egg White	7 ¹⁹ or 13 ²⁰	7 (2 in < 2 year old) ¹⁸
Cow's Milk	8 ¹⁹ or 12.5 ²⁰	15 (5 in < 2 year old) ¹⁸
Peanut	8 ¹⁹	14 ¹⁸
Fish	Undetermined	20 ²

Table 5**Component Resolved Diagnostics: Pearls**

Food	Components	Clinical Pearls
Peanut	Heat-stable: Ara h 1, 2, 3	Higher risk of systemic reactions
	Heat-labile: Ara h 8 (Bet v 1 homologue)	Low risk of systemic reactions
Hazelnut	Heat-stable: Cor a 8, 9, 14	Higher risk of systemic reactions
	Heat-labile: Cor a 1 (Bet v 1 homologue)	Low risk of systemic reactions
Wheat	Omega 5 gliadin Tri a 14	Associated with wheat-dependent exercise-induced anaphylaxis
Meat	Galactose a 1, 3 galactose "Alpha Gal"	Delayed anaphylaxis, three to six hours after ingestion of red meat
Peach	Pru p 3	Associated with food-dependent exercise-induced anaphylaxis
	Pru p 1 (Bet v 1 homologue)	Low risk of systemic reactions
Apple	Mal d 3	Higher risk of systemic reactions
	Mal d 1 (Bet v 1 homologue)	Low risk of systemic reactions
Cow's Milk	Caseins: Bos d 8	Casein-specific IgE <0.7 kUA/L is a very favorable prognostic factor for tolerance of baked milk
	Whey proteins: Bos d 4 α -lactalbumin Bos d 5 β -lactoglobulin Bos d 6 serum albumin Lactoferrin	For those exclusively allergic to whey proteins, many tolerate baked milk and yogurt Bos d 6; can also be allergic to beef
Egg White	Heat-stable: Gal d 1 (Ovomucoid)	Higher sIgE levels to ovomucoid associated with persistent egg allergy
	Heat-labile: Gal d 2: ovalbumin Gal d 3: ovotransferrin Gal d 4: lysozyme	Gal d 2: most abundant protein in egg white; heating may reduce allergenicity; lower ovalbumin sIgE/IgG4 ratio is associated with tolerance to heated egg; Gal d 4: might be important in occupational asthma

Table 6**Eosinophilic Gastro-Intestinal Disorders**

Disease	Location affected	Symptoms	Endoscopic Findings	Histology/Labs
Eosinophilic Esophagitis	Esophagus	Adults: Dysphagia, Food impaction ⁴² Children: Irritability, Feeding difficulties, Vomiting, Abdominal Pain, Malnutrition ⁴⁵	Ringed esophagus, Strictures, Linear furrows, Narrow esophagus, Vesicles on mucosal surface	15 Eosinophils per high powered field (eos/hpf) in middle esophagus, Peripheral eosinophilia
Eosinophilic Gastritis	Stomach and duodenum, though can affect esophagus to colon	Abdominal pain, Nausea, Vomiting, Diarrhea, Weight loss, Anemia, Malabsorption, Motility issues (affecting muscle layer), Ascites (serosal layer)	Nodular gastric mucosa, Erythema, Erosions	30 eos/hpf ³⁷ (no consensus), abnormal D-xylose and increased fecal fat (in malabsorption)
Eosinophilic Colitis	Large Intestine	Abdominal pain, bloody stools, diarrhea	Edema, Patchy granularity	Eosinophilic infiltration on biopsy

Table 7

Elimination Diets and Histological Remission

Diet	Histological Remission Rates
Elemental Diet (Hypoallergenic, amino acid formula)	90.8% (in 411 children, 18 adults; 13 studies)
Six Food Group Elimination Diet (milk, egg, wheat, soy, peanuts/tree nuts, fish/shellfish)	72.1% (in 75 children, 112 adults; 7 studies)
Four Food Group Elimination Diet (dairy, wheat, egg, legumes)	53.4% (in 15 children, 13 adults; 2 studies)
Allergy Directed Diet (based on + Skin Prick or Atopy Patch Testing)	45.5% (594 children, 32 adults, 14 studies) 30% (adults alone)
Gluten-Free Diet	58.7% (2 studies)
Milk Elimination Diet	68.2% (3 studies)