

Food Allergy and Anaphylaxis

Corinne A. Keet, MD, MS, Robert A. Wood, MD*

*Department of Pediatrics, Johns Hopkins School of Medicine, CMSC 1102,
600 North Wolfe Street, Baltimore, MD 21287, USA*

Food allergy is the most common cause of anaphylaxis. Up to one-fifth of the United States population avoids a food at some point because of concern about allergy, while 4% to 8% of children and 1% to 3% of adults have food allergy confirmable on testing [1–6]. For reasons that have not been explained fully, the incidence of food allergy is rising rapidly, and allergies may be getting more severe. Food allergy can be life-threatening and has effects on quality of life similar to other chronic diseases [7]. Although understanding of the immune system has advanced tremendously in recent years, basic mechanisms of tolerance and allergy remain obscure. New therapies hold hope for prevention, amelioration, and even cure.

Pathophysiology of food allergy and anaphylaxis

Tolerance

Understanding the normal and pathologic immune response to food allergens is a key part of understanding anaphylactic reactions to food. Unfortunately, mechanisms of both tolerance and sensitization have yet to be elucidated fully. Oral tolerance is thought to occur through various methods, including clonal anergy and deletion, active suppressive measures, and conversion of T helper cell 2 (Th2) responses to T helper cell 1 (Th1) and the more recently described T helper cell 3 (Th3) responses [8]. The relative contribution of each of these mechanisms is controversial, and may depend on the dose and route of administration of the foreign protein. At low doses, suppression may be accomplished by activation of regulatory T cells [9]. At higher doses, anergy and clonal deletion are likely the mechanisms of tolerance. Lack of inflammatory costimulatory signals may be a key component of these mechanisms. Antigen presenting cells (APCs), such as active

* Corresponding author.

E-mail address: rwood@jhmi.edu (R.A. Wood).

dendritic cells, activated macrophages, and activated B cells, present T cells with antigen and the appropriate costimulation for an inflammatory response; nonprofessional APCs, such as resting dendritic cells, epithelial cells, and naïve B cells are thought to induce tolerance in T cells [10]. These non-professional APCs are found in large numbers in the gut, perhaps explaining the long-time observance that systemic tolerance can be induced by oral administration of allergen. Regulatory cytokines, such as interleukin (IL)-4, IL-10, and transforming growth factor (TGF)-beta, are produced by the tolerized T cells and are important in maintenance of tolerance [8].

The allergic immune response is characterized by Th2 polarization. IL-4 and 5, which are produced by Th2 cells, promote class switching of B cells, and thus IgE production and eosinophilia [8]. Clinically, allergic diseases can be subdivided into those that are IgE-mediated, such as anaphylaxis, atopic dermatitis, and allergic asthma, and those mediated by the cellular immune system, such as eosinophilic gastroenteritis.

The developing immune system

Many factors likely contribute to the failure of development of tolerance in allergy, including immature gastrointestinal (GI) and immunologic systems in infancy, lack of normal infectious stimuli, specific patterns of allergen exposure, and genetic factors. Infants have an immature mucosal surface, with increased intestinal permeability and decreased gastric acid and pancreatic enzyme production. Thus, allergenic proteins are more likely to be absorbed intact in infants than in older children and adults [9].

In addition to the GI system, the immune system is also immature in infants. The newborn's immune system is skewed toward Th2 responsiveness. Normally, the balance between T helper cells shifts toward a Th1-dominated response to food proteins by age 5. In allergic disease, the Th2 response instead is amplified [8]. It is thought that the developing immune system requires particular stimuli for the attainment of this functional oral tolerance. Experiments with germ-free mice show that it is difficult to induce tolerance without intestinal microflora, and that germ free mice lack fully developed gut-associated lymphoid tissue, which may play a role in suppression and anergy [11]. In people, observational data point to a protective effect of certain types of early childhood infections. There is now a body of evidence that shows that having older siblings, living on a farm, and early daycare are protective against allergic disease [12,13]. For specific infections, the data are mixed, suggesting that certain infections are protective, while others may increase the risk of allergic disease [14].

Manner of allergen exposure

Type, frequency, and route of exposure to allergens are factors in development of a pathologic response to food, although the specific ways that

exposure affects allergy remain unclear. Some of the previous suppositions about sensitization have been challenged recently, with implications for attempts at primary prevention of food allergy. Consumption patterns certainly explain some of the geographical differences in rates of food allergy. Peanut allergy rates are higher in countries like the United States and United Kingdom, where rates of consumption are high. Shellfish, fish, and sesame allergy are much higher in areas where these foods are staples of the diet. Some have suggested that the increasing rate of peanut allergy is caused by increased consumption of peanut by pregnant and lactating women, and by earlier exposure to peanut in children's diets, although this is controversial [15]. Exposure levels themselves, however, do not explain population differences in allergy, much less why an individual will become allergic.

Both quantity and conformation of allergic proteins can be changed by gastric breakdown. Interruption of the normal gastric breakdown of proteins by antacid administration has been shown to increase IgE levels against dietary proteins [16]. This may be caused by degradation of allergens by gastric acids, as for example, with parvalbumin, the major fish allergen, which has been shown to bind to IgE with less avidity, and to trigger histamine release at much lower levels after exposure to gastric acids [17]. The relative lack of gastric acidity in infants may be yet another reason that they are at such high risk for food allergy.

Sensitization to food allergens is not limited to the gut. Use of peanut oil-containing body products in infants has been associated with a higher rate of peanut sensitization [18]. For shellfish allergy, a growing body of evidence links dust mite and cockroach aeroallergy to sensitization to shellfish. One of the allergenic proteins shared by dust mite, cockroaches, and crustaceans is tropomyosin. A study of orthodox Jews who had never consumed shellfish, but were sensitized to dust mite, found a high rate of skin prick sensitivity to shellfish, indicating that sensitization can happen without direct contact with shellfish [19]. This may help explain why shellfish allergy, in contrast to most other allergy, begins at later ages. The pollen—food allergy syndrome is perhaps the clearest example of aeroallergy causing food allergy. This typically mild allergy affects about one half of pollen-allergic adults, and consists of oral symptoms on exposure to raw fruits, vegetables, and nuts in patients who are allergic to pollen that shares homologous proteins with the foods [20].

The role of cross reactivity, timing of exposure, and type of allergen exposure in development still are being worked out. At this time, a unified theory explaining the role of exposure in development of allergy remains elusive.

Genetics

Genetic risk factors are also important for the development of food allergy. Peanut allergy is more common in siblings of peanut-allergic

patients than the general population [15], much more common in monozygotic twins than in dizygotic twins [21], and more common in children of atopic mothers. Atopic disease, in general, has been shown to be genetically determined, at least in part [22,23]. Linkage analyses have provided candidate areas of interest on the human genome [24], but the specific genetic basis for allergic disease has yet to be found, and allergy is likely polygenic.

Anaphylaxis

The pathophysiology of anaphylaxis is reviewed in more detail in the article by Brown elsewhere in this issue. Anaphylaxis to food is a multiorgan system response that occurs when antigen binds to membrane-associated IgE on mast cells and basophils, causing the release of inflammatory mediators. The mediators of anaphylaxis include histamine and other products of arachidonic acid metabolism, proteoglycans such as heparin, and neutral proteases such as tryptase and chemo-attractants. Histamine, which can reproduce most of the symptoms of anaphylaxis when administered intravenously to laboratory animals, binds to both H1 and H2 receptors. This causes smooth muscle spasm and vasodilatation and increases vascular permeability, eosinophil activation, and other effects. Tryptase and the other neutral proteases have various effects, including further activation and degranulation of mast cells [25].

There is some evidence that the pathophysiology of food-induced anaphylaxis differs from that of other types of anaphylaxis. In contrast to fatal venom- and drug-induced anaphylaxis, death by food-induced anaphylaxis almost always is caused by respiratory collapse. Distributive shock is seen infrequently, and almost never is seen in isolation. Some have suggested that basophils, rather than mast cells, are the predominant cells involved in severe food anaphylaxis. One piece of evidence for this is the apparent less frequent elevation of tryptase in cases of severe food-induced anaphylaxis [26–28]. Tryptase is concentrated preferentially in mast cells, rather than in basophils, whereas histamine and other mediators are found in both cells. In a series described by Yunginger and colleagues [29], only six of eight food-induced anaphylaxis victims had an elevation of tryptase, compared with nine of nine with hymenoptera stings, and two of two fatalities caused by diagnostic agents. Sampson and colleagues [28] reported on serial measurements of tryptase in five cases of food-induced anaphylaxis in 1992. In only one measurement was tryptase elevated above 2.5 ng/mL, and in that case only slightly so. These were very small series, however, and the data are mixed [30]. Whether these findings indicate true pathophysiological differences in the role of basophils versus mast cells remains to be elucidated. In the absence of further data, tryptase, which has been advocated as a diagnostic tool for anaphylaxis, cannot be said to be a reliable diagnostic tool for cases of food-induced anaphylaxis.

Epidemiology

The epidemiology of anaphylaxis is discussed in more detail in the article by Camargo and Clark elsewhere in this issue. To date, there have been no large-scale prospective studies of the incidence of anaphylaxis. Retrospective analysis in one county, Olmstead, Minnesota, placed the incidence at 21 per 100,000 person-years [31]. In another study of children in a large health maintenance organization (HMO), the incidence ranged from 10.5 per 100,000 person-years (range 8.1 to 13.8 per 100,000 person-years) using the most specific codes, to an estimated 68.4 per 100,000 person years if nonspecific codes were used [32]. In the United Kingdom, analysis of Health Service data gave a crude estimate of 8.4 per 100,000 person-years [33]. The diagnostic criteria for anaphylaxis remain controversial, and the diagnostic codes for anaphylactic reactions to food have been shown to miss many true cases of anaphylaxis, while capturing cases that are not anaphylaxis [32]. Consensus definitions of anaphylaxis will be required before a true estimate of incidence can be made. Based on the most conservative estimate, about 25,000 cases of anaphylaxis occur each year in the United States.

Contribution of food allergy to anaphylaxis

The contribution of food allergy to anaphylaxis varies across series, ranging from 15% to 57% of cases of anaphylaxis [33–38]. Nuts, fish, and shellfish are consistently the most common food allergens triggering anaphylaxis, with dairy, eggs, fruits, and vegetables also common causes. As discussed previously, the relative contribution of these foods varies by age and geography, according to both the natural history of food allergy and the patterns of exposure. Foods that frequently cause anaphylaxis in one region may not be a part of the diet in another part of the world.

Incidence and prevalence of food allergy

As with anaphylaxis, determining the true incidence of food allergy is hindered by a lack of uniform definitions, geographical and age heterogeneity, and lack of standardized reporting. Unlike anaphylaxis, however, there are several prospective studies of the incidence of food allergy. In a classic study, Bock [6] followed 480 children from birth to age 3. Adverse reactions to foods were described by parents in 28% of children, but in only 8% were these symptoms reproduced in open or blinded food challenges. Thirty-five percent of 3623 children were reported to have at least one adverse reaction to a food by age 2 in a series of surveys done by Eggesbo and colleagues [39]. These reports were not confirmed by food challenge or further testing, however. Venter and colleagues [40] followed 969 children from birth to 12 months. Overall, adverse reactions to food were reported in one quarter of children, and were confirmed in 4% of children. Rates of self-reported food allergy are lower in older children and adults, although, in general, still

substantially higher than confirmed rates. Rates of self-reported allergy range from 4.6% to 22% across developed countries. When confirmed by skin testing, history and/or food challenge, the rates of food allergy are 1.5% to 3.2% in older children and adults [1–5].

To both physicians and the lay public, food allergy seems to be increasing at an alarming rate. This anecdotal feeling is confirmed by epidemiologic studies. Sicherer and colleagues [41] conducted telephone surveys of United States households to assess for the rate of nut allergy. They used the same methodology in 1997 and 2002, and found a 100% increase in the rate of nut allergy [41,42]. Other atopic diseases, in general, also are increasing, although it appears that this increase has been occurring over a somewhat longer time period [43].

This rapid increase in prevalence makes it difficult to precisely define the prevalence of nut allergy. The survey studies done by Sicherer found a rate of 1.2% of overall nut allergy in children in 2002 [41]. Other surveys and studies that confirmed allergy by testing have found rates of nut allergy between 0.5% and 1.5% of the overall population of the United States and United Kingdom [41,42,44].

In contrast to peanut and tree nut allergy, in which children have a rate of allergy greater than or equal to that of adults [44], adults are more than four times as likely as children to have a convincing history of reaction to shellfish. In a survey of 5529 households and 14,948 individuals, convincing shellfish allergy was reported in 2.5% of adults and 0.5% of children, with an overall rate of 2.0% in the population as a whole. Fish allergy, which is immunologically distinct from shellfish allergy, was reported in 0.2% of children and 0.5% of adults in that same study [45].

Cow's milk allergy is estimated to effect 2% to 3% of infants in the developed world [46–48], with a sharp drop off after age 1. Data from a population study of allergy in general placed the rate of hen's egg allergy at 1.6% in children, but the rate of sensitivity is much higher in children who have eczema [5,49].

Natural history

Cow's milk

Cow's milk is the first allergen to which infants commonly react. Both IgE and non-IgE mediated allergic reactions are common, especially in infancy. Although allergy occurs in 0.5% of breastfed infants, it is much more common in formula-fed infants, often occurring in the first week after introduction of cow's milk-based formulas [48]. GI and cutaneous reactions are most common, while respiratory symptoms develop in 20% to 30% of patients [46,50]. In population-based studies, approximately one half of infants with both IgE- and non-IgE-mediated cow's milk protein allergy

recovered completely by 1 year of age. Sixty percent to 75% recovered by age 2, and 85% to 90% recovered by age 3 [47,48]. For those referred to an allergist for care, the prognosis is worse. In series from allergists' offices, recovery rates vary widely, with 22% to 67% of children with IgE-mediated milk allergy and 38% to 86% of non-IgE-mediated milk allergy recovering during follow-up [51]. As these data show, children with non-IgE-mediated milk allergy have earlier and more complete recovery. Despite the generally high rates of recovery from cow's milk allergy, these patients have a high risk of developing other allergies, with 50% developing adverse reactions to other foods by age 3, and 50% to 80% developing inhalant allergies [47,48].

Egg, wheat, and soy allergy

Egg allergy has been studied less than cow's milk allergy, but it is thought to recede by school age [39,51–53]. Egg allergy is associated strongly with atopic dermatitis, and egg-allergic children have more severe and persistent atopic dermatitis [54]. There is even less study devoted to wheat and soy allergy. From the larger studies of allergy development and persistence in general, it appears that these allergies frequently are lost by the age of 3 [6,55,56].

Peanuts and tree nuts

As children grow, peanut and tree-nut allergies remain among the most important food allergies. In a registry of 5149 people who had peanut or tree nut allergy, the median age of reaction to peanuts was 14 months, and the median age of reaction to tree nuts was 36 months. Before the first allergic reaction, there was no known previous exposure in 74% of peanut- and 68% of tree nut-allergic subjects. Anaphylaxis was commonly the manifestation of allergy, with more than one half of subjects reporting greater than one organ system's involvement [57]. It should be emphasized to clinicians and patients that at each subsequent reaction, a higher proportion of patients had severe symptoms and required treatment with epinephrine [58,59].

Until recently, it was thought that peanut and tree nut allergies were universally life-long. This thinking has been revised. It now is understood that approximately 20% of children outgrow peanut allergy, including some who previously had anaphylactic reactions and high initial peanut IgE. Patients who are able to successfully strictly avoid peanuts are more likely to outgrow their allergy, but initial reactivity, atopic disease, and other food allergies have not been shown to predict consistently whether a patient will outgrow peanut allergy [60]. Rechallenge may be appropriate when peanut IgE falls to 5 kua/L or lower, when more than half may be expected to have outgrown their allergy, and is even more likely to be successful at peanut

IgE levels less than 2 kua/L. Eight percent of children who outgrow their peanut allergy have a recurrence, and this risk is higher for those who continue to avoid peanut after passing a food challenge [61]. For tree nut allergy, approximately 9% outgrow their allergy. Fleisher and colleagues [62] recommend that patients 4 years or older with tree nut IgE levels less than or equal to 5 kua/L be considered for food challenge.

Shellfish allergy

Although data directly reporting the age of onset of shellfish allergy are not available, the natural history can be inferred from data showing that shellfish allergy is reported in only 0.1% of children aged 0 to 5 years and 0.8% of children aged 6 to 17 years, but is reported in 2.6% and 3.3% of 18- to 40-year-olds and 41- to 60-year-olds, respectively [45]. It generally is thought that shellfish allergy is permanent, although no studies systematically addressing this hypothesis are available.

Clinical presentation of food-induced anaphylaxis

Timing of onset

Anaphylaxis to food typically develops rapidly after exposure. In a series of children with anaphylaxis referred to an allergist, 57% of whom had reacted to food, the mean latent period between ingestion and symptoms was 15.4 minutes [63]. In a series of fatal and near-fatal cases of anaphylaxis caused by food, all had symptoms within the first 30 minutes after exposure, most within the first 5 minutes [28]. In contrast, for allergic reactions to food presenting to the emergency room, the latent period is longer, in general, with a median of 2 hours [64]. The more severe the reaction, the earlier it seems to occur after exposure [28].

Symptoms

The skin and respiratory system are the most commonly affected systems in food-induced anaphylaxis, with symptoms in 76% and 80%, respectively, of children in one series. Skin manifestations are not limited to urticaria, and can include generalized flushing. The GI system is involved more often than in other types of anaphylaxis (41% of food-induced anaphylaxis compared with 3.7% of food-independent anaphylaxis in that same series) [63]. Initial cardiovascular involvement is rare, and it is atypical for a patient to have isolated cardiovascular symptoms without respiratory arrest, even in severe or fatal cases [28,63,65,66].

Time course of reactions

Reactions can be uniphasic, biphasic, or protracted. Limited evidence suggests that biphasic reactions may be more common in cases of enteral

allergen exposure compared with parenteral allergen exposure [67]. Biphasic and protracted reactions were each reported in 3 of 13 cases of near-fatal or fatal food-induced anaphylaxis by Sampson and colleagues [28]. Biphasic reactions may be more common in cases of inadequate or delayed epinephrine administration [67].

Food-induced fatalities

Fatal anaphylactic reactions to food are the most feared outcome of food allergy, but they occur only rarely. Yunginger and colleagues [27] compiled the first case series of fatal food-induced anaphylaxis, providing a description of seven patients who died within a 16-month period throughout the United States. This was followed by series of six children and adolescents who had fatal reactions to food and seven who nearly died identified by Sampson and his colleagues in 1992 [28]. In 2001, Bock and colleagues [68] reported on 32 fatal cases of anaphylaxis that were reported to the Food Allergy and Anaphylaxis Network (FAAN) between 1994 and 1999. Although small, and with designs that likely do not capture atypical reactions or those that occurred in individuals without a history of food allergy, these series identify several risk factors of importance for fatal food-induced anaphylaxis.

Asthma

Most salient in these descriptions is the history of asthma in almost all patients with fatal anaphylactic reactions. In Yunginger's report, all four patients for whom history was available had a history of asthma [27]. All 13 patients in Sampson's report had a history of asthma, and in Bock's study, only one patient for whom a history was available did not have a history of asthma [28,68]. The importance of history of airway hyper-reactivity is underscored by the fact that respiratory arrest is the mechanism of almost all food-induced anaphylaxis fatalities [66].

Foods most commonly causing fatalities

Nuts are the cause of most fatal cases of anaphylaxis to food in the United States and the United Kingdom, with peanuts accounting for 50% to 62% of fatalities, and tree nuts accounting for 15% to 30% of fatalities in several series [27,28,66,68]. Other causes of fatal reactions have been shellfish, fish, milk, eggs, and fruit. Nearly all patients had a known history of allergy to the food to which they had a fatal reaction, but before reaction, nearly all subjects did not know that the food to which they were allergic was an ingredient in the food they were about to consume. Restaurants and educational settings were the most common locations of fatal reactions.

Baked goods and candy, Chinese food, and Mexican food were the most common foods that contained the undisclosed ingredients [27,28,68].

Lack of timely treatment

Despite the prior history of food allergy in almost all patients, and the history of severe reactions in many, lack of immediately available epinephrine was another factor that most fatalities shared. Of 32 patients in Bock's series, only four were known to have received epinephrine in a timely way [68]. None of the seven patients in Yunginger's series or the six patients in Sampson's series were given epinephrine immediately after symptom onset. Many of the patients did, however, take oral antihistamines, apparently believing that this medication would be sufficient treatment [27,28].

Diagnosis

The diagnosis of an anaphylactic episode is reviewed in detail here and in the article by Kemp elsewhere in this issue [69]. Anaphylaxis usually is defined by the involvement of two or more organ systems, and is characterized by:

- Respiratory symptoms, including wheeze and stridor
- GI symptoms, including abdominal pain and vomiting
- Cutaneous symptoms, such as urticaria, flushing, and angioedema
- Cardiovascular symptoms, such as hypotension and shock

For individuals with a history of allergic reaction, fewer symptoms are required for definition if the individual has a suspected exposure. A high index of suspicion for anaphylaxis should be maintained, as cases can present atypically [69].

Determining which, or if, food caused an anaphylactic episode is not always obvious by history alone. Allergens commonly are mixed with other, nonallergic foods, so identification of the specific allergen can be initially challenging. The most important diagnostic aids are measurements of IgE levels and skin tests. Food challenge is the gold standard for diagnosis of food allergy, but is often not necessary in cases where history and diagnostic testing are strongly suggestive of a food allergy. Attempts to use these tests to predict severity of community reactions have been mixed.

Skin testing

Skin puncture or prick testing historically has been the mainstay of diagnosis for IgE-mediated food allergy. Purified allergen is introduced percutaneously, and the resulting size of reaction is measured. Traditionally, a reaction of more than 3 mm has been considered positive. The sensitivity of skin testing is high, but specificity is poor, and in many clinical

populations the positive predictive value for clinical reaction is low. Attempts to improve the specificity by setting higher cutoffs have been mixed, but, in general, the larger the reaction, the more likely a patient is to have a clinical response on food challenge [70,71]. Skin testing is not recommended in patients who have severe skin conditions that could interfere with the test, who are pregnant, or who are taking medicines, such as antihistamines, that can interfere with skin reactivity. Infants have smaller reactions, reducing the sensitivity in this age group [72].

IgE levels

Whereas skin tests are a measure of bound IgE, serum tests of IgE directly measure circulating IgE. Like skin tests, IgE assays are more sensitive than specific. Perry and colleagues [73] looked at a retrospective series of children who had food challenge and IgE levels available. They determined that the 50% food challenge pass level was 2 kua/L for milk, egg, and peanut, while the data were less clear for wheat and soy [73]. Sampson and Ho [74] reported on the IgE levels where 95% of subjects had a positive food challenge and found that they were: egg (6 kua/L), milk (32 kua/L), peanut (15 kua/L), and fish (20 kua/L) [75]. For a given patient, the positive predictive value of these tests will depend on the likelihood that the patient's history was consistent with an allergic reaction to a specific food.

Food challenge

When the cause of an anaphylactic episode remains obscure, either because of continued reactions despite following an elimination diet, or because of nondiagnostic history and testing, a food challenge may be appropriate. Food challenges can be open, single-blinded (to the patient), or double-blinded (to both the patient and physician). For diagnosis of foods thought to be responsible for an anaphylactic reaction, open challenges are generally reasonable. These challenges should happen under physician supervision, and where emergency equipment is available.

Severity index

Currently, IgE levels, skin prick tests and food challenges, are used as dichotomous tests, giving the patient and clinician an answer only to the question of whether a patient is likely to react to a food in the community, but have not been used to predict the severity of possible reactions. The search to evaluate whether these tests have qualitative predictive value is hindered by the lack of standardized systems for reporting severity. Hourihane and his colleagues [76] have developed a scoring system for reactions to peanut in the community or during low-dose double-blinded placebo-controlled food challenge (DBPCFC); in this system the estimated dose of exposure and the extent of systems elicited are included in the score. When they

used this severity index, they did not find a significant correlation between severity scores in the community or on DBPCFC and IgE or skin tests. Vander Leek and colleagues [59] did find that children who had only skin reactions on exposure to peanut had significantly lower levels of IgE than those who had more severe reactions, but overlap of IgE levels between groups negated any clinical relevance for the individual patient. Similarly, Spergel and colleagues [77] did not find any significant relationship between size of skin wheal and severity of reaction on food challenge. Wensing and colleagues [78] found a relationship between threshold dose on DBPCFC and severity of reaction in the community, but while Hourihane and his colleagues [76] also found that the severity of reaction in the DBPCFC was related to the severity of the most recent community reaction, this association was weak ($r = 0.37$, $P = .03$). One reason for this lack of association is that the dose of community exposure varies widely. At this time, the severity index has found utility only for research. Clinical features such as asthma (as outlined previously) are currently the best predictors of a severe reaction.

Treatment

Treatment of anaphylaxis is reviewed in more detail in the article by Simons elsewhere in this issue and in a recent Joint Task Force on Practice Parameters [69]. Currently, the main approaches to food-related anaphylaxis are avoidance of triggers, and, when that fails, timely administration of epinephrine. Children especially, require close monitoring to ensure that nutrition is adequate, to continue education, and to assess for remission of allergies.

Avoidance

Patients, and when appropriate, their parents, should be educated about the need for allergen avoidance and potential pitfalls. They should be taught about foods that are most likely to contain hidden ingredients. For peanuts, tree nuts and milk, those foods are baked goods, candy, and snack foods. Eating in restaurants can be particularly challenging, and patients should be educated about the importance of communicating with restaurant staff about ingredients. Asian and Mexican restaurants have been common sites of hidden nuts and should be approached with care [28,68].

Label reading is an important skill that must be imparted. New regulatory requirements for food labeling came into effect in 2006, with the Food Allergen Labeling and Consumer Protection Act (FALCPA). This act requires that sources of ingredients derived from commonly allergenic sources be labeled using “plain English language.” For purposes of this law, milk, eggs, fish, crustacean shellfish, peanuts, soybeans, wheat, and tree nuts are identified as the most common allergenic foods. Highly refined

oils are exempted [79]. These regulations do not address accidentally included ingredients. Although there are no regulations mandating labeling of nonintentional ingredients, companies have adopted systems that identify such potential exposures. In the United States, commonly used labels are “may contain,” “manufactured on shared equipment with,” and “manufactured in shared facility with.” Patients who have had an anaphylactic reaction to an allergen should avoid food that is labeled with “may contain” and “manufactured on shared equipment with” for that allergen. Whether a patient should avoid food labeled “manufactured in a shared facility with” depends on the particular allergen, and the patient’s individual medical history.

Highly processed foods

Because processing can affect the level of allergenic proteins in end products strongly, the new labeling requirements may cause unnecessary dietary restrictions. Current labeling may cause overavoidance of some foods. For example, fish-allergic individuals have been shown to tolerate high levels of fish gelatin [80]. Soy lecithin and soy oil, which are common ingredients in various processed foods, contain only very small amounts of soy allergen [81]. The new regulations require only that a food be labeled “contains soy,” “contains fish,” and similar labels, which leaves the allergic patient to guess if a food contains a significant amount of the labeled allergen. Although the new requirements are an improvement over the state of labeling previously, where allergens could go unlabeled or be lumped under the term “natural flavoring,” they do not ensure complete clarity regarding the potential risks of processed foods to allergic patients [82].

Threshold doses

For both the individual food-allergic patient and the manufacturing industry, determining threshold doses of allergic proteins below which most of the food-allergic population is unlikely to react is a way toward clarity regarding allergen avoidance and labeling [82,83]. Although there is a body of literature available that relates to threshold doses for some of the major allergens, including peanut, cow’s milk and egg, a roundtable conference of prominent allergists in 1999 was not able to produce a consensus statement regarding threshold doses for even those foods. Reported series of food challenges use different forms of allergen, generally exclude patients who have a history of severe reactions, define positive results in different ways, and start with different quantities of allergic foods. Many patients react to the first administered dose of allergen, which likely results in systemic overestimation of threshold doses for reaction [84]. In response to these problems, a roundtable of prominent food allergists was convened in 2002 to establish consensus recommendations for design of studies of threshold

doses. They agreed on a format for these studies and suggested ways to systematically assess threshold levels for antigens [85].

In the studies done up to the time of the consensus recommendations, reactions were reported during food challenges to as little as 1 mg of peanut, 1 mg of egg, 0.02 mL of milk, 5 mg of fish, and 1 mg of mustard [84].

Resources

The impact of food allergy on quality of life has been shown to be similar to other chronic diseases [7], and patients need ongoing support. FAAN is source of reliable information and support services. (www.foodallergy.org or 1-800-929-4040). As patients become teenagers, they are at highest risk for severe anaphylactic reactions, and basic avoidance techniques may need to be revisited by their primary care physicians and allergists [27,28,66,68].

Epinephrine

When avoidance has failed, and an anaphylactic reaction ensues, epinephrine is the mainstay of treatment. Lack of timely epinephrine treatment is a common factor in fatal anaphylactic reactions [28,29,68]. Even after the patient is in the emergency department, epinephrine infrequently is given during acute attacks [35,64,65]. In a recent multicenter study of anaphylaxis treatment in emergency rooms in the United States, less than one quarter of patients with severe anaphylaxis were given epinephrine. Physicians do an even poorer job of prescribing self-administered epinephrine to patients who are at risk for anaphylaxis [64]. All patients who have potential for anaphylactic reactions should have ready access to epinephrine wherever they are, and prescriptions should be given at the time of emergency treatment for food allergy. Use of self-administered intramuscular epinephrine should be taught to patients and/or their parents, and enough should be prescribed so that it is available at all locations where they commonly spend time. Patients should give themselves epinephrine at the first sign of a potential anaphylactic reaction to a food, and proceed immediately to an emergency room. Because many patients will require more than one dose of epinephrine, twin or dual packs of epinephrine are being marketed; patients would self-administer another dose of epinephrine if they still had anaphylactic symptoms 10 minutes after the first dose. Although these packs may be helpful, they are not a substitute for emergency medical attention. In addition, health care providers need to emphasize to patients that antihistamines are not effective for sole treatment of anaphylactic reactions.

Continued monitoring

Because such a high percentage of children allergic to milk, egg, soy, and wheat outgrow their allergies, early and frequent monitoring to assess for

remission is warranted, as described previously. Nutritional monitoring is vital, especially in children allergic to milk or wheat. At each visit, patients should be asked about which foods they have been avoiding, and diets should be assessed to make sure that they adequately provide both macro- and micronutrients. Height and weight should be compared with growth curves, as these children are at risk for malnutrition [86].

Future directions for therapy

Recent years have seen the initial development of several promising strategies for food allergy treatment. Because there is not space to discuss all of the avenues of current research here, this article focuses on a few treatments that have shown early successes.

One area of active interest has been the use of anti-IgE therapy for peanut allergy. In 2003, Leung and colleagues [87] described a double-blind placebo-controlled study of TNX-901, a monoclonal antibody that binds to IgE, preventing interaction of IgE with mast cells and basophils. TNX-901 was given subcutaneously every 4 weeks. After 4 months, oral food-challenge threshold doses of peanut increased for all dosages of TNX-901, although only by a significant amount in the group given the highest dose (450 mg). In that group, the threshold for reaction to peanut increased from approximately one half peanut to almost nine peanuts [87]. Although this experimental drug was tolerated well, it suffers from several limitations. Monoclonal antibody pharmaceuticals are very expensive. The duration of effect was not studied; theoretically, protection is likely to wane quickly as antibodies degrade. Thus, patients would need regular injections indefinitely. Moreover, although threshold doses for reaction increased, peanut allergy was not cured, and peanuts must still be avoided.

Given the success of immunotherapy for inhaled allergens, it might be thought that immunotherapy for food allergy would be a logical treatment modality. Although subcutaneous immunotherapy was shown to decrease reactivity to peanut in one trial, patients had very high rates of systemic reactions, some severe, during treatment [88]. Sublingual immunotherapy may be an equally effective but safer alternative. Recently, Enrique and colleagues [89] conducted a randomized double-blinded placebo-controlled trial of sublingual hazelnut extract in patients with hazelnut allergy. Fifty percent of the treated patients were able to tolerate the highest tested dose of hazelnut (20 g), and the mean threshold dose increased fivefold. Although localized symptoms to therapy were common, systemic reactions were very rare.

In another attempt to create a safer kind of immunotherapy, researchers are modifying allergenic proteins so that they stimulate T cells without cross-linking IgE and causing mast cell and basophil degranulation. Both peptide fragments and mutated proteins that lack affinity for IgE are being

used. Mutated proteins have proven very effective in a mouse model, while peptide fragments were effective when used in cat-allergic patients [90]. Human trials of using modified peanut protein will be starting this year.

Herbal treatments for food allergy long have been used in China, and are another potential therapy for food allergy being evaluated in the United States. In a mouse model of peanut allergy, an herbal formula (FAHF-1) consisting of traditional Chinese herbs completely blocked anaphylactic reactions to peanut without significant adverse effects [91]. Animal studies of the formula and its components are ongoing, and human trials hopefully will start in the next few years.

Summary

As understanding of the physiology of tolerance and allergy advances, prospects for prevention, treatment, and cure of food allergy improve. There are several promising experimental treatments for food allergy in development, and ongoing prospective studies are exploring how allergy may be prevented. In the meantime, avoidance of allergenic foods and timely administration of epinephrine remain the mainstays of treatment for food-allergic patients. Monitoring for proper nutrition and remission of food allergy, as well as continued education and support, are necessary complements to these interventions.

References

- [1] Venter C, Pereira B, Grundy J, et al. Prevalence of sensitization reported and objectively assessed food hypersensitivity amongst six-year-old children: a population-based study. *Pediatr Allergy Immunol* 2006;17(5):356–63.
- [2] Pereira B, Venter C, Grundy J, et al. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol* 2005;116(4):884–92.
- [3] Woods RK, Thien F, Raven J, et al. Prevalence of food allergies in young adults and their relationship to asthma, nasal allergies, and eczema. *Ann Allergy Asthma Immunol* 2002;88(2):183–9.
- [4] Woods RK, Abramson M, Bailey M, et al. International prevalences of reported food allergies and intolerances. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991–1994. *Eur J Clin Nutr* 2001;55(4):298–304.
- [5] Osterballe M, Hansen TK, Mortz CG, et al. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol* 2005;16(7):567–73.
- [6] Bock SA. Prospective appraisal of complaints of adverse reactions to foods in children during the first 3 years of life. *Pediatrics* 1987;79(5):683–8.
- [7] Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol* 2001;87(6):461–4.
- [8] Prescott SL, Macaubas C, Smallacombe T, et al. Development of allergen-specific T-cell memory in atopic and normal children. *Lancet* 1999;353(9148):196–200.
- [9] Nowak-Węgrzyn A, Sampson HA. Adverse reactions to foods. *Med Clin North Am* 2006;90(1):97–127.

- [10] Smith KM, Eaton AD, Finlayson LM, et al. Oral tolerance. *Am J Respir Crit Care Med* 2000;162(4 Pt 2):S175–8.
- [11] Sudo N, Aiba Y, Oyama N, et al. Dietary nucleic acid and intestinal microbiota synergistically promote a shift in the Th1/Th2 balance toward Th1-skewed immunity. *Int Arch Allergy Immunol* 2004;135(2):132–5.
- [12] Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299(6710):1259–60.
- [13] McKeever TM, Lewis SA, Smith C, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. *Thorax* 2001;56(10):758–62.
- [14] Liu AH, Leung DY. Renaissance of the hygiene hypothesis. *J Allergy Clin Immunol* 2006;117(5):1063–6.
- [15] Hourihane JO, Dean TP, Warner JO. Peanut allergy in relation to heredity, maternal diet, and other atopic diseases: results of a questionnaire survey, skin prick testing, and food challenges. *BMJ* 1996;313(7056):518–21.
- [16] Untersmayr E, Jensen-Jarolim E. Mechanisms of type I food allergy. *Pharmacol Ther* 2006;112:787–98.
- [17] Untersmayr E, Poulsen LK, Platzer MH, et al. The effects of gastric digestion on codfish allergenicity. *J Allergy Clin Immunol* 2005;115(2):377–82.
- [18] Lack G, Fox D, Northstone K, et al. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348(11):977–85.
- [19] Fernandes J, Reshef A, Patton L, et al. Immunoglobulin E antibody reactivity to the major shrimp allergen, tropomyosin, in unexposed Orthodox Jews. *Clin Exp Allergy* 2003;33(7):956–61.
- [20] Ma S, Sicherer SH, Nowak-Węgrzyn A. A survey on the management of pollen–food allergy syndrome in allergy practices. *J Allergy Clin Immunol* 2003;112(4):784–8.
- [21] Sicherer SH, Furlong TJ, Maes HH, et al. Genetics of peanut allergy: a twin study. *J Allergy Clin Immunol* 2000;106(1 Pt 1):53–6.
- [22] Rasanen M, Laitinen T, Kaprio J, et al. Hay fever—a Finnish nationwide study of adolescent twins and their parents. *Allergy* 1998;53(9):885–90.
- [23] Lichtenstein P, Svartengren M. Genes, environments, and sex: factors of importance in atopic diseases in 7-9-year-old Swedish twins. *Allergy* 1997;52(11):1079–86.
- [24] Kere J, Laitinen T. Positionally cloned susceptibility genes in allergy and asthma. *Curr Opin Immunol* 2004;16(6):689–94.
- [25] Lieberman P. Anaphylaxis. *Med Clin North Am* 2006;90(1):77–95, viii.
- [26] Lin RY, Schwartz LB, Curry A, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol* 2000;106(1 Pt 1):65–71.
- [27] Yunginger JW, Sweeney KG, Sturner WQ, et al. Fatal food-induced anaphylaxis. *JAMA* 1988;260(10):1450–2.
- [28] Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327(6):380–4.
- [29] Yunginger JW, Squillace DL, Jones RT, et al. Fatal anaphylactic reactions induced by peanuts. *Allergy Proc* 1989;10(4):249–53.
- [30] Low I, Stables S. Anaphylactic deaths in Auckland, New Zealand: a review of coronial autopsies from 1985 to 2005. *Pathology* 2006;38(4):328–32.
- [31] Yocum MW, Butterfield JH, Klein JS, et al. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol* 1999;104(2 Pt 1):452–6.
- [32] Bohlke K, Davis RL, DeStefano F, et al. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004;113(3):536–42.
- [33] Peng MM, Jick H. A population-based study of the incidence, cause, and severity of anaphylaxis in the United Kingdom. *Arch Intern Med* 2004;164(3):317–9.

- [34] Yocum MW, Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994;69(1):16–23.
- [35] Brown AF, McKinnon D, Chu K. Emergency department anaphylaxis: a review of 142 patients in a single year. *J Allergy Clin Immunol* 2001;108(5):861–6.
- [36] Mehl A, Wahn U, Niggemann B. Anaphylactic reactions in children—a questionnaire-based survey in Germany. *Allergy* 2005;60(11):1440–5.
- [37] Thong BY, Cheng YK, Leong KP, et al. Anaphylaxis in adults referred to a clinical immunology/allergy centre in Singapore. *Singapore Med J* 2005;46(10):529–34.
- [38] Pastorello EA, Rivolta F, Bianchi M, et al. Incidence of anaphylaxis in the emergency department of a general hospital in Milan. *J Chromatogr B Biomed Sci Appl* 2001;756(1–2):11–7.
- [39] Eggesbo M, Halvorsen R, Tambs K, et al. Prevalence of parentally perceived adverse reactions to food in young children. *Pediatr Allergy Immunol* 1999;10(2):122–32.
- [40] Venter C, Pereira B, Grundy J, et al. Incidence of parentally reported and clinically diagnosed food hypersensitivity in the first year of life. *J Allergy Clin Immunol* 2006;117(5):1118–24.
- [41] Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random-digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003;112(6):1203–7.
- [42] Grundy J, Matthews S, Bateman B, et al. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002;110(5):784–9.
- [43] Downs SH, Marks GB, Sporik R, et al. Continued increase in the prevalence of asthma and atopy. *Arch Dis Child* 2001;84(1):20–3.
- [44] Emmett SE, Angus FJ, Fry JS, et al. Perceived prevalence of peanut allergy in Great Britain and its association with other atopic conditions and with peanut allergy in other household members. *Allergy* 1999;54(4):380–5.
- [45] Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol* 2004;114(1):159–65.
- [46] Schrander JJ, van den Bogart JP, Forget PP, et al. Cow's milk protein intolerance in infants under 1 year of age: a prospective epidemiological study. *Eur J Pediatr* 1993;152(8):640–4.
- [47] Host A, Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45(8):587–96.
- [48] Host A. Frequency of cow's milk allergy in childhood. *Ann Allergy Asthma Immunol* 2002;89(6 Suppl 1):33–7.
- [49] Giusti F, Seidenari S. Patch testing with egg represents a useful integration to diagnosis of egg allergy in children with atopic dermatitis. *Pediatr Dermatol* 2005;22(2):109–11.
- [50] Martorell A, Plaza AM, Bone J, et al. Cow's milk protein allergy. A multicentre study: clinical and epidemiological aspects. *Allergol Immunopathol (Madr)* 2006;34(2):46–53.
- [51] Wood RA. The natural history of food allergy. *Pediatrics* 2003;111(6 Pt 3):1631–7.
- [52] Heine RG, Laske N, Hill DJ. The diagnosis and management of egg allergy. *Curr Allergy Asthma Rep* 2006;6(2):145–52.
- [53] Ford RP, Taylor B. Natural history of egg hypersensitivity. *Arch Dis Child* 1982;57(9):649–52.
- [54] Wolkerstorfer A, Wahn U, Kjellman NI, et al. Natural course of sensitization to cow's milk and hen's egg in childhood atopic dermatitis: ETAC study group. *Clin Exp Allergy* 2002;32(1):70–3.
- [55] Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985;107(5):669–75.
- [56] Sampson HA, Scanlon SM. Natural history of food hypersensitivity in children with atopic dermatitis. *J Pediatr* 1989;115(1):23–7.

- [57] Sicherer SH, Furlong TJ, DeSimone J, et al. The US peanut and tree nut allergy registry: characteristics of reactions in schools and day care. *J Pediatr* 2001;138(4):560–5.
- [58] Sicherer SH, Furlong TJ, Munoz-Furlong A, et al. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. *J Allergy Clin Immunol* 2001;108(1):128–32.
- [59] Vander Leek TK, Liu AH, Stefanski K, et al. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. *J Pediatr* 2000;137(6):749–55.
- [60] Fleischer DM, Conover-Walker MK, Christie L, et al. The natural progression of peanut allergy: resolution and the possibility of recurrence. *J Allergy Clin Immunol* 2003;112(1):183–9.
- [61] Fleischer DM, Conover-Walker MK, Christie L, et al. Peanut allergy: recurrence and its management. *J Allergy Clin Immunol* 2004;114(5):1195–201.
- [62] Fleischer DM, Conover-Walker MK, Matsui EC, et al. The natural history of tree nut allergy. *J Allergy Clin Immunol* 2005;116(5):1087–93.
- [63] Novembre E, Cianferoni A, Bernardini R, et al. Anaphylaxis in children: clinical and allergologic features. *Pediatrics* 1998;101(4):E8.
- [64] Clark S, Bock SA, Gaeta TJ, et al. Multicenter study of emergency department visits for food allergies. *J Allergy Clin Immunol* 2004;113(2):347–52.
- [65] Cianferoni A, Novembre E, Mugnaini L, et al. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985-1996). *Ann Allergy Asthma Immunol* 2001;87(1):27–32.
- [66] Pumphrey RS, Roberts IS. Postmortem findings after fatal anaphylactic reactions. *J Clin Pathol* 2000;53(4):273–6.
- [67] Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol* 2005;95(3):217–26; [quiz 226, 258].
- [68] Bock SA, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;107(1):191–3.
- [69] Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol* 2005;115(3 Suppl 2):S483–523.
- [70] Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998;9(4):186–91.
- [71] Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg, and peanut in children. *Clin Exp Allergy* 2000;30(11):1540–6.
- [72] Adkinson NF. Middleton's allergy: principles and practice. 6th edition. Philadelphia: Mosby, Inc.; 2003.
- [73] Perry TT, Matsui EC, Kay Conover-Walker M, et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004;114(1):144–9.
- [74] Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100(4):444–51.
- [75] Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107(5):891–6.
- [76] Hourihane JO, Grimshaw KE, Lewis SA, et al. Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? *Clin Exp Allergy* 2005;35(9):1227–33.
- [77] Spergel JM, Beausoleil JL, Fiedler JM, et al. Correlation of initial food reactions to observed reactions on challenges. *Ann Allergy Asthma Immunol* 2004;92(2):217–24.
- [78] Wensing M, Penninks AH, Hefle SL, et al. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J Allergy Clin Immunol* 2002;110(6):915–20.

- [79] Taylor SL, Hefle SL. Food allergen labeling in the USA and Europe. *Curr Opin Allergy Clin Immunol* 2006;6(3):186–90.
- [80] Hansen TK, Poulsen LK, Stahl Skov P, et al. A randomized, double-blinded, placebo-controlled oral challenge study to evaluate the allergenicity of commercial, food-grade fish gelatin. *Food Chem Toxicol* 2004;42(12):2037–44.
- [81] Awazuhara H, Kawai H, Baba M, et al. Antigenicity of the proteins in soy lecithin and soy oil in soybean allergy. *Clin Exp Allergy* 1998;28(12):1559–64.
- [82] Simons E, Weiss CC, Furlong TJ, et al. Impact of ingredient labeling practices on food-allergic consumers. *Ann Allergy Asthma Immunol* 2005;95(5):426–8.
- [83] Moneret-Vautrin DA, Kanny G. Update on threshold doses of food allergens: implications for patients and the food industry. *Curr Opin Allergy Clin Immunol* 2004;4(3):215–9.
- [84] Taylor SL, Hefle SL, Bindslev-Jensen C, et al. Factors affecting the determination of threshold doses for allergenic foods: how much is too much? *J Allergy Clin Immunol* 2002;109(1):24–30.
- [85] Taylor SL, Hefle SL, Bindslev-Jensen C, et al. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? *Clin Exp Allergy* 2004;34(5):689–95.
- [86] Christie L, Hine RJ, Parker JG, et al. Food allergies in children affect nutrient intake and growth. *J Am Diet Assoc* 2002;102(11):1648–51.
- [87] Leung DY, Sampson HA, Yunginger JW, et al. Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003;348(11):986–93.
- [88] Nelson HS, Lahr J, Rule R, et al. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;99(6 Pt 1):744–51.
- [89] Enrique E, Pineda F, Malek T, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005;116(5):1073–9.
- [90] Pons L, Burks W. Novel treatments for food allergy. *Expert Opin Investig Drugs* 2005;14(7):829–34.
- [91] Srivastava KD, Kattan JD, Zou ZM, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. *J Allergy Clin Immunol* 2005;115(1):171–8.