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Michelle E. Conroy, MD

Food Allergy: Review of Epidemiology, Risk Factors, and Future Treatments

Abstract: Food allergy has established itself as a matter of significant public health importance and relevance. It has had substantial impacts across the world and continues to represent the most common cause of anaphylaxis seen in emergent settings. However, its increasing incidence has yielded a silver lining of increased interest and investment, which has powered major research in the field. Much has been learned about food allergy as a result. Recent work has elicited increased understanding about food allergy prevalence, mechanisms, and risk factors. In turn, this has allowed for application of this understanding to potential treatments. Current practice of food allergy treatment through restricted exposure may ultimately be replaced with novel therapies including, perhaps ironically, introduction of the allergenic foods in question. This review presents broad highlights of the rapidly increasing understanding into food allergy mechanisms and experimental therapies.

Keywords: food allergy; anaphylaxis; atopic dermatitis; immunotherapy; treatment

The apparent explosion in the incidence of food allergies, both nationally and internationally, has elicited significant responses from public health, academic research, the food industry, and the public at large. If there is any silver lining to the increased incidence of food allergies, it rests in the progress that has been made in identification, diagnosis, and treatment of food allergy. While there is much work to be done,

food ingestion. Symptoms range from general abdominal discomfort to hypotension and cardiovascular collapse due to anaphylaxis. Food-induced reactions can be broadly categorized into immunologic (allergic) and nonimmunologic (intolerance) reactions. According to the National Institute of Allergy and Infectious Diseases (NIAID) Food Allergy Management Guidelines published in 2010, food allergy is defined

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there has been exceptional evolution in the understanding of food allergies. This has yielded an expanding list of possibilities for their future management.

Food-Induced Reactions

There are a number of adverse reactions that can occur in the context of

as follows: “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.”¹ This initial distinction is critically important, as it renders pertinent diagnostic and prognostic information. Examples of nonimmunologic reactions include lactose intolerance, toxin-mediated

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reactions (food poisoning), and reflux/gastritis. Immunologically mediated food-induced symptoms include anaphylaxis, urticaria, eosinophilic infiltrative disorders (eosinophilic esophagitis), and others. The immunologically mediated reactions can again be subdivided into those that are IgE antibody mediated (urticaria, anaphylaxis) and those that are of mixed immunologic mechanisms (eczema, eosinophilic disorders). These distinctions seem clear enough, but similar perception of symptoms can sometimes blur the lines between these various reactions. This is particularly true for persons experiencing reactions, who subsequently make presumptions of allergy in the context of these symptoms. Given the potentially significant risks associated with food allergies, providers are also prone to attributing nonallergic reactions to "allergy." This results in a marked difference between perceived and diagnosed food allergies,² a misperception that has enormous public health implications. It is therefore absolutely essential to appreciate these basic differences given the possibility of IgE-mediated anaphylaxis and risk of death.³ The remaining focus of this review we will be on immunologically based, IgE antibody-mediated food allergy that elicits signs and symptoms including urticaria, bronchospasm, gastrointestinal symptoms, syncope, and hypotension leading to shock.

Epidemiology of Food Allergy

Despite the difficulties in making an accurate diagnosis of food allergy, there clearly are increasing numbers of people with IgE-mediated food allergies. Determining the actual prevalence is challenging due to self and provider overreport. In 2010, a meta-analysis was published suggesting that the prevalence of food allergy was more than 1% to 2% but less than 10%.⁴ In this study, the authors specifically commented on the lack of uniformity in diagnostics as a major challenge in food allergy epidemiology. In another study, participants from 30 sites across the

United States took part in the National Health and Nutrition Examination Survey, which demonstrated an estimated prevalence of food allergy of 2.5%. The study also found notable age-based trends—under 5 years of age there was a prevalence of 4.2% and the number generally decreased with increasing age.⁵ This prevalence estimate of food allergy closely correlates with other recent findings. The CDC/NCHS published a brief in 2008 suggesting 4 out of 100 children have food allergy. Hospital discharges for children with food allergic reactions were almost 4 times greater from 2004 to 2006 than from 1998 to 2000.⁶ A very recent study aimed at determining the prevalence of food allergies in urban minority children found a prevalence of 3.4% in a group of just over 9000 children with "physician-documented" food allergy. However, only 1.4% of the total group had "most convincing" evidence for food allergy including both a relevant history and positive testing.⁷ This study again illustrates the recurrent discordance between reported food allergy history and accurately diagnosed food allergy. A recent study of a population of children in Minnesota indicated that peanut allergy has increased 3-fold between 1999 and 2007.⁸

Risk Factors

Studies have sought to understand potential risk factors contributing to food allergies and their rise over the past 2 decades. There is increasing evidence that risk factors for food allergy occur across the life span. Examples are summarized below.

Genetics

Family history is a very strong risk factor for the development of food allergy. A child with a peanut allergic parent or sibling has a 7-fold risk of experiencing the same food allergy.⁹ A study of monozygotic twins found a concordance rate for peanut allergy to be more than 60% compared to less than 10% among dizygotic twins.¹⁰ Given the complex processes involved in food

exposure, intake, and absorption, a variety of genes have been implicated in allergy. These genes control a wide spectrum of functions including barrier dysfunction, food allergen processing, alterations in immune cells and regulation of the larger immune response, and many others.¹¹

Atopic Dermatitis

Atopic dermatitis is often the initial hallmark of allergic disease with the majority of affected children ultimately experiencing a subsequent allergic condition. Many of those affected have elevated IgE levels, which may correlate with disease severity as well as indicate sensitization to both environmental and food allergens.¹² More recently, it has become clear that a defective skin barrier is a major pathophysiologic cause of atopic dermatitis. At the cellular level, it was determined that filaggrin, a protein generated by keratinocytes, helps improve the integrity of the outer skin layers.¹³ With this information, the possibility of filaggrin dysfunction as a contributing factor to atopic dermatitis seemed plausible. In 2011, Brown et al published a study demonstrating loss-of-function mutation in filaggrin as a significant risk factor for development of clinically significant peanut allergy.¹⁴ A prior study demonstrated an increased incidence of peanut allergy in children living in homes with high consumption of peanut.¹⁵ It seems possible that, in the context of a defective skin barrier, transcutaneous sensitization to foods may occur via environmental exposures. These allergens "land" in an immunologic milieu that is primed for an allergic response with an increased number of allergic T cells in both the skin and peripheral blood in persons with atopic dermatitis.¹⁶

Prenatal Exposures

As food allergy can occur in the first months of life, prenatal exposures that may potentiate development of allergy are a major focus of current research. It seems logical to consider maternal diet during pregnancy as a possible route of sensitization. IgE antibodies in the

newborn have been used as a potential marker for sensitization induced in utero. IgE antibodies are found in cord blood and may predict risk for future atopic phenotype.¹⁷ There is, however, controversy regarding the role of maternal diet during pregnancy and the development of food allergy. Sicherer et al showed that maternal consumption of peanut during pregnancy correlated with a higher likelihood of peanut-specific IgE found in infants.¹⁸ Other recent studies have shown no relationship between in utero exposures to allergenic foods and the risk of subsequent food allergy.¹⁹ The 2010 NIAID-sponsored Expert Panel report suggested that there was insufficient evidence to implicate maternal diet in the development of food allergy.¹ A recent Cochrane review similarly concluded that evidence to support the avoidance of highly allergenic foods during pregnancy in order to reduce atopic disease in the child was lacking.²⁰ A Danish birth cohort study of over 60 000 mothers also came to a similar conclusion about maternal diet. In fact, the authors suggested a possible protective effect resulting from ingestion of peanuts and tree nuts during pregnancy.²¹ The American Academy of Allergy, Asthma and Immunology Adverse Reactions to Foods committee recently released guidelines that suggest that there is no convincing evidence to recommend maternal avoidance of milk and egg during pregnancy. However, the report highlighted contradictory evidence regarding peanut and tree nut ingestion during pregnancy and made no clear recommendation for these particular foods.²²

In addition to the impact of maternal diet, maternal environmental exposures and their influence on the fetal immune response have also been studied. Dr David Strachan initially proposed the so-called "hygiene hypothesis" in 1989, citing evidence from his study documenting a lower incidence of allergic rhinitis in families with increasing numbers of siblings.²³ Since originally proposed, the hygiene hypothesis has generated tremendous controversy.

Several studies have demonstrated findings consistent with its general principle. A European study demonstrated variable food allergen sensitization patterns between children who lived on farms compared to those who do not.²⁴ The PASTURE (Protection against Allergy-Study in Rural Environments) birth cohort involves the ongoing study of about 800 children from 5 European countries. A very recent study from the cohort demonstrated significant fluctuation of allergen-specific IgE in the first year of life.²⁵ Notably, food-specific IgE more commonly appears *transiently* during this first year compared to that due to inhalant allergens, which seem more persistent. This raises important questions as to the relevance and function of food-specific IgE in cord blood and early life. Consistent, specific sensitization seems to occur after 1 year of life in atopic children. A prior study from the same cohort found decreased levels of interferon- γ in newborns in whom IgE antibodies were found in cord blood which suggests a "pro-allergic" tendency at birth.²⁶ These studies reinforce the idea that allergy is truly a condition influenced substantially by both genetics and environmental exposures.

The role of hypovitaminosis D as a risk factor for allergic disease has recently been evaluated. With regard to food allergy, it was demonstrated that prescriptions of self-injected epinephrine occurred with a "north-south gradient" in the United States. Given that sunlight exposure at extreme north and south latitudes does not support vitamin D production,²⁷ the authors proposed a potential relationship to vitamin D deficiency and food allergy.²⁷ One recent study found that high levels of maternal vitamin D level at 34 weeks gestation correlated with food allergy or sensitization in the first 2 years of life.²⁸ The same study also found reduced cord blood T regulatory cells in the context of elevated vitamin D levels. These regulatory T cells are akin to immune system "brakes," and if reduced, allergic inflammation may proceed unchecked. However, Jones et al showed that while

eczema seemed correlated to low maternal vitamin D levels, IgE-mediated food allergy did not.²⁹ Interestingly, Vassallo et al showed that infants born during the fall and winter months had a higher risk of food allergy, implying that low vitamin D levels in infants at birth may predispose to allergy.³⁰ The role for vitamin D in the pathogenesis of food allergy needs further clarification.

Early Life Exposures

Food allergy begins not uncommonly in the first year of life. As discussed above, it has been documented that the presence of food-specific IgE can occur quite early as well. Given this finding of early sensitization, early life exposures have been considered as potential risk factors for allergy. A 2008 review of 26 epidemiologic studies showed that birth by cesarean section might pose an increased risk for food allergy.³¹ The mode of delivery results in significantly different initial newborn microbial colonization of the gut. Proper colonization ultimately leads to education and maturation of the immune system, with oral tolerance to foods chief among these important outcomes.³² Studies have shown "gut dysbiosis," alterations in typical gut colonization, in infants with food allergy.³³ For example, increased amounts of bacteria including *Clostridia* were found in infants who had cow's milk allergy compared to those without allergy.³⁴ These findings led to attempts at early treatment with probiotics, intended to restore and encourage growth of normal flora, which in turn, might act as a preventive measure against development of allergies. The results of these studies have been mixed. A 5-year follow-up study of over 120 children treated postnatally with probiotics did not show significant reduction of allergy in the treated group.³⁵ The World Allergy Organization recently took the position that "probiotics do not have an established role in the prevention or treatment of allergy." They did suggest that further, multidisciplinary research should be undertaken given encouraging basic science findings.³⁶

Feeding in infancy has been a topic of significant investigation relative to food allergy. The NIAID-sponsored Food Allergy Management Guidelines recommended that all infants be breast fed for the first 4 to 6 months of life.¹ This recommendation was made despite conflicting data on the subject. Several studies have linked breast feeding in infancy to reduced risk of atopic dermatitis.^{37,38} As atopic dermatitis is a clear risk factor for allergy, these findings have been applied to clinical recommendations that breast feeding may be protective against atopic dermatitis. In addition, major revisions have been made to the recommendations for introduction of solid foods in the first year of life. In 2008, the American Academy of Pediatrics Committee on Nutrition reversed prior recommendations and stated there was no clear evidence that presumptive dietary interventions beyond 4 to 6 months of age altered the course of atopic disease in children.³⁹ The 2010 Food Allergy Management Guidelines noted only 2 randomized controlled trials aimed at addressing issues of solid food introduction. The report did cite one study of 900 families where significant risk for developing food allergy occurred at ages 1 and 3 years when the introduction of solid food was delayed.⁴⁰ Citing evidence from multiple prior studies, the American Academy of Allergy, Asthma and Immunology Adverse Reactions to Foods Committee suggested that even highly allergenic foods could be introduced early.²² The Committee suggested that typical developmentally appropriate considerations (ie, aspiration risk) must be considered and foods should be introduced at home initially, and in small amounts.

Cutaneous Exposures

One possible means by which exposure and allergy induction could occur is by contact or transcutaneous exposure. In the context of atopic dermatitis, which suggests inflammation and skin barrier dysfunction, application of peanut-containing oils to dry skin is a

risk factor for peanut allergy.⁴¹ One study demonstrated a dose-response relationship between the amount of peanut eaten in a household and risk for development of peanut allergy. The same study showed that maternal ingestion of peanut during pregnancy and lactation did not affect the risk of food allergy.⁴² A subsequent study showed that peanut allergic subjects had memory T cells that proliferated in response to peanut exposure and showed markers indicating their ability to “home” to the skin. The authors speculate that this may be a basic science correlate that reinforces the role of cutaneous sensitization in the development of food allergy.⁴³

Tick Bites

In 2007, a report of infusion reactions with use of Cetuximab, a mouse-human chimeric IgG antibody, was published, which demonstrated notable geographic specificity.⁴⁴ These reactions were ultimately determined to be related to preexisting IgE antibody directed against galactose- α -galactose (α -gal), which is present on the murine component of Cetuximab.⁴⁵ It is interesting to note that α -gal is also present on tissue from nonprimate mammals including cows, pigs, and lambs. In 2009, Commins et al published a study where 24 patients with history of *delayed* reactions including anaphylaxis, angioedema, or hives had detectable antibodies to α -gal. These reactions were delayed between 3 and 6 hours after ingestion of foods such as beef, pork, or lamb.⁴⁶ More than 90% of subjects with demonstrated serum IgE against α -gal indicated a positive history of tick bites by questionnaire. Three patients were followed prospectively and demonstrated increases in specific IgE to α -gal that occurred in the 2 to 4 weeks after tick bites. Over time these levels would decrease, only to again spike with subsequent bites.⁴⁷ This finding is exciting not only due to the implications for tick borne sources of cross-reactive IgE but also due to the fact that α -gal is a carbohydrate. Carbohydrates were previously considered to be unlikely sources of major allergic reactions.⁴⁸ It may be that anaphylaxis with previously

unclear triggers could be explained by carbohydrate-based IgE antibodies. This has major implications for the understanding of food allergy overall.

Treatment

Standard of care in treatment of food allergy has largely revolved around restriction of the implicated food and carrying self-injectable epinephrine. However, this is an imperfect treatment for those with food allergy. Fortunately, fatal food-induced anaphylaxis is not common and occurs in less than 1% of anaphylactic episodes. Adolescents and young adults *previously diagnosed with food allergies* seem to be at particular risk and represent the majority of fatalities. Peanut and tree nut allergies were the cause of greater than 90% of fatal reactions in one study.⁴⁹ Fatal reactions were more commonly associated with respiratory symptoms than with hypotension often because these reactions are mistaken for asthma exacerbations.⁵⁰ This results in either lack of or delayed use of epinephrine. In one study, only 10% of people who died from food allergy had immediate access to injectable epinephrine.⁵¹

Complete restriction of a food from the diet requires significant knowledge to implement fully. While this seems like a straightforward recommendation, it can be tremendously challenging. At a very basic level, people must be able to recognize the food to which they are allergic, but this is often not the case. In a study of over 1000 people, less than half were able to identify visual images of peanuts and tree nuts. This was true for allergic patients as well. In addition, parents of allergic children were not able to identify these foods with any more accuracy than parents of nonallergic children. Less than 25% of children ages 6 to 18 could recognize these foods accurately.⁵² While fatal reactions are uncommon in food allergy, there is a perpetual need for maximal vigilance to prevent these reactions. This constant need for surveillance has a major impact on the quality of life for people with food allergy and their families. One study

of almost 50 families demonstrated that children with food allergy felt their allergy affected the overall quality of their lives as well school performance.⁵³ Mothers from the same families had high scores for anxiety. In 2010, a study showed that nearly 25% of children with food allergy experienced bullying because of their allergy.⁵⁴

Full restriction of foods also dictates extensive evaluation of ingredients and processing before a potentially allergic food is ingested. Reading food labels and ingredients can be cumbersome and confusing. Various phrases such as “processed in a facility with” and “manufactured on shared equipment with” are not regulated by any labeling laws and are applied only at the discretion of the manufacturer. Almost 10% of nearly 180 products labeled as “may contain peanut” did, indeed, contain peanut protein. More than 40% of products tested for milk contamination were positive. Dark chocolate may be particularly risky as almost 80% of those products tested contained milk.⁵⁵ These findings underscore the real risks and challenges of food restriction. As a result, much work has been undertaken to try and identify novel approaches to food allergy treatment.

Food allergy is understood to represent a lack of immunologic tolerance against certain food proteins. As such, it seems logical that creating a situation in which tolerance to these foods can be *induced* may lead to therapy for food allergic patients. The means through which this can be accomplished has been under investigation. With inhalant, venom, and drug allergy, introduction of allergen via gradually increasing doses (immunotherapy) allows for temporary tolerance while there is continuous exposure to the relevant allergen. This concept has been increasingly applied to food allergy and seems to be yielding promising results.

Extensively Heated Foods

It is well established that heating can radically alter the structure and therefore allergenic properties of food proteins. Antibodies recognize very particular

regions called epitopes in any given protein. Often IgE antibodies recognize epitopes clustered in certain areas of *folded* proteins. These food protein epitopes are often referred to as “conformational epitopes” given the requirement of intact underlying 3-dimensional structure for optimal antibody binding. Processes such as heating or digestion, which undermine this 3-dimensional structure, can lead to reduction in allergen potential as the binding site for IgE is no longer intact. For example, ovalbumin, a major egg protein allergen, is quite sensitive to structural changes via heating.⁵⁶ As such, many people with egg allergy can ingest heated/cooked egg safely. In one study, 70% of children with known egg allergy tolerated extensively heated egg.⁵⁷ This pattern of heating and tolerance suggests that ovalbumin contains conformational epitopes. This is in contrast to epitopes that are more sequential in arrangement and referred to as “linear” epitopes. This literal description indicates that epitopes are in line and therefore antibody binding is not dependent on folding. In turn, this has an effect on the allergenicity of the protein. For example, children with IgE antibodies specific for sequential epitopes of major egg proteins seem to have more persistent allergy.⁵⁸ Similar findings have been seen with respects to cow’s milk protein, where children who had persistent allergy were more likely to have milk-specific antibodies recognizing linear epitopes than children who experienced transient allergy.⁵⁹

However, given the various protein components of egg have differential ability to elicit reactions, it stands to reason that many allergic children should be able to tolerate extensively heated versions of these foods. This can help reduce the substantial burden of complete dietary elimination. One study in milk-allergic children ages 2 to 17 years showed that 75% of the children tolerated baked but not unheated milk.⁶⁰ In a double-blinded, placebo-controlled study of over 70 children with egg allergy, more than half tolerated heated egg white even though they failed a challenge with unheated egg.⁶¹ Many of

the children eating extensively heated egg also seemed to acquire tolerance to the unheated egg more rapidly than children who were not regularly eating the heated food. Another study showed that children who tolerated heated milk initially were almost 30 times more likely to tolerate unheated milk compared to children who did not tolerate heated milk early on.⁶² Thus, introduction of extensively heated egg and milk may be a relatively low-risk way by which tolerance can be induced. Gradual introduction of a “modified” version of an allergenic protein seems to allow for more rapid acquisition of tolerance to various structural variations of that protein.

Oral Immunotherapy

For many years, the process of allergen immunotherapy has been utilized to induce tolerance to aeroallergens, venoms, and medications. Recently, similar strategies have been applied to food allergy. Immunotherapy usually involves introduction of increasing amounts of allergen to reduce the risk of reaction over time. The first double-blinded, placebo-controlled study of peanut immunotherapy via the oral route was published in 2011. Eighty-four percent of the study participants completed the protocol, which involved ingestion of increasing amounts of peanut protein over time. Ultimately, these subjects were able to tolerate the equivalent of roughly 20 peanuts.⁶³ Those receiving placebo developed symptoms on ingestion of the equivalent dose of 1 peanut. Certainly this level of tolerance can allow for significantly reduced morbidity in the context of accidental ingestions. Injectable epinephrine was required for 2 of 19 subjects on the day of their initial introduction, raising questions about safety of this treatment strategy. A review of 6 case series with similar oral immunotherapy protocols, representing 85 subjects in total, showed that oral immunotherapy was a “promising new therapy for short- to medium-term management of carefully selected and monitored patients with peanut allergy.”⁶⁴

Similar work has been done for children with egg allergy. In a double-blinded, randomized, placebo-controlled study, 75% of children in the oral immunotherapy group were considered desensitized by 22 months on the protocol.⁶⁵ Three years after initiation of the protocol, all of the children who had passed a challenge at 2 years were regularly consuming egg. In this study, adverse events occurred most often in the first year of immunotherapy. None of these were severe and for the most part were restricted to local oropharyngeal symptoms. However, it is notable that these occurred in about 25% of the doses ingested during the first year of oral immunotherapy. The frequency of these symptoms decreased to less than 10% after about a year of therapy.

The underlying immunologic dynamics that occur during oral immunotherapy are fascinating. A very recent study echoed and duplicated prior work, suggesting that peanut oral immunotherapy resulted in the reduction of peanut-specific IgE in subjects on treatment.⁶⁶ Concurrently, IgG4, a subclass of IgG, seems to increase during treatment and likely inhibits binding of IgE, which suggests a “blocking” effect. Peanut oral immunotherapy leads to suppression of basophil activity in the context of allergen exposure.⁶⁷ Basophils play a significant role in food allergy as they express the high affinity receptor for IgE and have granules containing similar mediators to those found in mast cells.⁶⁸

These studies provide a very promising foundation for future food allergy therapy. Ongoing trials are currently being undertaken to understand the longevity of tolerance induced via this method. In addition, strategies are being investigated to improve safety for this type of introduction.

Other Possible Strategies

Other approaches are being investigated as potential therapies for food allergy. Unlike the above, these are not food allergen specific and do not carry the inherent risk of potential food-related reactions. Anti-IgE antibody therapy, widely used to treat allergic

asthma, has been used in trials to treat food allergy. In one study, almost half of subjects in the anti-IgE-treated group were able to tolerate the goal dose of peanut at 24 weeks of treatment compared to placebo.⁶⁹ This study was stopped early due to 2 severe episodes of anaphylaxis during peanut challenges. As anti-IgE therapy is known to reduce serum-free IgE levels overall, active therapy may simply reduce the relevant antibody that drives the reaction. Sustainability off therapy, however, is not known.

In animal models, a mixture of 11 herbs referred to as the Food Allergy Herbal Formula (FAHF-1) has been studied as a novel method through which peanut-allergic animals may be protected against anaphylaxis. This mixture was identified due to its prior use in managing symptoms of intestinal parasite infections and gastrointestinal conditions. For peanut-allergic mice treated twice daily over 7 weeks after sensitization with FAFH-1, none experienced anaphylaxis during a peanut challenge. This was compared to the placebo-treated group who showed clear evidence for anaphylaxis by widely accepted assessment methods.⁷⁰ Based on this and other animal model studies, treatment trials using a modified formula, FAHF-2, have been initiated in human participants. A multicenter trial is underway to study the safety of this potential treatment in humans and to identify and characterize its active constituents.⁷¹

Vaccines have also begun to be investigated as a means through which the immune system can be “educated” to tolerate food proteins. These food proteins can be altered so as not to trigger an IgE-mediated reaction, but perhaps, instead, to elicit an immunologically tolerant response. Early trials are underway with vaccines containing modified peanut protein.⁷²

Each of these potential therapies provides hopeful alternatives to the current accepted practice of dietary restriction. However, none of them is ready for integration into widespread clinical practice. In due time, though,

these may provide alternative means through which food allergy can be managed and, perhaps, ultimately cured.

Conclusion

Food allergy continues to be an issue with significant public health consequences. Its repercussions have extended to schools, airlines, restaurants, and many other public settings. For many years, it seemed that the “epidemic” of food allergy would be unstoppable, with only restriction of foods available as reasonable therapy. However, there have been significant advances in both the understanding and treatment of food allergy. While it seems like a relatively simple problem, food allergy clearly involves a complex interplay of genetics, environment, food preparation, and many other factors. Each of these variables contributes input to the intricate equation of food tolerance. As our understanding of food allergy increases, so does the concept of acquisition of tolerance. In due time, perhaps allergy can be avoided completely and tolerance will prevail as the default food reaction.

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