Diagnosis, Management, and Investigational Therapies for Food Allergies

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Abstract

Food allergies have increased in prevalence over the past 20 years, now becoming an important public health concern. Although there are no therapies currently available for routine clinical care, recent reports have indicated that immunotherapies targeting the mucosal immune system may be effective. Oral immunotherapy is conducted by administering small, increasing amounts of food allergen; it has shown promise for desensitizing individuals with peanut, egg, or milk allergies. Sublingual immunotherapy also desensitizes allergic patients to foods—2 major studies have examined the effects of sublingual immunotherapy in subjects with peanut allergies. We review the complex nature of IgE-mediated food allergies and the therapies being evaluated in clinical trials. We focus on the diagnosis and management of food allergies and investigational therapies.

Food allergies are defined as an adverse health effect arising from an immune response to a given food.[1] The immune response can be IgE-mediated, non–IgE-mediated, or a combination of both. For the purpose of this review, *food allergies* refers to IgE-mediated allergies. IgE-mediated allergic reactions have an acute onset (typically developing < 2 h after ingestion) and most often involve the skin, gastrointestinal tract, and respiratory tract. Food-specific IgE is required for allergic reactions, although the presence of specific IgE does not mean that an individual will have an allergic reaction to the antigen. In other words, a person can be sensitized with detectable levels of specific IgE but does not react upon ingestion of the food.

IgEs bind to the cell surface of mast cells in tissues and basophils in the blood through the high-affinity IgE receptor FcERI. Upon subsequent exposure to the offending food, in individuals with allergies, the allergens cross-link IgE on the surface of mast cells and

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basophils, causing degranulation of these effector cells. The release of histamine, leukotrienes, and other mediators ultimately lead to allergic symptoms.[2] Symptoms can range from mild irritation, such as mouth itching, to full anaphylaxis with hypotension and cardiovascular collapse, which can be fatal if not treated appropriately.

Epidemiology

It is estimated that 4%–6% of the US population is allergic to foods.[3] However, it is difficult to determine the actual prevalence of food allergies because the standard for diagnosis is the double-blind, placebo-controlled food challenge (DBPCFC). These trials are time consuming, expensive, and can elicit severe reactions. A systematic review of epidemiologic aspects of food allergy found that 2%–10% of the US population has a food allergy.[4] The foods most commonly associated with allergies in the United States are milk, eggs, peanuts, tree nuts, wheat, soy, fish, and shellfish.[1] In European countries, sesame, lupine, mustard, and celery also have been identified as major allergenic food sources.

There have been several reports indicating that food allergy prevalence has increased since the 1990s. A study from the US Centers for Disease Control reported an 18% increase in food allergies from 1997 to 2007.[5] A study in China showed an increase in prevalence from 3.5% to 7.7% from 1999 to 2009.[6] Australian researchers have reported similar increases in food allergies.[7] Another study conducted in the United States used a random-calling telephone survey to estimate the prevalence of peanut and tree nut allergies in 1997, 2002, and 2008. This study found that peanut allergies increased from 0.4% in 1997 to 0.8% in 2002, and had reached 1.4% by 2008.[8] Tree nut allergies also were found to have increased from 0.2% to 1.1% during this time period.[8] Although these findings confirm clinical experience that food allergies are increasing, the reasons for this increase are not well understood.

Factors that might affect the onset of food allergies include the timing of food introduction into the diet, route of exposure to food allergens, and exposure to microbial products (the hygiene hypothesis). Although the optimal timing for introducing a food into a child's diet is unknown, retrospective studies have indicated early ingestion of peanut may prevent allergy. An analysis of Jewish children from Israel and the United Kingdom found that peanut was introduced earlier, eaten more frequently, and in larger quantities in Israel than the United Kingdom.[9] Interestingly, there was a 10-fold higher prevalence of peanut allergy in the UK cohort (1.85%) than in the Israeli cohort (0.17%). Similar findings have been reported from studies of early introduction of egg[10] and milk.[11] These results imply that early introduction of potentially allergenic foods actually may prevent allergies, although prospective studies are needed.

Cutaneous exposure also has been proposed to cause an allergy, and has been shown in mouse models.[12] Mice with disruptions in the gene encoding filaggrin, a skin barrier protein, produce high levels of specific-IgE upon cutaneous exposure to allergens. These findings indicate the importance of the skin's barrier function in the development of an allergy.[13] Filaggrin mutations have since been associated with peanut allergy in human beings.[14] These findings fit with those from studies of mice showing that oral exposure to an antigen

results in immune tolerance (ie, oral tolerance), whereas other routes of exposure can lead to hypersensitivity.[15]

Interestingly, ecologic studies of household dust in homes where peanuts are consumed detected biologically active peanut proteins. These might be involved in early cutaneous exposure and sensitization.[16] The hygiene hypothesis states that the modern environment and lack of early exposure to microbial and viral agents, gut flora, and parasites also may account for increases in atopic conditions. Some studies have shown that probiotics can reduce atopic dermatitis but not food allergies.[17] Further studies on the microbiome and its role in food allergies may provide new insight into the pathogenesis of food allergies.

Diagnosis of a Food Allergy

The first step in the diagnosis of a food allergy is to distinguish IgE-mediated reactions from other non–IgE-mediated processes. Table 1 summarizes the typical clinical history reported by patients with IgE-mediated food allergies. The differential diagnosis of IgE-mediated food allergies includes lactose intolerance, celiac disease, food protein–induced enterocolitis syndromes, and eosinophilic gastrointestinal disorders, among others. Histamine intolerance is a nonimmunologic reaction to the ingestion of histamine-containing foods. Most IgE-mediated reactions are elicited by a small number of foods such as milk, egg, peanut, tree nuts, wheat, soy, fish, or shellfish.[1,18] These reactions are induced by allergenic proteins in the foods and are characterized by rapid onset (usually < 2 h). Sensitivity to carbohydrates in mammalian meat is an exception to this temporal pattern—symptoms can be delayed for as long as 6 hours.[19]

The most common symptoms associated with food allergic reactions are cutaneous, gastrointestinal, and respiratory (Table 2). Neurologic symptoms or anaphylaxis also may occur, but are less common. Severe reactions typically only occur after oral ingestion of foods. Exceptions include some patients with fish or shellfish allergy, who develop reactions after inhalation of airborne allergens, and skin reactions, which occur in some patients with food reactions after cutaneous exposure. Severe reactions are reported most commonly to peanuts, tree nuts, fish, and shellfish, but any food exposure is capable of eliciting anaphylaxis.[20] Risk factors associated with mortality include age (adolescents and young adults are at highest risk), comorbid conditions (asthma), and delayed administration of epinephrine.[7,21,22]

Atopic conditions (atopic dermatitis, asthma, and allergic rhinoconjunctivitis) often are comorbid in patients with food allergies. Physical examination commonly shows eczematous rash and pale edematous nasal turbinates, which are consistent with these conditions. In children with moderate to severe atopic dermatitis, the prevalence of a coexisting food allergy has been estimated to be as high as 35%.[23] Although IgE-mediated reactions to foods commonly present as acute urticaria, most cases of new-onset urticaria in children are infectious in origin.[24] Moreover, chronic idiopathic urticaria is not typically related to food ingestion.[20] A family history of any atopic disease, such as asthma, allergic rhinitis, or atopic dermatitis in first-degree relatives, increases the risk of food allergy.[25]

A careful dietary history should be obtained from all patients. This may include encouraging the patient to provide labels or lists of ingredients from foods suspected of eliciting reactions. In cases in which more than one food is suspected, dietary logs may prove helpful. For allergens such as milk or egg, it is important to discern whether the food can be tolerated in baked forms. Often, children who develop a natural tolerance to milk or egg will tolerate them in baked goods first.[26,27] Because only small amounts of food are required to elicit a reaction, clinicians should assess the potential for cross-contamination. Common places where this may occur include Asian restaurants, bakeries (peanut and tree nuts), and buffets (all foods). Foods consumed regularly in the diet, especially those tolerated since the time of reaction, should not be tested.[20]

In addition to assessing possible food exposures, it is also important to consider ancillary factors. Some factors such as exercise, use of nonsteroidal anti-inflammatory drugs, alcohol consumption, and concurrent febrile illness may decrease the threshold for reactions. For example, patients with wheat-dependent, exercise-induced anaphylaxis undergo physiologic changes during exercise that result in a temporary loss of tolerance to omega-5 gliadin.[28,29] Analysis of a patient's history of drug use or infection can provide insights into possible causes of acute urticaria.

Patients with a history consistent with food allergy are assessed further by skin prick tests, measurement of antigen-specific IgE (sIgE), and oral food challenge (OFC). The skin prick test is a quick and relatively inexpensive method to determine food sensitization. A small amount of allergen is placed in the epidermis, which causes formation of a wheal; a flare reaction is mediated by histamine release from the tissue's mast cells. Wheal diameters are measured approximately 15 minutes after placement and compared with positive (histamine) and negative (saline) controls. However, patients cannot take antihistamine drugs before the test is performed, and results can be complicated by skin conditions such as eczema. Furthermore, there are variations among testers and skin prick devices. Although skin tests detect food allergies with high levels of sensitivity (estimated at ~90%), their specificity is only approximately 50%.[30] They should not be used to screen individuals for food allergies because false-positive results can lead to unwarranted dietary restriction.[20]

Serum levels of sIgEs are measured by a variety of methods, including the automated enzyme-linked immunosorbent assay capture system. Serum sIgE tests are superior to skin tests in that serum IgE levels can be measured in patients taking antihistamines, and levels are not reduced after an acute reaction. Furthermore, measurements are not operator-dependent and can be compared.

Levels of sIgE against certain allergens can be used to predict which children and adolescents with histories of food allergy are likely to react to challenges with specific foods (Table 3). Threshold levels of sIgE required to induce a clinical reaction are lower in infants younger than age 2 than in older children.[31,32] These types of studies have not been performed in adults.

It is important to note that most of these thresholds were generated from a population of highly atopic children and adolescents—most with a history of atopic dermatitis.[33]

Consequently, these cut-off values can be used only for children or adolescents with a high pretest probability of clinical allergy. Similar thresholds, generated from population-based cohorts, differ considerably and could be much higher for certain foods in nonallergic individuals.[34] Levels of sIgE must be evaluated in an appropriate clinical context.

Another important consideration is that these values do not exist for all foods. Moreover, IgE measurements below these cut-off levels do not preclude clinical reactivity. The ImmunoCAP system has been used to determine cut-off values. Lower and upper limits reported from this system are set at 0.35 and 100 KU/L, respectively. Comparative studies of several IgE detection systems have suggested that established parameters could not be applied reliably to measurements made with other systems.[35]

It is important to note that results from skin prick tests and measurements of sIgE are markers of sensitization—they either indirectly or directly measure the presence of antibodies to a particular antigen. The presence of food sIgE is requisite for allergic reactions to occur but does not equate to a clinical allergy, therefore, tests must be ordered and interpreted in the context of an accurate clinical history. Moreover, sIgE levels and results from skin prick tests do not correlate with the reaction severity.[36,37] As a result, some patients with near-undetectable levels of sIgE still may be at risk for anaphylaxis. The DBPCFC is the standard for the diagnosis of a food allergy.[20] A single-blind or open OFC, however, is used more often in the clinic, given the labor- and time- intensive nature of the DBPCFC. When the result of an open OFC is indeterminate, more rigorous evaluation with a DBPCFC is indicated.

OFCs are particularly useful for ruling out allergy when the patient's clinical history is not consistent with their diagnosis. This approach is cost effective and efficient. OFCs also can be used to determine whether an individual has outgrown an allergy. Certain food allergies tend to persist over time, such as an allergy to peanut, tree nuts, fish, and shellfish.[38] Food allergies to soy, wheat, egg, and milk, however, often resolve.[39] Re-introduction of some of these foods can improve quality of life[40] and provide nutrients essential for growth and development.

Differences in allergies to foods that are baked vs un-heated forms can be attributed to changes in protein conformation or exposure of specific epitopes with heat-induced denaturation. For example, heating the major egg allergens, ovalbumin and ovomucoid, reduces binding by IgE, increases susceptibility to simulated gastroduodenal digestion, and decreases the ability of these allergens to cause basophil degranulation.[41] Peanut allergies, however, usually involve a response to peanut protein epitopes that are unaffected by heat-induced denaturation. Some studies suggest the development of tolerance to milk or egg proteins can be induced by consumption of baked forms of these foods after passing an OFC.[42,43]

In clinical practice, supervised OFCs usually are performed when the negative predictive value for clinical reactivity to antigen exposure by skin tests and measurement of sIgE is 50% or higher (Table 3), and the patient is willing to introduce the food into his/her diet. Challenges should not be performed in individuals with a recent history of severe

anaphylaxis, regardless of skin prick test results or sIgE measurements.[39] In addition, recent measurements of sIgE levels and results from skin prick tests are needed (within 1 year), to ensure that sensitivity has not changed. Generally, testing is performed every 12–18 months for the first 5 years of life. Less frequent monitoring (every 2–3 years) is necessary for patients who are less likely to outgrow their food sensitivity, such as older patients (>5 years old) and those individuals with a sensitivity to tree nuts, fish, and shellfish.[39] Decreased findings from skin prick tests and levels of sIgE can help to determine the appropriate time to perform an OFC.

Component-resolved diagnostic tests have been advocated as a means to improve the diagnostic capacity of sIgE levels—they are available for milk, egg, peanut, tree nuts, fish, and shellfish. Most of the available data from studies of component-resolved diagnostic tests are relevant to peanut allergy. Early studies have suggested sIgE to peanut components (ie, allergens, referred to as *Ara h proteins*) may improve the sensitivity and specificity of sIgE testing to identify patients with a peanut allergy.[44] For patients with levels of peanut IgE less than 2 kU/L, levels of Ara h 1, 2, and 3 might identify patients who still are likely to react to OFC. In addition, patients sensitive to Ara h 8 and Ara h 9, but not Ara h 1, 2, and 3, also might react to birch pollen; this phenotype is consistent with oral allergy syndrome. More studies are needed to elucidate the role of component testing in food allergy diagnosis.

Management of Food Allergy

Currently, the standard of care for food allergy management is strict dietary avoidance of culprit foods and ready availability of self-injectable epinephrine. Although simple in principle, in practice, dietary avoidance is quite challenging. In 1989, Bock and Atkins[45] reported that half of children with food allergies have an accidental ingestion within 5 years, and 75% had reactions over more than 10 years. In 2000, it was reported that half of children with a peanut allergy had an accidental exposure in a 2-year period,[46] and a large number were likely to have reactions. The risk of an unexpected, possibly severe, reaction while eating causes anxiety for patients and their families, reducing their quality of life.[47,48]

To minimize risk, individuals with food allergies must take great care in gathering information about the ingredients in their food. Food-labeling laws have been implemented in the United States, the European Union, Canada, Australia, Japan, and Singapore.[39] These laws require food manufacturers to list, in plain language, any ingredient from a common allergenic food source or an ingredient derived from an allergenic food (eg, casein must be labeled as milk). Although this can help patients navigate what is safe to consume, special care must be taken when eating foods prepared at a restaurant or by others outside the home.

Annual physician visits are recommended to assess the course of a child's food allergy. The allergist may recommend a skin prick test, sIgE quantification, or a food challenge. A key aspect of managing food allergies is to educate patients and their families about how to recognize and treat symptoms of an allergic reaction. An emergency action plan should be developed with patients; it should describe signs and symptoms of mild, moderate, and severe reactions and explain how to treat them.[39] Action plans are particularly important for

children attending school where a school nurse or staff member may be the first responder in the event of an allergic reaction.

The first-line treatment for an allergic reaction caused by a food is epinephrine. Epinephrine can be administered by a self-injectable device (eg, EpiPen or Auvi-Q), which requires a prescription and is given as an intramuscular injection. If the patient weighs 10–25 kg, 0.15 mg of epinephrine should be given; for patients heavier than 25 kg, then 0.3 mg should be administered.[39] After receiving epinephrine, the patient should be transported immediately to an emergency facility for further treatment and observation. Patients may receive additional medication depending on symptoms and severity, including bronchodilators, antihistamines, corticosteroids, supplemental oxygen, intravenous fluids, vasopressors, glucagon, or atropine. Patients experiencing anaphylaxis should be observed in a hospital setting for at least 4—6 hours to monitor symptoms, because food allergies can produce biphasic reactions.

Patients with food allergies and their families also must be educated on adequate nutrition. There is evidence that a restricted diet can put children at risk for malnutrition, which may cause delays in growth.[49] Patients with a milk allergy, for example, are prone to vitamin D and calcium deficiencies.[50] Therefore, it is important to work closely with a dietician to identify appropriate substitutes that ensure adequate nutrition while excluding any known allergens.

Investigational Therapies

Proactive therapies for food allergies are needed because avoidance is not a long-term solution for the millions of individuals at risk for accidental reactions. In the 1980s, subcutaneous immunotherapy (SCIT; also known as an allergy shot) was tested for peanut allergy—this form of therapy is effective and safe for the treatment of allergies to environmental factors and insect stings. Trials have shown some efficacy of SCIT for a peanut allergy, but there was an unacceptably high rate of severe allergic reactions.[51] SCIT has not been tested for food allergies since these trials. Instead, researchers have turned to other routes of administration for immunotherapy. It is important to note that the therapies discussed in this section are investigational and not ready for routine clinical practice.[52]

A key concept in immunotherapy for food allergies is desensitization vs sustained unresponsiveness (also referred to as *tolerance*). Desensitization means increasing the allergen reactivity threshold in subjects receiving daily immunotherapy. Sustained unresponsiveness means retention of an increased reactivity threshold after immunotherapy has been discontinued for weeks or months.

Oral Immunotherapy

Oral immunotherapy (OIT) typically is conducted in 3 phases, with allergens in a flour form and ingested with a food vehicle. Phase 1 is a modified rush desensitization, starting with minute quantities of allergen, which increases in dose several times during a single day. Phase 2 is a buildup dosing period in which subjects ingest daily doses of the allergens at home. Doses increase approximately every 2 weeks under clinical observation. Phase 3 is

the maintenance dosing period in which subjects ingest the target dose of allergen daily, at home, for months or years. OIT was reported to induce desensitization in some subjects in a preliminary case series of various food allergies,[53] but rigorous studies were needed to show safety, efficacy, and mechanism. OIT trial outcomes now have been reported for peanut, egg, and milk allergies.

Peanut OIT—Findings from an open-label study of peanut OIT, performed in children in the United States, first were reported in 2009.[54] Subjects began taking 0.1 mg of peanut protein; the dose increased for several months to a maintenance dose of 300 mg peanut protein daily. Twenty-seven of 29 subjects subsequently were able to accept a peanut challenge of 3900 mg of peanut protein (approximately 13 whole peanut kernels). Side effects occurred most often during the modified rush and build-up phases.[55] Skin, gastrointestinal, and upper respiratory symptoms were most common. Other open-label studies since have reported findings from the United Kingdom[56] and Germany.[57] Results from these trials confirm that reactivity thresholds can be increased via OIT.

A multicenter, double-blind, randomized, placebo-controlled trial of peanut OIT provided strong evidence that this approach can desensitize children with peanut allergies.[58] Twenty-eight subjects, ages 1–16 years old, randomly were assigned to groups given peanut OIT (n = 19) or placebo (n = 9). In subjects receiving peanut OIT, the peanut protein was increased to a maintenance level of 4000 mg. After 12 months of dosing, subjects underwent a DBPCFC to 5000 mg of peanut protein. All 16 of the subjects continuing on peanut OIT passed the challenge, compared with none of the subjects given placebo (they could ingest only a median of 280 mg peanut protein).

The largest trial to date was a cross-over study in the United Kingdom of 99 children with a peanut allergy (age, 7–16 y).[59] In phase 1, the subjects received OIT with peanut protein or continued to avoid peanuts (standard of care, controls). Then, in phase 2, subjects from the control group in phase 1 were crossed-over and received peanut OIT. Subjects underwent 6 months of peanut OIT and then underwent a peanut challenge. After this period, 84% of subjects who received OIT in phase 1 were able to ingest 800 mg of peanut (the daily maintenance dose), as were 91% of those who received OIT in phase 2.

In the food challenge outcome at the end of phase 1, 62% of subjects who received OIT could tolerate 1400 mg of peanut without symptoms, whereas none of the controls could tolerate 1400 mg of peanut. These findings indicate that peanut OIT can desensitize most patients within 6 months. Notably, side effects were deemed mild for most subjects.

Although peanut OIT appears to desensitize patients, it only recently was reported that OIT also can lead to tolerance, or sustained unresponsiveness.[60] Vickery et al[60] reported findings from an open-label study of 24 children who received daily doses of peanut for up to 5 years, then stopped the OIT for 1 month and were challenged again. All subjects passed the desensitization challenge, ingesting 5000 mg of peanut protein without symptoms. After abstaining from peanut OIT for 1 month, 50% of subjects were able to pass a DBPCFC, and were considered tolerant. It is important to note that the patients who did not pass the

tolerance challenge still tolerated a median challenge dose of 3750 mg—which is much greater than would be expected if the OIT effect had subsided completely.

This study shows that peanut OIT can lead to sustained unresponsiveness, indicating that long-term use of daily maintenance doses may not be necessary for all subjects. However, interpretation of these results is limited because there was no placebo control group. Some people with peanut allergies spontaneously develop tolerance—estimated at 20% in a disease progression study.[38] A randomized, placebo-controlled trial is required to determine rates of sustained unresponsiveness caused by OIT vs subjects who spontaneously develop tolerance while taking placebo.

Egg OIT—A multicenter, double-blind, randomized, placebo-controlled trial was reported in 2012 by the Consortium of Food Allergy Research[61] on 55 subjects (age, 5–11 y) with a persistent egg allergy. After 10 months of receiving OIT, 40 subjects participated in a DBPCFC; the OIT was found to be effective for 22 subjects (55%), but for none of the 15 subjects in the placebo group. Subjects in the active OIT group continued to receive exposure to egg for an additional 12 months and then participated in a second DBPCFC. After 22 months of OIT, 30 of 40 subjects (75%) did not have symptoms after an egg challenge and were considered desensitized.

To assess sustained unresponsiveness, subjects stopped OIT for 6–8 weeks, and then were challenged again. Eleven of 40 subjects (28%) did not develop symptoms after the challenge. This study nicely showed the efficacy of OIT and showed that it is easier to induce desensitization than sustained tolerance. The researchers are studying the effects of giving doses for longer periods of time and the long-term effects on sustained unresponsiveness.

Milk OIT—A multicenter, double-blind, randomized, placebo-controlled study was reported in 2008[62] on 19 subjects with milk allergies; 12 received milk OIT and 7 received placebo. After approximately 6 months of therapy, subjects who received milk OIT went from a baseline average threshold of 40 mg milk protein to a final level of 5140 mg before developing symptoms. Placebo subjects had no change in threshold and continued to react to a median of 40 mg. A greater proportion of subjects receiving OIT had symptoms during the dosing period than subjects receiving placebo (45% vs 11%), as expected. Symptoms were most commonly local and treatable.

Multifood OIT—Many patients have multiple food allergies; in a DBPCFC trial, the majority of 196 patients had clinical reactions to more than 1 food.[33] A phase 1 study was conducted to examine the safety of multifood OIT.[63] In a study of 40 subjects (age, 4–46 y), 15 were given only peanut OIT and 25 were given multifood OIT, including peanut for all subjects, plus various tree nuts, egg, milk, or sesame customized to each individual's allergies. The 2 groups had comparable rates of allergic side effects, indicating that multifood OIT is not inherently more risky than single-food OIT. However, the researchers did not report outcomes of food challenges because the primary end point was allergic reactions during OIT. Further randomized, placebo-controlled studies are needed to confirm that multifood OIT is safe and effective.

Combination therapies—OIT is risky—patients with a known food allergy intentionally ingest proteins that cause reactions. It has been proposed that anti-IgE therapies, such as omalizumab, could be given to bind free circulating IgEs before OIT, to increase safety and dose. The highest dose of the humanized monoclonal antibody TNX-901, given without concurrent OIT, was shown to reduce reactions to peanut protein in 75% of subjects with a peanut allergy.[64]

In a pilot phase 1 study, omalizumab was given to subjects for 9 weeks before they began milk OIT.[65] All subjects experienced some reactions during OIT, although most were deemed mild and did not require treatment. Nine of 11 subjects tolerated desensitization to a dose of 2000 mg of milk protein within 7 to 11 weeks after the initial desensitization. Findings from a study of omalizumab plus peanut OIT were reported later.[66] In this study, researchers found that 13 subjects all were able to accept a 500-mg dose of peanut on the first day of desensitization. Twelve of 13 subjects reached a 4000-mg maintenance dose, in a median time of only 8 weeks. Peanut OIT then was effective for all participants in a DBPCFC. Administration of omalizumab before OIT therefore appears to allow subjects to ingest large quantities of allergen, faster than peanut OIT protocols without omalizumab. Further studies, especially randomized, placebo-controlled trials, are needed to assess this strategy better.

Mechanisms of OIT

The immunologic changes caused by OIT are beginning to be elucidated. Because direct measurement of mucosal immune tissue is not feasible, mechanistic studies are a challenge. Typically, systemic immune responses are measured indirectly, primarily in skin tissue (by a skin-prick test) and in whole blood. Markers of immune responses in mucosal secretions, such as antibodies and cytokines in saliva or stool, might be better indicators of clinical response, although this remains to be determined. Changes that occur in allergic effector cells and humoral responses, as well as alterations in T-cell phenotypes, are presented in Figure 1. Mast cell reactivity, measured by skin-prick tests, decreases after several months of OIT, and has been shown in many OIT trials.[67] Basophils also become hyporesponsive to antigen, based on studies of peanut and egg OIT.[61,68] Although effector cell responses to antigen are reduced, little is known about the mechanisms and signaling pathways that lead to this outcome. Changes in effector cells appear to be linked to clinical reactivity; it follows that patients undergoing desensitization have reductions in mast cell and basophil responses.

Changes in antibody levels also have been observed in trials of peanut, milk, and egg OIT. Many trials have reported increases in antigen-specific IgG4.[67] Researchers have proposed that IgG4 is a blocking or protective antibody that prevents allergic reactions, whereas others believe that increases in IgG and IgG4 are simply natural immune responses to repeated antigen exposure. Changes in levels of IgE also have been reported in studies of OIT: typically as an increase in the first several months on OIT, but eventually, as OIT is continued for years, levels of antigen -sIgE decrease.[60] The decrease in sIgE is likely to be required for sustained unresponsiveness; a study associated lower levels of IgE at the time OIT is stopped with sustained unresponsiveness to allergen challenge. The role of IgA has not been investigated extensively.

Primed antigen-specific T cells are required for he production of IgE, so changes in T-cell activities also must be part of tolerance induction by OIT. Several studies have reported decreases in T-helper (Th)2-type cytokines, such as interleukin-4 (IL4), IL5, and IL13, whereas increases in regulatory cytokines, such as IL10 and transforming growth factor-β, have not been widely reported.[67] Increases in numbers and functions of T-regulatory cells have been reported[54,69]; these cells are thought to contribute to down-regulation of Th2 cells and could have direct effects on B-cell production of IgE or IgG4. There is much to learn about interactions among effector cells, B cells, and T cells in the development and treatment of food allergies. Other cell types, such as dendritic cells, also are likely to be involved but have not been widely studied.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) is performed by placing allergen extract, in a liquid solution, under the tongue for as long as several minutes; then it is spit out or swallowed. Langerhans cells in the oral mucosa take up the allergens and are thought to induce tolerance. SLIT has been used to reduce allergies to environmental allergens in Europe for several decades, and recently was approved in the United States for treatment of grass pollen allergy. SLIT is thought to be safer than OIT because smaller quantities of allergen are administered.

Kim et al[70] performed a randomized, double-blind, placebo-controlled trial of SLIT for pediatric patients with a peanut allergy. The dose increased from 0.25 μg peanut protein to 2000 μg in approximately 6 months. Subjects then continued to receive 2000 μg of peanut protein per day for the next 6 months. Twelve months after the trial started, all subjects participated in a DBPCFC. Researchers observed a significant difference between subjects who received peanut SLIT (n = 11) and those who received placebo (n = 7). The SLIT group tolerated a median of 1710 mg of peanut protein in the DBPCFC, whereas the placebo subjects tolerated only 85 mg. Immunologic changes were discovered by skin-prick tests—basophil reactivity to peanut decreased in subjects receiving SLIT, but not in those given placebo. Levels of peanut-specific IgG4 also were increased in the SLIT group. Interestingly, salivary peanut-specific IgA was increased with SLIT and correlated with clinical outcome, indicating that salivary IgA could be a marker of desensitization.[71] Further studies are needed to identify biomarkers to predict which subjects are mostly likely to benefit from SLIT.

The Consortium of Food Allergy Research conducted a multicenter, double-blind, randomized, placebo-controlled trial of SLIT in 40 subjects with a peanut allergy.[72] This study included an older population than the study by Kim et al[70] (median age, 15 y; range, 12–37 y). After 44 weeks, 70% of subjects given SLIT could tolerate increased levels of peanut protein, compared with only 15% of subjects given placebo. The median tolerated dose was 496 mg in subjects who received SLIT, compared with 3.5 mg at enrollment. After 68 weeks of SLIT, the median tolerated dose among SLIT recipients was 996 mg, which was much lower than the final doses tolerated after OIT (typically several grams of allergen).

In an open-label study that compared SLIT with a combination of SLIT and OIT for milk allergy, researchers found that although SLIT could increase reaction thresholds, it was less effective than OIT.[73] A retrospective analysis that compared the efficacy of OIT vs SLIT in reducing peanut allergy reached a similar conclusion.[74] SLIT therefore might be used to treat patients with peanut or milk allergies with minimal side effects and lead to desensitization in some subjects. However, there appears to be a trade-off between safety and desensitization (Table 4).

Epicutaneous Immunotherapy

Epicutaneous immunotherapy (EPIT) is a new approach in which a circular disk that contains dried allergens is applied to intact skin. The allergen is solubilized by moisture from the skin and taken up by dendritic cells on the outer layer of the skin. One advantage of EPIT over other forms of immunotherapy is that administration of small doses of allergen to the skin could decrease the likelihood of systemic reactions, which can occur after allergen ingestion. EPIT is effective in animal models of food allergy and is being investigated in clinical trials for food allergies.[75]

Findings from only 1 clinical trial of EPIT for food allergies have been published.[76] Children with a milk allergy (age, 3 mo to 15 y) received EPIT with milk protein or placebo for 30 days, and then were challenged. The amount of milk the EPIT group was able to drink increased from 1.77 ± 2.98 mL at baseline to 23.61 ± 28.61 mL after 3 months, whereas the placebo group had only a modest increase over this time period. Adverse events were mostly mild skin symptoms. Studies are underway in North America and Europe to investigate EPIT for peanut allergy.

Future Directions

It is important to understand how and why food allergies develop in some individuals but not others; this information might be used to prevent the onset of allergies. Investigational treatments for individuals with food allergies show promise, but we need a better understanding of their safety and efficacy before they can be used in routine practice. Additional studies are needed to determine the mechanisms of OIT, SLIT, and EPIT for food allergies; these could lead to biomarkers of desensitization or tolerance induction. The microbiome is important in the development of food allergies in mice,[77] so the gut flora also might be manipulated to treat the allergy. Studies are needed to determine the role of the microbiome in food allergy.

In conclusion, it is exciting to see large-scale clinical trials underway to determine the best therapeutic options for food allergies. Although we likely are several years away from treating food allergies routinely in clinical practice, the field is moving closer to developing safe and effective approaches to treat food allergic individuals.

Acknowledgments

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Abbreviations used in this paper

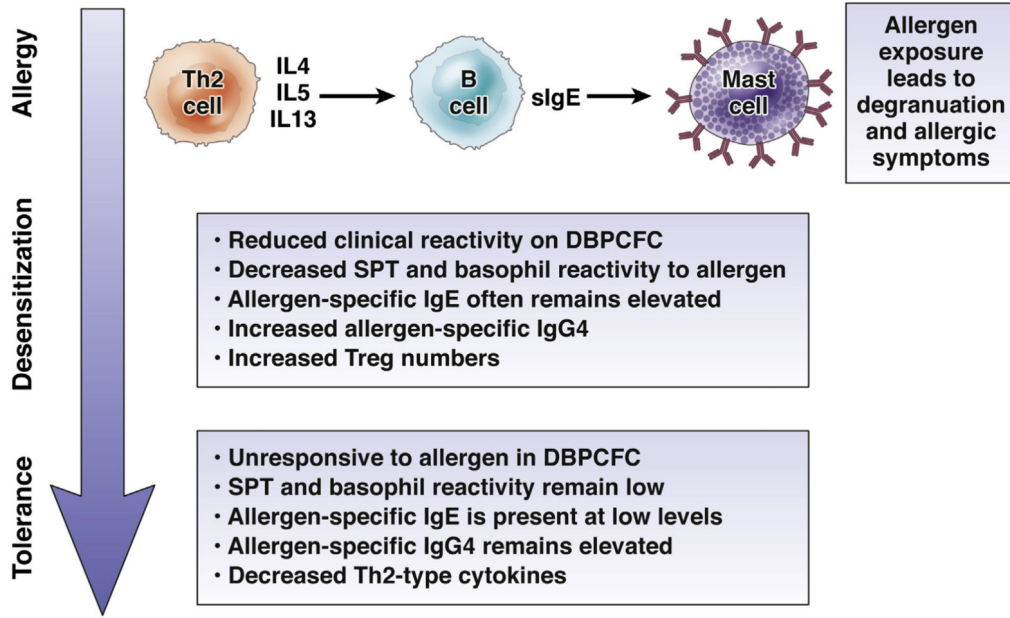|	
Ara h	allergens
DBPCFC	double-blind, placebo-controlled food challenge
EPIT	epicutaneous immunotherapy
IL	interleukin
OFC	oral food challenge
OIT	oral immunotherapy
SCIT	subcutaneous immunotherapy
sIgE	antigen-specific IgE
SLIT	sublingual immunotherapy
Th	T-helper

Figure 1.
Mechanisms associated with desensitization and tolerance after OIT. In patients with allergies, allergen-specific Th2 cells secrete IL4, IL5, and IL13, which induce production of sIgE. sIgE binds to mast cells and basophils via FcERI; future encounters with the allergen leads to degranulation and release of mediators that cause symptoms of allergy. In the desensitized state after OIT, patients can ingest large amounts of allergen without a reaction. Tolerance is achieved in some patients after long courses of OIT, when daily maintenance doses are stopped for several weeks or months. SPT, _____.

Table 1

Collecting a Patient's History of Food-Induced Allergic Reactions

Timing of exposure	Symptoms usually occur within minutes to hours (usually within 2 h of ingestion)
Route of exposure	Severe reactions occur only after oral ingestion of specific foods; mild skin reactions can occur with cutaneous exposure
Nature of reaction	Cutaneous, gastrointestinal, and respiratory symptoms predominate; food allergy should be investigated in any patient with anaphylaxis temporally related to food ingestion
Food ingested	Egg, milk, and peanut are common food allergens in young children; peanut, tree nuts, fish, and shellfish induce reactions in teenagers and adults
Dietary history	Foods tolerated before and after a reaction usually are not implicated as inducers; assess current diet and avoidance patterns
Duration of symptoms	Symptoms usually resolve relatively quickly, generally within several hours; however, biphasic and late-phase reactions can occur many hours after ingestion of the food
Treatment	Assess response to medications/interventions, if any
Ancillary factors	Inquire regarding alcohol consumption, use of nonsteroidal anti-inflammatory drugs, and exercise; some patients only have reactions if they ingest specific foods in association with these factors

Table 2

Symptoms of Food-Induced Allergic Reactions

Target organ	Symptoms
Cutaneous	Erythema
	Pruritus
	Urticaria
	Morbilliform eruption
	Angioedema
	Eczematous rash (late)
Ocular	Pruritus
	Conjunctival erythema
	Tearing
	Periorbital edema
Oropharyngeal	Angioedema of the lips, tongue, or palate
	Oral pruritus
	Tongue swelling
	Metallic taste
Upper respiratory	Nasal congestion
	Pruritus
	Rhinorrhea
	Sneezing
	Laryngeal edema
	Hoarseness
Lower respiratory	Cough
	Chest tightness
	Dyspnea
	Wheezing
	Increased work of breathing
Cardiovascular	Tachycardia
	Bradycardia (late)
	Hypotension
	Dizziness
	Syncope
	Pallor
Gastrointestinal	Nausea
	Abdominal pain
	Reflux
	Vomiting
	Diarrhea
Neurologic	Anxiety
	Confusion
	Loss of consciousness

Target organ	Symptoms
	Sense of impending doom

Table 3

Predictive Value of IgE Tests, Based on OFC Results[20,78]

Food	>95% Positive		~75% Positive		~50% Negative	
	SPT	sIgE	SPT	sIgE	SPT	sIgE
Egg white	7	7 (2 if age <2 y)			3	2
Cow's milk	8	15 (5 if age <1 y)				2
Peanut	8	14			3	2 (history of prior reaction) 5 (no history of prior reaction)
Fish		20				
Soybean				30		
Wheat				26		

Table 4

Comparison of OIT and SLIT

	OIT	SLIT
Drug product	Flour prepared from the food, administered in a food vehicle	Liquid extract prepared from the food source
Typical daily maintenance dose	300–4000 mg	2–7 mg
Common side effects	Oral, gastrointestinal	Oropharyngeal
Severe side effects	Anaphylaxis; development of eosinophilic esophagitis	Systemic reactions are exceedingly rare
Desensitization	Vast majority of subjects completing the protocol	Can increase the threshold for reactions, but not as robust as OIT
Sustained unresponsiveness (tolerance)	Achieved in some subjects; may depend on length of dosing period	Unknown