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DEPARTMENT OF INTERNAL MEDICINE
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FOOD ALLERGY: Current Recommendations & Future Therapeutics

J. Andrew Bird, M.D.
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This is to acknowledge that J. Andrew Bird, M.D. has disclosed (any) financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Bird will be discussing off-label uses in his presentation.

J. Andrew Bird, M.D.
Assistant Professor of Pediatrics and Internal Medicine
Division of Allergy and Immunology

Drew joined the faculty at UT Southwestern in 2009. He is a Dedman Family Scholar in Clinical Care and the director of the Food Allergy Center at Children's Medical Center. His research interests are in understanding and treating adverse reactions to foods, and he is currently working with colleagues in several ongoing clinical trials using food proteins for immunotherapy.

Overview & Purpose: The term food allergy is often loosely applied to numerous real or perceived reactions following ingestion of food. The purpose of today's discussion is to provide a broader understanding of the appropriate application of this diagnosis and to provide the attendant with a basic knowledge of ongoing research in the field of food allergy.

At the conclusion of the presentation the participant should be able to:

1. Discuss key elements of food allergy diagnosis.
2. Appropriately interpret relevant tests for the diagnosis of food allergy and eosinophilic esophagitis.
3. Appropriately manage a patient with a life-threatening food allergy.
4. Be familiar with ongoing food allergy research efforts.

Introduction

Allergy is a hypersensitivity reaction initiated by specific immunologic mechanisms,[1] and thus when the term is applied to a hypersensitivity reaction to a food, implies involvement of the immune system in response to a food in producing the physical response. This definition is descriptive of a number of food-related diseases ranging from non-IgE mediated diseases such as celiac disease to IgE-mediated reactions to foods resulting in anaphylaxis and includes diseases such as eosinophilic esophagitis (EoE) which involves both IgE and non-IgE mediated mechanisms.

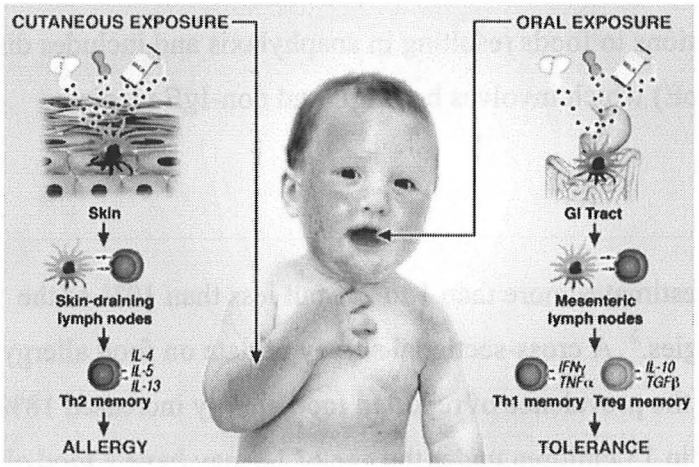
Prevalence

A recent systematic review estimates more than 1 to 2% but less than 10% of the population is affected by food allergies.[2] A cross-sectional survey of data on food allergy among children < 18 years of age revealed the prevalence of reported food allergy increased 18% from 1997 through 2007.[3] As many as 1 in 13 children under the age of 18 may have a food allergy with a significantly higher proportion of children under the age of 5 years affected compared to those from 5 to 17 years.[4] An increasing number of affected children is supported by self-reported surveys examining the incidence of peanut, tree nut and sesame allergy in US children.[5] They report that tree nut allergies have increased from 0.2% in 1997 to 1.1% in 2008 in children less than 18 years, and peanut allergy increased from 0.2% to 1.4% in the same time period.[5]

The underlying causes of the increased prevalence of food allergy are largely unknown.[6] Genetic predisposition in combination with various environmental factors is likely to play a large role. Hypotheses regarding potentially contributing factors include:

1. Timing of exposure to the most allergenic foods (e.g. early introduction of highly allergenic foods vs. avoidance early in life).[6]
2. Changes in dietary composition in the past 3 decades (e.g. decreased consumption of animal fat and an increase in consumption of ω-6 polyunsaturated fatty acids,[7] and both Vitamin D excess[8] and deficiency[9] have been postulated as potential contributors).
3. The hygiene hypothesis[10] has been used to explain an overall increase in allergic disease though literature regarding its role in the development of food allergy in particular is lacking.

4. Environmental food exposure may sensitize an individual, particularly a child with a compromised skin barrier (e.g. atopic dermatitis), bypassing allergen exposure through the oral route and thus preventing the development of oral tolerance.[6] (Figure 1)



Lack G. Epidemiologic risks for food allergy. J Allergy Clin Immunol. 2008;121:1331-6.

Figure 1. Primary exposure to allergen through the skin may lead to the development of a Th2, allergic response; whereas, primary exposure to allergen through the GI tract is more likely to lead to the development of tolerance.

The majority of IgE-mediated reactions secondary to food ingestion are caused by a limited number of foods. Milk, egg and peanut are most common in children, followed by tree nuts as a group, wheat, soy, fish, shellfish, and sesame.[11] The most common food allergens in adults are those that are least likely to be outgrown – shellfish, fish, peanuts and tree nuts (Figure 2).[11]

Previous studies had shown that the majority of children will outgrow milk allergy by 3 years of life,[12,13] and will outgrow egg allergy by early school-age years.[14-16] Traditionally it has been assumed that soy and wheat allergy are outgrown by pre-school age years though few studies had been performed to establish that recommendation.[17] Since 2007, data published from a major food allergy center suggests that food allergies to these foods may actually persist longer than originally believed.

In a series of publications, Dr. Robert Wood's group at Johns Hopkins University reported a later age of tolerance development than had been reported in other published studies. They showed that cow's milk allergy resolved in 64% of their population by 12 years of age,[18] egg allergy resolved in 68% by 16 years of age,[19] wheat allergy resolved in 62% by 10 years of age,[20] and soy was outgrown by approximately 50% by 7 years of age.[21] This data must be

	Children	Adults
Milk	2.2 – 3%	0.3%
Egg	0.8 – 1.5%	0.2%
Peanut	0.6 – 2%	0.6%
Tree nuts	0.4 – 1%	0.6%
Fish	0.2 – 0.5%	0.4%
Shellfish	0.5 – 1.4%	2%
Wheat	0.4%	0.3%
Soy	0.4%	0.3%

Figure 2. Prevalence of the most common food allergens identified in the United States.

interpreted in light of the fact that the population being studied was followed at a major food allergy center, thus children with persistent allergy were more likely to follow-up and were included in the analysis. Data suggests, however, that children may outgrow food allergies to some foods later than previously accepted.

Prevention of Food Allergy

Currently there is no uniformly accepted recommendation for preventing food allergy. Common concerns include the effect of maternal diet during pregnancy and lactation and the timing of solid food introduction into the developing infant's diet. Interventional studies aimed at preventing food allergy are currently ongoing. The leading hypotheses aim towards understanding the importance of the timing of complementary food introduction and its role in the development of food allergy.

In 2000, the American Academy of Pediatrics (AAP), Committee on Nutrition recommended delayed introduction of the most commonly allergenic foods based on few studies showing reduction in food-associated atopic dermatitis, urticaria and gastrointestinal disease by 12 months[22]. Multiple studies since this time have suggested that delayed introduction may contribute to the development of food allergy and evidence has been contradictory regarding a protective effect against development of other allergic diseases. In light of the newer evidence, in 2008 the AAP released a statement that complementary foods may be introduced between 4 and 6 months of age, and during this same time period, potentially allergenic foods may be introduced as well.[23] Interventional studies in high risk populations powered to directly answer the questions regarding the effect of allergenic food introduction on the development of food allergy are underway and have not been completed at this time.

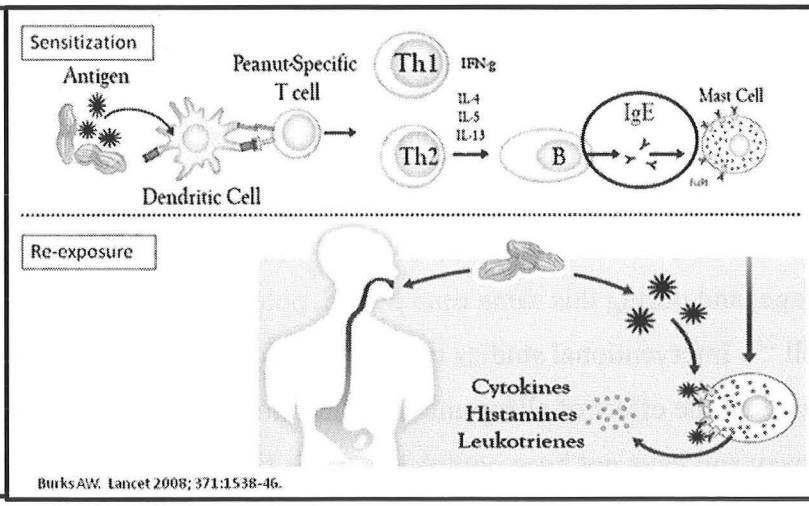
Regarding the role of maternal diet during pregnancy and lactation, sufficient evidence does not exist to suggest that maternal diet during pregnancy or lactation affects the development or clinical course of food allergy. Results from a systematic review of the literature did not suggest that maternal dietary antigen avoidance during pregnancy or lactation had a protective

effect on the incidence of atopic eczema in the first 18 months of life. [24] Restrictive diets during pregnancy or lactation may adversely affect maternal or fetal nutrition and are not recommended.

Pathophysiology of Food Allergy and the Development of Oral Tolerance

In order for an IgE-mediated reaction to occur, an individual must first be sensitized (Figure 3). After ingestion, proteins are absorbed through the gut mucosa, and taken up by specialized epithelial cells called M cells. Antigen presenting cells (APC), such as dendritic cells acquire the protein, and process the protein into peptide fragments. The peptides are then presented on the cell surface by class II MHC molecules. Antigen receptors on naïve helper T cells recognize the peptide. In a non-allergic individual, a Th1 response occurs, characterized by cytokines such as IFN-γ. Th2 cells are activated in an allergic individual releasing interleukins including IL-4, IL-5, and IL-13. B cells are then stimulated to make IgE specific for the particular food to which the person is allergic. IgE binds to the high affinity surface IgE receptor on mast cells and basophils, FcεRI. Upon re-exposure to the allergen, the IgE molecules are cross-linked by the allergen and mast cells and basophils release their inflammatory contents including histamine, cytokines, and leukotrienes, leading to symptoms typically associated with an allergic reaction.

Figure 3. Pathophysiology of an immediate, IgE-mediated, allergic reaction.



Oral tolerance refers to a state of active inhibition of immune responses to an antigen by means of prior exposure through the oral route.[25] Several excellent reviews addressing this subject have been published in the past several years, and the reader is encouraged to read these

reviews for more in-depth discussion of the mechanisms behind the development of oral tolerance.[26-29] Briefly, murine research has shown that oral tolerance may be induced by either high dose or prolonged low-dose exposure to an allergen. With high-dose exposure, tolerance is achieved via T-cell receptor ligation either in the absence of co-stimulatory molecules such as IL-2 or in the absence of interaction between costimulatory receptors on T-cells (CD28) and APCs (CD80 and CD86), leading to anergy.[30] Alternatively, high-dose exposure may also lead to clonal deletion of the effector T-cell via FAS-mediated apoptosis (CD95).[31]

Prolonged low-dose exposure leads to the development of tolerance primarily through the up-regulation of regulatory T-cells (CD4+CD25+), which express the transcription factor forkhead box P3 (FOXP3).[32] FOXP3 is thought to inhibit Th1 and Th2 reponses.[33] Immune responses are also suppressed through soluble or cell-surface associated down-modulatory cytokines such as TGF-β, IL-10, and IL-4. These antigen-specific regulatory cells migrate to lymphoid organs and inhibit the generation of effector T-cells, thus suppressing the immune response. They also migrate to target organs, suppressing disease by releasing antigen non-specific cytokines.[26]

Recently, attention has turned to the influence of TGF-β in maternal breast milk, and its influence on the development of tolerance.[34] TGF-β acts to regulate Th1 and Th2 responses and promote regulatory T-cell development. It is believed that it is not the amount of TGF-β present in breast milk that determines whether or not allergy develops, but rather the strength of the signals from the cells to the nucleus.[35] However, investigators have shown that orally administered TGF-β retains biological activity. The presence of TGF-β enhances oral tolerance development in ovalbumin-sensitized mice,[36] and influences the development of a Th1 immune response profile in allergy-prone rats.[37] This evidence argues in favor of earlier introduction of food antigens suggesting that early oral antigen exposure concomitant with breast-feeding or TGF-β supplementation may be beneficial for promoting tolerance development.[34]

Diagnostic Testing for Food Allergy

IgE-mediated reactions to food are the most widely-known food-induced allergic reactions and may be life-threatening. Examples of IgE-mediated reactions include acute urticaria and/or angioedema, flushing, pruritus, acute onset of wheezing or bronchospasm, oral allergy syndrome, food and exercise-induced anaphylaxis, and generalized anaphylaxis (Figure 4). Reactions are characterized by having a sudden onset, and typically symptoms develop within minutes to 2 hours. Rarely, an IgE-mediated reaction may present with symptoms more than 2 hours after ingestion.[38-40] An IgE-mediated reaction occurs when specific IgE bound to mast cells or basophils is cross-linked by the food-specific antigen and leads to release of pre-formed inflammatory mediators.

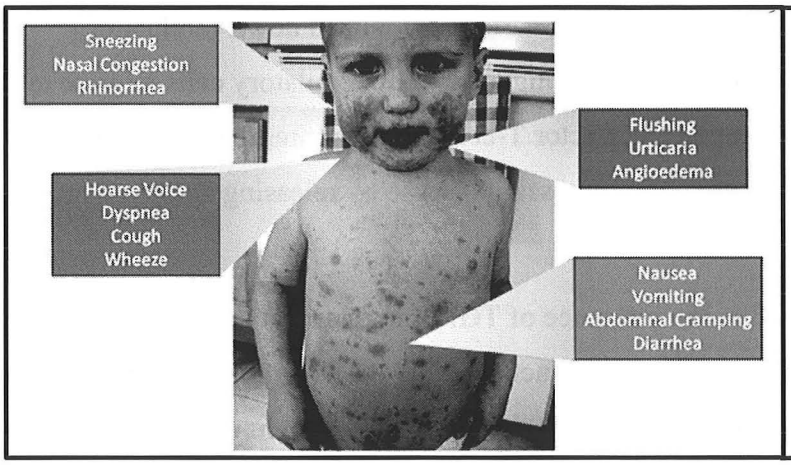


Figure 4. Signs and symptoms of an IgE-mediated allergic reaction.

Mast cell activation leads to release of histamine, prostaglandins, proteases and the synthesis of lipid mediators and cytokines. Symptoms may present in any organ system, but are characteristically seen at the sites where mast cells are typically found – in tissues of the respiratory tract, gastrointestinal tract, cardiovascular system and skin. Commonly, multiple organ systems are involved. Evidence has not substantiated a role for food allergy in chronic conditions such as chronic urticaria, behavioral disorders such as autism, and allergic rhinitis.

A double-blind, placebo-controlled food challenge is the gold-standard for diagnosis of food allergy. More commonly, however, clinicians rely on serum specific IgE testing, skin prick tests, and observed open oral food challenges when necessary. *In vitro* quantification of specific IgE has been used by investigators to determine the likelihood of having an allergic reaction (Figure 5).[41] Skin prick tests (SPT) are commonly used by allergists. This method involves

using a needle, bifurcated needle, probe, or lancet to puncture the epidermis through an extract of a food. [42] Positive and negative results must be interpreted in light of the historical reaction, with the predictive value decreasing if used in an unselected population. Negative results have a greater than 95% NPV. A positive skin test (a wheal measured 3 mm larger than the negative control) has a PPV of only approximately 50%; though investigators have shown the larger the wheal diameter, the greater the PPV of the test for some foods. [43] An oral food challenge may be necessary in some circumstances in order to confirm or refute clinical allergy.

Figure 5. Positive predictive values established using ImmunoCAP methodology.

Interpreting ImmunoCAP Levels

Age Group	Food	Serum IgE (kU/L) ~95% react
Child	Egg	≥ 7
≤2 years		≥ 2
Child	Milk	≥ 15
≤2 years		≥ 5
Child	Peanut	≥ 14
Child	Fish	≥ 20

Sampson H. J Allergy Clin Immunol 2004;113:805-19
Garcia-Ara C, et al. J Allergy Clin Immunol 2001;107(1):185-90

Management of an Acute Allergic Reaction

Current recommendations for food-allergic individuals include strict avoidance of the food allergen, education regarding potential cross-contamination or cross-reacting foods and nutritional counseling when necessary to ensure adequate nutritional supplementation for an individual on an avoidance diet. Despite best efforts to avoid the allergenic food, reports have shown between 14%[45] and 50%[46] of allergic individuals may experience accidental ingestion of a food they are trying to avoid, and 93% of individuals reported to have fatal anaphylaxis were known to have a food allergy.[47]

Table 1. **Risk factors for a fatal or near-fatal food-induced allergic reaction.**[44]

- Concomitant asthma, especially severe asthma with adrenal suppression caused by chronic glucocorticoid therapy
- Lack or delayed administration of epinephrine
- Lack of skin symptoms
- Denial of symptoms
- Concomitant intake of alcohol (which may increase absorption of the food allergen)
- Reliance on oral antihistamines alone to treat symptoms
- Allergy to peanut, tree nut, fish or crustacean shellfish

Severity of the reaction may be influenced by multiple factors. Factors associated with a fatal or near-fatal reaction are shown in Table 1. It is recommended 2 doses of auto-injectable epinephrine be carried by all food-allergic

individuals with (1) a history of a prior systemic allergic reaction, (2) a patient with food allergy and asthma, or (3) patients with a known food allergy to peanut, tree nuts, fish and crustacean shellfish.[44]

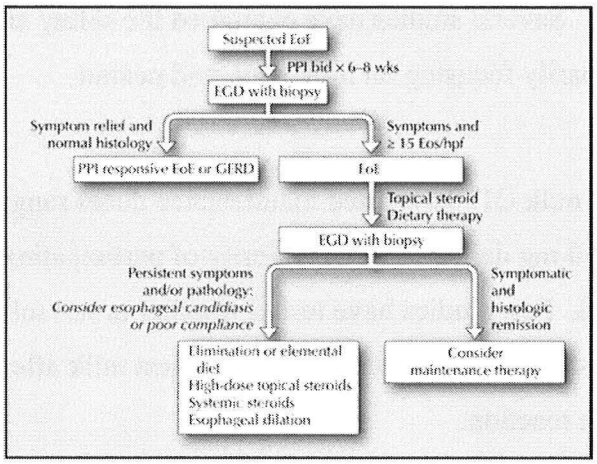
Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is an example of mixed IgE/non-IgE mediated food allergy. Literature regarding the recognition, diagnosis, pathogenesis and treatment of EoE has increased numerous fold over the past decade. Diagnostic guidelines require clinical symptoms in addition to pathologic findings.[48] Symptoms vary with age, presenting as failure to thrive, frequent emesis and abdominal pain in young children and with dysphagia and food lodging in adolescents and adults.[49] Minimal pathologic criteria include a minimum of 15 eosinophils per high power field in the absence of GERD (lack of responsiveness to high-dose PPI or normal pH monitoring of the distal esophagus).[48]

Treatment options include dietary interventions (e.g. specific food elimination diets, avoidance of common food allergens, and elemental diets) or topical steroid (e.g. swallowed budesonide or fluticasone). Investigators have shown that elemental dietary therapy exceeds all other elimination diets[50]; however, formulas lack palatability and adherence to elemental formulas alone is challenging. The six food elimination diet, empirically eliminating the 6 most commonly allergenic foods (milk, eggs, nuts (peanuts and tree nuts), soy, wheat, and seafood (fish and shellfish) has been proven beneficial for 70 to 80% of individuals.[50,51] Specific food elimination based on results of skin prick testing and atopy patch testing has variable efficacy (60 to 70%),[50,52] and patch testing reagents are not standardized.

For those unable to comply with dietary therapy, swallowed topical steroids are an appropriate treatment option. While no therapy is FDA approved for the treatment of EoE, clinicians have recommended use of swallowed inhaled fluticasone and swallowed budesonide with some benefit, with approximately 55% of participants in one study improving significantly on swallowed fluticasone[53] and another study showing 87% improvement with swallowed budesonide.[54]

A recommended treatment approach is outlined below in Figure 6.



Garrean C and I Hirano. *Current Gastroenterology Reports* 2009, 11:175-81.

Figure 6. Suggested evaluation and treatment approach for a patient with suspected eosinophilic esophagitis (EoE).

Food Allergy Research

Ongoing research for treatment of food allergies has centered around 2 major approaches, allergen-specific immunotherapy and allergen-non-specific immunotherapy. Allergen-specific immunotherapy deals predominately with the concepts of desensitization and tolerance (Figure 7). Desensitization refers to increasing the threshold of allergen needed to cause allergic symptoms and is dependent on regular allergen exposure. Tolerance implies a permanent loss of allergic reactivity independent of regular allergen exposure. Allergen-non-specific immunotherapy, on the other hand, focuses on suppressing the immune response rather than directly altering *antigen-specific* responses. .

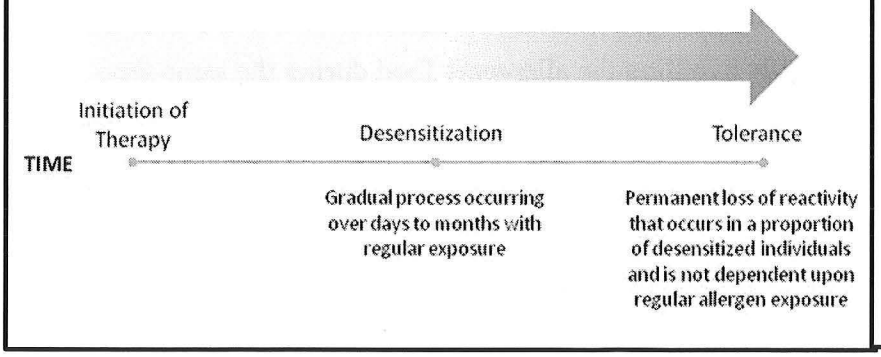


Figure 7. Desensitization vs. Tolerance

Oral Immunotherapy (OIT)

The concept of oral desensitization involves giving increasing amounts of a known allergenic food via the gastrointestinal tract. Several studies have examined the safety and efficacy of oral immunotherapy (OIT), primarily focusing on milk, egg, and peanut desensitization.

Studies investigating the efficacy of milk OIT have used maintenance doses ranging from as little as 165 mg daily[55] to as much as 8250 mg daily.[56,57] The majority of participating subjects have been successfully desensitized. Few studies have tested whether or not tolerance develops, meaning that if daily exposure is stopped the subject is able to ingest milk after a period of milk avoidance without an allergic reaction.

Egg OIT has also been used successfully in several studies. Patriarca *et al.*[58] desensitized 11 of 13 subjects after 3 to 8 months of therapy. Another group has reported successful desensitization in 7 children undergoing an egg OIT protocol,[59] though on follow-up analysis two subjects out of 21 enrolled were unable to continue secondary to daily symptoms.[60] In a report by Staden *et al.*[56] 16 of 25 children with either cow's milk (n=14) or hen's egg allergy (n=11) were able to successfully complete an OIT protocol. Nine of the 25 subjects achieved permanent tolerance.

The challenges facing both egg and milk OIT trials include the fact that a significant number of children will outgrow their allergy to egg or milk by avoidance rather than through desensitization, and few studies have directly compared avoidance vs. desensitization. In the study mentioned above by Staden *et al.*[56] 35% of children in the control group were able to achieve tolerance by avoidance only. One study from France did show that children participating in an oral desensitization trial to either milk or egg were more likely to pass a food challenge than those who were strictly avoiding the allergenic food during the same time period.[61] However, there were still a significant number of children able to pass a challenge at study completion through strict avoidance. Entry challenges were not performed in either group. Laboratory testing at this point is unable to predict which patients will eventually develop tolerance without intervention, thus making it difficult to identify which patients will benefit most from intervention.

Unlike milk and egg allergy, peanut allergy is rarely outgrown.[62] Jones *et al.*[63] reported successful desensitization in 27 of 29 subjects enrolled in a peanut OIT desensitization protocol. The same group has shown that of 8 subjects who had completed from 32 to 61 months of desensitization, all 8 demonstrated clinical tolerance by passing an oral food challenge 4 weeks after stopping maintenance OIT.[64] Varsney, et al. published results from their double-blind, placebo-controlled trial demonstrating the ability to ingest 5000 mg of peanut protein (approximately 20 peanuts) for the 16 subjects receiving treatment; whereas subjects receiving the placebo powder were able to ingest only 280 mg of peanut protein (approximately 1 peanut).[65]

Sublingual Immunotherapy (SLIT)

The first double-blind placebo-controlled trial using sublingual immunotherapy (SLIT) for the treatment of allergy was published in 1986 investigating the use of SLIT for the treatment of dust mite allergy.[66] Investigation into the use of SLIT for the treatment of *food allergy* has not been thoroughly investigated.

In 2005, Enrique, et al. examined the utility of SLIT in hazelnut allergic subjects.[67] A double-blind placebo-controlled trial was conducted in adults with hazelnut allergy, which was confirmed by a positive SPT as well as a positive oral food challenge. After 8 to 12 weeks of therapy the active group was able to tolerate a significantly greater amount of hazelnut compared to entry and compared to the placebo group. Systemic and local reactions secondary to the SLIT drops were rare. However, the study was hampered by the fact that a large portion of those enrolled had oral allergy syndrome alone as their presenting complaint.

More recent work has examined the efficacy of SLIT for Class I food allergy (food-induced reactions characterized by the rapid onset of IgE-mediated symptoms which can progress to anaphylaxis). The only study investigating the utility of SLIT for treatment of peanut allergy reported that by administering small amounts of allergen beneath the tongue, the dose of allergen required to elicit an allergic reaction in peanut-allergic individuals was

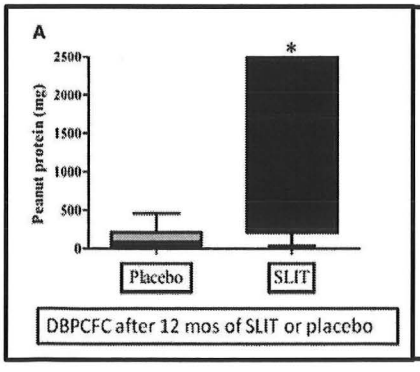


Figure 9. Efficacy of peanut SLIT after 12 months of therapy.

Kim EH, et al. J Allergy Clin Immunol. 2011 Mar; 127(3):640-6.

increased 20-fold. Moreover, this clinical finding was accompanied by significant changes in peanut-specific IgE and IgG_4, basophil reactivity, Th2 cytokine expression,[68] and salivary IgA.[69] It was also reported that peanut SLIT is extremely well-tolerated with minimal side-effects or changes in daily activities. Clinical treatment of peanut allergy using SLIT is not recommended. This study must be interpreted in light of the small sample size and wide range of the amount of peanut ingested at study completion in subjects receiving therapy.

One study directly compared the effects of milk SLIT vs. milk OIT.[70] Investigators found that OIT was more efficacious for desensitization to cow's milk than SLIT alone bus was accompanied by more systemic side effects. Interestingly, clinical desensitization was lost in some participants within one week of therapy.

Epicutaneous Immunotherapy (EPIT)

EPIT consists of repeated application of allergens to intact skin. Treatment in animal models has shown promise, and studies investigating treatment in humans are in their infancy. The only report using EPIT in humans treated cow's milk allergic children. One mg of skimmed cow's milk powder was applied to the interscapular area in three, 48-hour applications per week for 3 months utilizing an epicutaneous delivery system.[71] Investigators reported in their pilot trial that utilization of the therapy was safe and suggested some efficacy in a few individuals. However, the trial was conducted for only 3 months and was not powered adequately to measure efficacy. Phase II trials investigating the utility of peanut EPIT will soon be underway.

Engineered Recombinant Proteins

Another allergen-specific approach to treating food allergy is to generate mutated proteins, decreasing the allergenicity of the food. This has been investigated in peanut allergic mice. By substituting amino acids on Ara h1, 2 and 3, the 3 major allergenic peanut proteins, the ability of IgE to bind to the protein is eliminated or drastically reduced.[72] Using site-directed mutagenesis, amino acids necessary for IgE binding were altered but T-cell proliferation was not inhibited. Investigators were able to generate *Escherichia coli* clones expressing modified Ara h1, 2 and 3 and administer 3 different doses in a methylcellulose carrier to peanut allergic mice

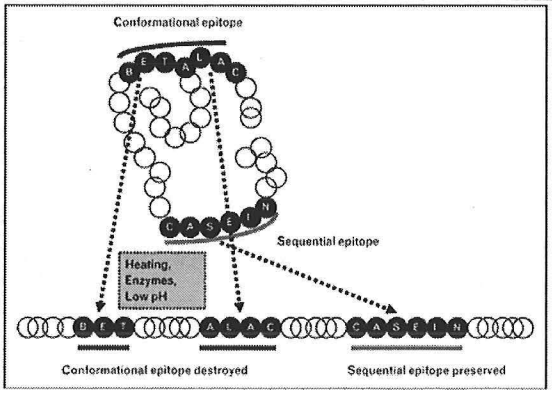
weekly for 3 doses. Mice were then challenged to peanut from 2 to 10 weeks after therapy.

Mice receiving the medium and high doses remained protected against anaphylaxis for up to 10 weeks after treatment. Investigators also noted a significant reduction in plasma histamine levels and IgE levels in all treated groups. The group receiving the highest doses showed depressed IL-4, IL-13, IL-5, and IL-10 production by splenocytes and increased IFN-γ and TGF-β production. Human studies are currently underway.

Effect of heating on food protein allergenicity

IgE binding to food proteins may be specific for either conformational or sequential epitopes within the protein itself (Figure 8). Conformational epitopes are formed by amino acid residues from different regions of the allergen and are dependent on protein folding.[73] They may be affected by heating, enzymatic digestion or low pH. Sequential epitopes, on the other hand, are comprised of sequential amino acids and generally are not affected by such factors. Reactivity to sequential epitopes rather than conformational epitopes is proposed to explain why some milk and egg allergic children are able to tolerate the baked forms of either milk or egg.

The majority of those labeled as milk and egg allergic are in fact able to eat the baked forms of milk and egg without having an allergic reaction.[74,75] In the heated milk study,[74] children with milk allergy were challenged with heated milk products and then subsequently challenged with unheated milk. Those who tolerated heated milk, but reacted to unheated milk, ingested heated milk products for 3 months and were then re-evaluated. At 3 months investigators found significantly smaller skin prick test (SPT) wheal diameters and higher casein IgG_4 compared with baseline. Those who were able to tolerate heated milk had significantly smaller SPT wheal diameters and lower milk-specific and casein-specific IgE levels at entry than the reactive group.



Nowak-Wegrzyn A and A Fiocchi. *Curr Opin in Allergy & Clin Immunol.* 2009;9:234-7.

Figure 8. Conformational epitopes may be affected by food processing methods involving heating, an acidic environment, or enzymatic degradation; however, sequential epitopes are generally not affected by processing.

Subjects with documented egg allergy were enrolled in a study looking at extensively heated egg tolerance with a similar design as that mentioned above for investigating heated milk tolerance.[75] Children who were reactive to regular egg but tolerant of heated egg (as confirmed by observed challenges) were told to incorporate heated egg into their diets. Similar to the findings in the heated milk study, children tolerant of heated egg had smaller SPT wheal diameters at baseline. They also had significantly lower egg white-specific, ovalbumin-specific and ovomucoid-specific IgE levels compared to the reactive group. At 3 months, continued ingestion of heated egg showed that SPT wheal diameters and ovalbumin-specific IgE levels had decreased significantly and ovalbumin-specific and ovomucoid-specific IgG_4 levels had increased significantly.

The immunologic findings mentioned above are similar to what has been described in oral immunotherapy trials and suggests that introduction of baked milk or baked egg may be an alternate route for attaining tolerance.[73]

Anti-IgE Therapy

Non-specific immunotherapy for peanut allergic subjects was investigated using an anti-IgE monoclonal antibody, TNX-901.[76] TNX-901 is a humanized IgG1 monoclonal antibody against IgE that recognizes and masks an epitope in the CH3 region of IgE responsible for binding to the high-affinity Fcε receptor on mast cells and basophils. A double-blind, multi-center trial included 84 adolescent and adult subjects with a history of immediate hypersensitivity to peanut. Threshold doses of reactivity were confirmed by a double-blind, placebo-controlled food challenge (DBPCFC) at entry and then within 2 to 4 weeks of the fourth dose. Subjects were randomly assigned to receive one of 3 doses of TNX-901 or placebo every four weeks for four doses.

The study concluded that subjects receiving the highest dose of TNX-901 had a significantly increased threshold of sensitivity to peanut on oral food challenge from 178 mg (equivalent to approximately ½ of a peanut) at study entry to 2.8 g (equivalent to approximately 9 peanuts) at study end. However, approximately 25% of subjects in the highest-dose group tolerated the entire peanut challenge (10 grams of peanut protein or more than 20 peanuts), and another 25% in the same group had no change in the amount of peanut flour required to induce a

reaction. There were no identifiable characteristics including peanut-specific IgE values or total serum IgE concentration that differentiated reactors and non-reactors.

While the study showed promise that TNX-901 would provide protection against accidental ingestion of peanut in the majority of those treated, drug development was discontinued. A trial using omalizumab (Xolair, Genentech, San Francisco, CA), an alternate anti-IgE monoclonal antibody, for the treatment of peanut allergy showed initial promise but the trial was discontinued secondary to safety concerns from an external Data Monitoring Committee.[77]

Chinese herbal medicine

Traditional Chinese Medicine (TCM) has been used in Asia for centuries to treat numerous diseases. Over the past decade, TCM has been investigated as a potential treatment for food allergies. Original studies were performed in mice delivering a combination of 11 herbs and labeled as Food Allergy Herbal Formula-1 (FAHF-1).[78] Mice sensitized to peanut were given FAHF-1 for a total of 7 weeks. Mice were then challenged to peanut and peanut-induced anaphylaxis symptoms were completely abrogated, and mast cell degranulation and histamine release were also significantly reduced. Peanut-specific serum IgE levels decreased by 2 weeks of treatment and remained lower 4 weeks after discontinuation of treatment.

Secondary to concerns for potential toxicity in the original formulation, a second product, FAHF-2, was developed which contained the original ingredients except for 2 herbs.[79] In murine experiments, peanut-sensitized mice were given FAHF-2 daily for 6 weeks. Peanut challenges were performed monthly and FAHF-2 treated mice were found to have full protection more than 36 weeks after treatment. The long-lasting protection seen clinically is coupled with a shift in allergen-specific immune responses largely mediated by elevated CD8+ T-cell IFN-γ production.[80] Peanut-specific IgE levels were reduced as much as 50%, and IgG_{2a} levels were increased as much as 60%.

More recently, FAHF-2 has entered into human trials. Phase 1 studies are complete and report that FAHF-2 appears to be safe and well-tolerated in food allergic subjects.[81] Phase 2 studies are underway.

Conclusions

Over the past 20 years much progress has been made in understanding the natural development of oral tolerance, opening doors for investigators to more clearly examine methods of tolerance induction. Therapies such as Chinese herbal medicines may offer hope to families of children with multiple food allergies, and specific oral tolerance induction using either SLIT or OIT may provide an avenue for allowing protection against accidental ingestions and possibly the development of permanent tolerance. The risks of therapy versus avoidance, proper dosing, patient selection, reaction patterns, precautions after desensitization, and allocation of clinical resources must continue being investigated[82] before any specific therapy is ready for standard clinical practice, but there is certainly hope that a practical treatment for food allergy is in the near future.

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