Food Allergy: Review, Classification and Diagnosis

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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 westernized 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. New knowledge is being developed on the pathogenesis of both IgE and non-IgE mediated disease. Currently, management of food allergies consists of educating the patient to avoid ingesting the responsible allergen and initiating therapy if ingestion occurs. However, novel strategies are being studied, including sublingual/oral immunotherapy and others with a hope for future.

KEY WORDS
allergen specific IgE, food allergy, food protein induced enterocolitis, non-IgE, peanut hypersensitivity

ABBREVIATIONS
TH2, T helper cells type 2; MHC, major histocompatibility complex; OIT, oral immunotherapy; CLA, cutaneous lymphocyte antigen; PAF, platelet-activating factor; DBPC, double-blinded and placebo controlled.

INTRODUCTION
Approximately 25% of the United States population believes that they have an allergic reaction to foods. However, the actual incidence confirmed by history and challenges suggests a prevalence rate closer to 2-8% in young infants and less than 2% in adults. The most common food allergies in the United States are milk, egg, peanut, soy, wheat, tree nuts, fish and shellfish. The individual food allergy does vary by culture and population. Imamura’s recent survey of 1383 Japanese patients from 878 families in found milk, eggs, wheat, peanuts, and soybeans, followed by sesame and buckwheat were the most common allergies similar to the United States.¹ Bird’s nest allergy is the most common in Singapore.² The type of food allergies can even vary across regions of Northern Europe. In Russia, Estonia, and Lithuania; citrus fruits, chocolate, apple, hazelnut, strawberry, fish, tomato, egg, and milk were most common self-reported allergy. But, in Sweden and Denmark; tree nuts, apple, pear, kiwi, stone fruits, and carrot were the most common self-reported food allergy.³ Reactions to foods are not new and have been described for two thousand years. The ancient Greek physician, Hippocrates, describes a reaction to milk in the 1st century. Anaphylactic reactions to egg and fish have been described as earlier as the 16th and 17th century.⁴

CLASSIFICATION
Adverse food reaction is a broad term representing any abnormal clinical response associated with ingestion of a food and they are further classified as food intolerance or food allergy based on the pathophysiological mechanism of the reaction. Food intolerance refers to an adverse physiologic response to a food and may be due to inherent properties of the food (i.e. toxic contaminant, pharmacologic active component) or to characteristics of the host (i.e. metabolic disorders, idiosyncratic responses, psychological disorder), they may not be reproducible, and they are often dose dependent. It is believed that food intolerance represents the majority of the adverse reactions to food. Food allergy refers to an abnormal immu-
nologic response to a food that occurs in a susceptible host. These reactions are reproducible each time the food is ingested and they are often not dose dependent. 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-characterized food allergy reactions; b) cell-mediated when the cell component of the immune system is responsible of the food allergy and mostly involve the gastrointestinal tract; c) mixed IgE mediated-cell mediated when both IgE and immune cells are involved in the reaction (Fig. 1).

**EPIDEMIOLOGY**

Many studies in the past few decades have shown that although 40%-60% of parents believed their child’s symptoms are related to food consumption, only 4%-8% of children have symptoms reproduced by oral food challenges. The prevalence of food allergy is highest in infants and toddlers (6-8%) and decreases slightly with age, affecting almost 4% of the adults.

Food allergy is the leading cause of anaphylaxis treated in hospital emergency departments in Western Europe and the United States. Food allergy alone in the United States appears to account for approximately 30,000 anaphylactic reactions, 2,000 hospitalizations, and possibly 200 deaths each year. In children, food allergy is the most common cause of anaphylaxis. Children with moderate to severe atopic dermatitis have a higher prevalence of IgE-mediated food allergy, estimated at about 10-30% depending on the severity of atopic dermatitis. Food allergies appear to play a role in over 90% of children with eosinophilic esophagitis.

The most common food allergens in the pediatric population include cow’s milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish, whereas peanuts, tree nuts, fish, and shellfish predominate in adults in the United States (US). The prevalence of sensitization to the specific food allergens varies based on the age and characteristics of the studied population, but studies incorporating diagnostic food challenges currently estimate that the prevalence of cow’s milk allergy in infants is 2.5%, egg hypersensitivity prevalence in young children is 1.6% and peanut allergy is estimated to be between 0.8 and 1.5% in young children in US and England. Most infants with non-IgE mediated cow’s milk allergy “outgrow”
their sensitivity by the third year of life, but about 10-25% of infant with IgE mediated cow’s milk allergy retain their sensitivity and about 50% develop sensitivity to other foods. Most children with egg allergy are also likely to develop egg tolerance by late childhood, with the exception of patients with an egg IgE greater than 50 kU/L, who are unlikely to develop egg tolerance. Peanut, sesame seeds and tree nuts allergies are more persistent with a chance of becoming tolerant is about 20% for peanut and sesame seeds and about 10% for tree nuts. Sensitization to either cow’s milk or egg in infancy are associated with an increased risk of environmental allergy sensitization and asthma. Indeed they appear to be the first steps of the atopic march, that initiates in infancy with food sensitization and atopic dermatitis and continues with environmental allergies and rhinitis and asthma development after 1-2 years of age.

There has been a significant increase in the incidence of food allergies including a rise of Emergency Department visits for food allergic reactions. Moreover peanut allergy prevalence in children in US and England doubled in the last few years in identical telephone surveys. The reasons for the increase in food allergy prevalence are not known, but, the short period of time over which the increase occurred, suggests that environmental factors are more likely to be relevant than genetic factors as part of the hygiene hypothesis. It is likely that additional factors play an important role such as methods of food preparation, increased use of antacids, and exposure to medicinal creams containing food allergens. The introduction of food later in the infant diet has been postulated to play a role in the increase of food allergy.

**PATHOGENESIS**

Food allergy is an immunological reaction against a food allergen and is typically IgE mediated, not-IgE mediated (i.e. cell mediated) or mixed IgE and not-IgE mediated.

IgE-mediated classic food allergic reactions are those that are immediate, reproducible, and readily diagnosed by detection of food-specific IgE. In food allergic individuals the majority of acute allergic reactions to foods are due to the engagement of allergen specific IgE antibody with its high-affinity receptor (FcεRI), that is expressed on mast cells and basophils, and low affinity receptor (FcεRII), which is present on macrophages, monocyte, lymphocytes and platelets. When a specific antigen binds the IgE linked to the FcεRI it determines a receptor cross-linking and consequent release of mediators. Even if initially it was thought that mast cells were the principal effector cells in IgE-mediated acute reaction, further studies have shown that basophils play also a major role in acute food allergy symptoms. Indeed patients with atopic dermatitis and food hypersensitivity have higher rates of spontaneous release of histamine from basophils that normalizes after the offending food has been removed from the diet. Normal serum tryptase levels (a specific marker of mast cell activation) in patients with food-induced anaphylaxis have been reported on occasion suggesting an involvement of histamine release from tryptase negative cells, such as basophils.

The intrinsic properties of the food allergens may contribute to whether the allergen favors allergic immune responses. Indeed relatively few foods (egg, milk, peanut, tree nuts, fish, shellfish, wheat, and soy) account for most of the allergic reactions. Characteristics common to “major” food allergens are that they are water-soluble glycoproteins, are 10 to 70 kD in size, and are relatively stable to heat, acid, and proteases. In addition, the presence of immunostimulatory factors in the food may also contribute to such sensitization. For example, the major glycoprotein allergen from peanuts, Ara h 1 is not only very stable and resistant to heat/digestive enzyme degradation but also acts as a TH2 adjuvant due to the expression of a glycan adduct. However, the biochemical characteristics of a food allergen cannot explain alone its allergenicity, as only a minority of patient exposed to it develop allergy. Indeed the natural consequence of exposure to new foods is tolerance.

Oral tolerance depends on an intact and immunologically active gastrointestinal barrier. This barrier includes the epithelial cells joined by tight junctions and a thick mucus layer, as well as lumenal and brush border enzymes, bile salts, and extremes of pH, which contribute to make antigens less immunogenic. In addition, innate (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells, and toll-like receptors) and adaptive immunity (intraepithelial and lamina propria lymphocytes, Peyers patches, IgA, and cytokines) provide an active barrier to foreign antigens.

As food allergy is more common in infants, higher permeability of the intestinal mucosa in infants and early exposure to allergenic antigens have been proposed as a possible cause of sensitization in infant. However, it has been shown that the gastrointestinal mucosa reaches its maturity in terms of permeability at day 2-3 of life and the increased permeability observed in some children with food allergy is a consequence rather than a cause of the allergic inflammation. In contrast, early exposure to foods might prevent the development of food allergy under some conditions. This is suggested by a recent study that has shown that Israeli children, who frequently consume a popular peanut snack beginning before age 1 year, have a 10-fold lower prevalence of peanut allergy compared with children in the United States and United Kingdom, where rarely peanuts are consumed before age of 12 months. Additional fac-
tors have been proposed as necessary to breach the oral tolerance. A temporary increase of permeability due to a infectious inflammatory process may increase the absorption of allergenic antigens and favor sensitization.\textsuperscript{50} Alternatively sensitization is facilitated, if the gastrointestinal barrier is bypassed by presentation of proteins via alternative routes, such as the respiratory tract or skin. In oral allergy syndrome, also known as pollen-food-related syndrome, oral tolerance is bypassed because sensitization occurs through the respiratory route, due to cross-reactivity between the pollen allergen and allergen contained in fruit (i.e. birch pollen protein Bet \textit{v} 1 and the a homologous apple protein, Mal \textit{d} 1) that usually are well tolerated when ingested due to their instability in presence of digestive enzymes.\textsuperscript{56} Data from murine models demonstrate that epicutaneous application of food proteins may result in very strong allergenic sensitization and TH2 inflammation.\textsuperscript{57} Indirect evidence in human of possible skin sensitization to food allergens is a study, Lack et al.,\textsuperscript{58} where an increased risk of peanut allergy in offspring was found to be related with the use of infant skin creams containing peanut and not to maternal peanut ingestion during pregnancy or lactation.

Oral tolerance may also be breached due a TH2-biasing dysregulation of the active immunological barrier that favors sensitization.\textsuperscript{49-53} Recent epidemiological studies identify potential environmental influences that may promote such dysregulation, including reduced exposures to bacteria and infections (the “hygiene hypothesis”), a rise in consumption of omega-6 and decreased consumption of omega-3 polyunsaturated fatty acids, reduced dietary antioxidants, and excess or deficiency of vitamin D.\textsuperscript{50,59,60} It has been proposed that the TH2-dysregulation is due to an altered equilibrium in the finely regulated relationship between epithelial cells, antigen-presenting cells (dendritic cells), and regulatory T cells, that ultimately determine the type of T cell response that a food allergen elicits. Intestinal epithelial cells may act as nonprofessional antigen-presenting cells for T lymphocytes as they express a class II major histocompatibility complex (MHC), however they lack a “second signal,” essential for T cell expansion after antigen presentation, suggesting their potential role in induction of tolerance to food antigens.\textsuperscript{52} Several regulatory T cells have been found to be important for oral tolerance: Th3 cells, a population of CD4+ cells that secrete transforming growth factor (TGF)-\textit{β}; Tr1 cells, cells that secrete IL-10; CD4+CD25+ regulatory T cells, that express the transcription factor FoxP3; CD8+ suppressor T cells; and gamma-delta T cells. The role for regulatory T cells in food allergy comes from a family with severe food allergy carrying with a FOXP3 mutation.\textsuperscript{61} Furthermore, increased levels of T regulatory cells have been reported to be associated with acquired tolerance to cow’s milk.\textsuperscript{62}

T cell homing to target organs may explain why some food-allergic diseases are localized and not systemic as in the case of food-associated atopic dermatitis or eosinophilic esophagitis. Indeed the CLA (cutaneous lymphocyte antigen) is upregulated in food-responsive T cells only in patients with food-responsive atopic dermatitis.\textsuperscript{63} In eosinophilic esophagitis a gene microarray analysis of esophageal tissue has shown that the mRNA for eotaxin-3 was the most highly upregulated transcript in eosinophilic esophagitis tissue compared to healthy control esophagus and was correlated with tissue eosinophilia.\textsuperscript{64}

The non-IgE mediated food allergies represent the minority of immunologic reactions to food and occur in the absence of demonstrable food-specific IgE antibody in the skin or serum. They are less well characterized, but typically are due to an acute or chronic inflammation in the gastrointestinal tract, where eosinophils and T cells seem to play a major role.\textsuperscript{8,43,44} For patients with food protein-induced enterocolitis, TNF-\textit{α} appears to have an important role. TNF-\textit{α} can be cultured \textit{in vitro} from peripheral blood monocytes in infants with food-protein-induced enterocolitis syndrome.\textsuperscript{65} Chung and colleagues also found increased staining for TNF-\textit{α} in duodenal biopsies of infants with food-protein-induced enterocolitis syndrome.\textsuperscript{66} For eosinophilic esophagitis, eosinophils and their growth and chemotactic factors play a key role. Eotaxin-3 is upregulated 50X in the esophageal tissue compared to controls with chronic eosinophilic esophagitis.\textsuperscript{64} Also, IL-13 and IL-5 play a key role in the pathogenesis in murine models\textsuperscript{67} and increased VCAM-1, TGF-\textit{β} in the tissue samples leading to increased tissue fibrosis.\textsuperscript{68}

Finally food allergy is at least in part genetically determined. Peanut allergy, for example, is about tenfold more likely to occur in a child with a sibling who is peanut allergic compared to the general population risk; however, specific genes have not been identified.\textsuperscript{69} Similar for non-IgE-mediated food allergies, there is a large familial and ethnic difference with a predominance of Caucasian males with the disorder.\textsuperscript{70-72}

**DIAGNOSIS**

The patient’s history can be a powerful tool, especially if the patient and family are objective historians. But the family’s own perceptions and knowledge often influence history. Food allergy is clearly suspected more often than it is found by accurate diagnostic procedures and is confirmed by challenges in less than 20\% of the time. In general, the history can be more helpful in IgE-mediated disorders, because these reactions occur so soon after food ingestion and because multiple target organs are affected. History is harder for food-protein induced enterocolitis, where symptoms occur hours later or days later in eosinophilic esophagitis.
Thus a systematic review of the patient’s diet is a highly useful first step. Important historical considerations include the following: 1.) Is the reaction reproducible? Does it occur each time the food is ingested? If not, it is an unlikely trigger. 2.) What is the time frame for the reaction? Immediate hypersensitivity reactions generally occur rapidly, often within minutes and virtually always within 2½ hours.73 Mixed and T-cell mediated reactions have a characteristically delayed onset. Therefore patients with FPIEC typically begin to have symptoms later than 1 ½ hours after ingestion. Additional clinical history elements can be helpful. Timing of the first and last occurrences can reveal whether sensitivity is increasing or waning. These considerations together with the quantity necessary to trigger a reaction are helpful for planning diagnostic challenge procedures as well. Occasionally, the history can be complicated by the fact that trace amounts of foods may occur in certain products.

LABORATORY STUDIES
Immediate hypersensitivity skin tests (prick skin tests) examine for the presence of food protein specific IgE. In general, skin tests have positive predictive accuracies of about 50%; but their negative predictive values are in excess of 95%.74 The larger the size of wheal on skin test, the more likely a patient will react to the food74-76 (Table 1). The size of the wheal or flare on skin test unfortunately does not predict the severity of the reaction. Furthermore, the age of the patient, previous exposure/reactions to the food and the type of food changes the predictive value for a wheal size. In general, the younger the age, the smaller the skin test needs to be positive predictive value; a negative skin test for IgE-mediated problems is very helpful as false negative reactions are rare.

An alternative method to detect food protein specific IgE is by in vitro methods, (FEIA-CAP or “RAST test”). Some investigators may prefer to use in vitro testing when there is persistent dermatographism (rare), severe eczema, or when families are reluctant either to discontinue H1 blockers. Similar to prick skin tests, a “cut-off” value can be developed for predicting 95%77,78 or even 50% predictive values79 on food challenges (Table 1). However, similar to prick skin test, the predictive values changes for the food, age of the patient or the history of previous reaction. Predictive values can only be developed for milk, egg, peanut, tree nuts, sesame seed and fish. 95% predictive values can not be developed for soy and wheat. The younger patients have a lower “cut-off” value for 95% predictive value, while no previous exposure to the food or clear history has a higher predictive value (Table 1).

For non-IgE-mediated disorders, fewer laboratory diagnostic tools exist. Atopy patch test have been used for eosinophilic esophagitis, food protein induced enterocolitis and atopic dermatitis.80-84 Compared to prick skin test, atopy patch test is more specific, but less sensitive.81,85-87 The negative predictive value is close to 90% except for milk, where it is close to 60%. Therefore, atopy patch test can be provide guidance but not absolute for dietary advice for non-IgE mediated food allergy. Eosinophils in the blood or stool may point to an ongoing enteropathy, but these findings are certainly nonspecific. Serum levels of allergen-specific IgG are not helpful. Endoscopy followed by examination of biopsy specimens are the most important tools in non-IgE-mediated disorders and critical for the diagnosis of eosinophilic esophagitis. Challenges are needed to identify specific food triggers in all cases.

There are no tests that indicate the severity or what patients are at high risk for severe allergic reaction or anaphylaxis.73 However, recent work by Vadas and colleagues examining patients with experienced fatal and nonfatal peanut-induced anaphylaxis compared to normal controls, patients with food allergy and patients with mild peanut reactions. The patients with peanut anaphylaxis had elevated platelet-activating factor (PAF) and decreased PAF acetylhydrolase suggesting failure of PAF acetylhydrolase to inactivate PAF contributes to anaphylaxis.88

**Table 1** 95% Predictive values for prick skin test and specific IgE

<table>
<thead>
<tr>
<th>Food</th>
<th>Specific IgE (kU/L)</th>
<th>Wheal Size</th>
</tr>
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<tbody>
<tr>
<td>Egg</td>
<td>7 (&gt;2 yr) (78)</td>
<td>13 mm (108)</td>
</tr>
<tr>
<td>Egg</td>
<td>2 (&lt;2 yr) (109)</td>
<td>6 mm (109)</td>
</tr>
<tr>
<td>Egg</td>
<td>17.5 (not previous exposed to eggs) (110)</td>
<td>5 mm (110)</td>
</tr>
<tr>
<td>Peanut</td>
<td>15 (111)</td>
<td>8 mm (111)</td>
</tr>
<tr>
<td>Peanut</td>
<td>15 (78)</td>
<td>8 mm (112)</td>
</tr>
<tr>
<td>Milk</td>
<td>32 (78)</td>
<td>12.5 mm (108)</td>
</tr>
<tr>
<td>Milk</td>
<td>None found (77)</td>
<td>6 mm (112)</td>
</tr>
<tr>
<td>Soy, Wheat</td>
<td>None (77, 78)</td>
<td></td>
</tr>
</tbody>
</table>

ORAL FOOD CHALLENGES
Often an elimination diet provides diagnostic information as well as symptomatic relief. If not, it is possible that not all responsible foods have been eliminated.
FUTURE THERAPIES

One alternative approach to prevent food allergies was to delay the introduction, promote breast feeding or remove the allergen from the mother’s diet during pregnancy. Overall, these therapeutic options have not been successful. In fact, the recent study by Lack and colleagues suggest that the delayed introduction of peanut in the England can account for the increased food allergy compared to “genetically” matched control group in Israel with 10 fold peanut allergy. The natural history of peanut allergy is well documented. In contrast, no sign of anaphylactic reactions was observed.

CHINESE HERBAL THERAPIES

Recent work by Li has suggested the unique combination of herbs Zhi Fu Zi (Radix Lateralis Aconiti Car- michaeli Praeparata) and Xi Xin (Herba Asari), could also help with the induction of tolerance. These herbs have been successful in murine models of peanut allergy and anaphylaxis. All placebo-treated mice developed severe anaphylactic signs, increased plasma histamine levels, and marked vascular leakage. In contrast, no sign of anaphylactic reactions was observed.

FOOD ALLERGY THERAPY

The only proven therapy is food elimination. However, many families find it is difficult to read labels as many foods have multiple ways to call an ingredient (for example, casein, whey and lactoalbumin for milk). Therefore, governments enacted labeling laws. For example, in Japan, labeling of food for common allergies by Ministry of Health, Labour and Welfare (2001) mandate labeling for 5 food (milk, egg, peanut, wheat and buckwheat) with Ministerial Ordinance No.23 of 2001 and recommended labeling for 19 more foods (abalone, squid, salmon roe, shrimp/prawn, orange, crab, kiwifruit, beef, tree nuts, salmon, mackerel, soybeans, chicken, pork, Matsu-take mushrooms, peaches, yams, apples and gelatin). The United States enacted FALPCA in 2005 to help with reading labels to prevent accidental exposure to foods for 8 most common food allergens (milk, egg, peanuts, tree nuts, fish, shellfish, soy, and wheat). All patients at risk for anaphylaxis must be trained to identify early symptoms and be prepared to treat appropriately. Auto-injectable epinephrine is essential together with education to help identify avoidable risks.
observed in actively-treated mice.\textsuperscript{101,102} But, this therapy has not been tried in any clinical trials in humans. Other potential therapies including anti-IgE antibodies, cytokine/anticytokine therapies, and novel immunotherapies utilizing engineered proteins.\textsuperscript{103} For example, development of non-allergic protein can prevent binding to IgE and anaphylaxis, but allow binding to T cells and induce tolerance. Hypoallergenic proteins have been made for peanut,\textsuperscript{104} fish,\textsuperscript{105} and others. This model has been successful in a murine peanut model with decreased anaphylaxis.\textsuperscript{106} Advances in the understanding of anaphylaxis may also lead to new therapies for food allergy. The finding by Vadas and colleagues of elevated PAF levels in patients with peanut anaphylaxis suggesting the importance of the PAF pathway.\textsuperscript{88} They continued their work and have now found that blockade of PAF pathway can also prevent anaphylaxis in a murine model.\textsuperscript{107}

**CONCLUSION**

Food allergies are a common pediatric condition affecting 4-6% of the US population. Food allergies are continuing to rise similar to other food allergies, but the exact cause for the rise is unknown. Increased understanding for the pathogenesis of both IgE and non-IgE mediated reactions have been done with the use of new techniques and murine models. These advances are creating the opportunities for novel therapies for food allergy. However, at the current time, the only treatment is avoidance.

**REFERENCES**


35. Nickel R, Kulig M, Forster J et al. Sensitization to hen’s egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997;99:613-7.


of peanut allergen Ara h 3: effects on IgE binding and T cell stimulation. *Int Arch Allergy Immunol* 2002;128:15-23.


