OVERVIEW OF FOOD ALLERGY DIAGNOSIS

IRENA MANEA[1], ELENA AILENEI[2], DIANA DELEANU[1]

[1]Department of Allergy and Immunology, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[2]Department of Stroke, Stafford Hospital NHS Trust, Stafford, United Kingdom

Abstract

Food allergy is a condition with significant social and economic impact and a topic of intense concern for scientists and clinicians alike. Worldwide, over 220 million people suffer from some form of food allergy, but the number reported is just the tip of the iceberg. Recent years have brought new perspectives in diagnosing food allergy. Elucidating incriminated immunological mechanisms, along with drawing the clinical phenotype of food hypersensitivity reactions ensures an accurate diagnosis of food allergy. Moreover, molecular based allergy diagnosis, which is increasingly used in routine care, is a stepping-stone to improved management of food allergy patients.
The aim of this review is to summarize the topic of IgE-mediated food allergy from the perspective of current diagnostic methods.

Keywords: food allergy, IgE-mediated hypersensitivity, diagnostic tests

Background

Food allergy is a condition with significant social and economic impact and a topic of intense concern for scientists and clinicians alike. Worldwide, over 220 million people suffer from some form of food allergy, but the number reported is just the tip of the iceberg. In the United States of America, 4 to 6 percent of children and 4 percent of adults suffer from food allergy, accounting for approximately 15 million people, according to the Center for Disease Control and Prevention [1]. According to estimates by the European Academy of Allergology and Clinical Immunology (EAACI), the prevalence of food allergy has doubled in the last ten years, and in Europe the number of people suffering from food allergies currently exceeds 17 million. Furthermore, an increasing number of severe life-threatening reactions in children have been linked to food allergies [2].

The umbrella term of food hypersensitivity reactions encompasses "any adverse reaction to food" [3]. Food allergy refers to the subgroup of reactions triggered by food allergens in which immunologic mechanisms are involved, IgE mediated, non IgE-mediated or mixed IgE and non IgE-mediated [4]. Non-allergic food hypersensitivity reactions, known in the past as "food intolerance", have different etiologies, clinical presentation and approach from immune mediated reactions to trophallergens and are not the focus of this paper.

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The aim of this review is to summarize the topic of IgE mediated food allergy from the perspective of current diagnostic methods.

Food allergy diagnosis

Clinical history and examination are the first-line approach in diagnosing food allergy. The evaluation of a patient with suspected food allergy begins with obtaining a thorough clinical history that considers the symptoms indicative of allergic reactions to food. The clinical presentation of food allergy reactions varies within wide ranges and provides information about the incriminated mechanism (Table I).

Table I. Food allergy – clinical presentation and mechanisms.

Pathology	Clinical presentation
1. IgE mediated	• **Generalized** – anaphylaxis, food associated, exercise-induced anaphylaxis; • **Cutaneomucous** – urticarial ± angioedema, contact urticaria, atopic dermatitis/eczema; • **Digestive** - oral allergy syndrome (pollen-associated food allergy syndrome), immediate gastrointestinal hypersensitivity; • **Respiratory** – allergic rhinitis, asthma. • **Other[1]**
2. Non-IgE or cell-mediated	• **Cutaneous** – allergic contact dermatitis, atopic dermatitis/eczema; • **Digestive** – food protein induced-enterocolitis syndrome, food protein-induced allergic proctocolitis, Coeliac disease; • **Respiratory** - Heiner syndrome.
3. Combined IgE and cell-mediated	• **Cutaneous** – atopic dermatitis; • **Digestive** – allergic eosinophilic esophagitis, eosinophilic gastroenteritis.

[1]An unusual form of delayed allergy to mammalian meat (which sets on about 4-6 hours after ingestion) has been recently described and linked to the production of IgE to alpha-gal protein, a carbohydrate found in beef, lamb and pork. This type of reaction was documented in individuals with a history of tick bite, so it was possible to elucidate the mechanism involved: exposure to certain proteins in tick saliva can induce a specific humoral immune response against alpha-gal. This results in delayed anaphylaxis after consumption of red meat [10,11].

Potential triggers, the existence of co-factors, reaction type, the evaluation of the temporal relationship between food ingestion and onset of symptoms, as well as clinical reproducibility are key-points when obtaining the medical history.

IgE-mediated food allergy most often presents with immediate symptoms, with onset within two hours after ingesting the culprit food. There are no pathognomonic symptoms for food allergy; however, immediate onset of oropharyngeal or skin signs and symptoms make the diagnosis of food allergy more likely. Age is another factor indicative of an IgE-mediated hypersensitivity to food. Therefore, a systemic reaction occurring in a child upon exposure to a food allergen is highly suggestive of an IgE-mediated disease [5,6].

In order to improve the accuracy of diagnosing an allergic reaction to food, the clinician should consider food that consistently elicits allergic reactions. Eight types of food cause approximately 90% of food allergies: milk, eggs, fish, crustacean shellfish, nuts, peanuts, wheat and soy [7]. Nevertheless, any food can trigger an allergic reaction.

The quantity ingested, preparation of the suspected food, frequency of symptoms associated with ingestion are relevant historical aspects, which must be taken into consideration by the clinician. Food that has been tolerated in numerous previous occasions is less likely to be incriminated. However, exposure to small amounts of certain preparations (extensive baking, for instance) might result in ingestion without reaction [8,9]. Review of food labels might be useful when considering hidden or unidentified allergens in processed food. Review of the history might also reveal the existence of co-factors, such as exercise, alcohol consumption, or drugs. Absence of such co-factors is equivalent to tolerance of the otherwise incriminated food. Although rarely serving as diagnostic on their own, food diaries may be helpful in identifying food containing hidden ingredients, food that was overlooked by the patient, or patterns of reactions (existence of co-factors). Food diaries are written records of everything that is ingested by a patient, including condiments, alcohol, and candies.

Physical examination may reveal signs of an immediate acute reaction or chronic findings compatible with atopic diatheses (asthma, allergic rhinitis, atopic dermatitis). However, physical examination is not *per se* relevant in diagnosing food allergy.

The clinical history and examination lack sufficient specificity and sensitivity to establish the diagnosis of food allergy. In vivo (skin testing) and in vitro (food-specific serum IgEs) investigations of sensitization are essential adjunct tools in assessing patients with a suggestive clinical history of food allergy and represent the second line of approach of these patients.

In vivo testing

Skin prick tests (SPTs) are a fast and effective method of assessing sensitization to food allergens. Commercially prepared food extracts or fresh food can be used. In evaluating sensitisation to fruit and vegetables, or to food for which extracts are not available, the prick-to-prick method may be used with fresh food or slurry made from food and sterile saline solution. SPTs are highly reproducible and less expensive than *in vitro* testing. Skin testing can be safely performed in patients of any age; it causes minimal patient discomfort, and yields results within 15 minutes.

SPTs for food allergens are highly sensitive (greater than 90%), but moderately specific (approximately 50%) [12]. However, there are a few exceptions to this rule, as it was shown that a positive skin test indicates a greater than 95% likelihood of clinical reactivity in patients with a relevant clinical history to certain food and in whom sensitization to the respective food is documented (see Table II). In addition, the accuracy of negative predictive values provided by skin testing is uniformly high; a negative skin test to food excludes an IgE-mediated reaction by 90 to 95% [13]. Thus, skin testing is highly useful to confirm the absence of an IgE-mediated food allergy [14,15]. Apart from low specificity, STPs were reported to lead to variable wheal sizes depending on the population and the food being studied [16]. Therefore, skin reactivity should not be interpreted as clinical reactivity. When considering the diagnosis of food allergy, the clinician should perform STPs only for the suspected food allergens, and interpretation of results should be considered in the light of the clinical history. Determining the clinical relevance of sensitization is crucial to reducing over-diagnosis and unnecessary dietary eliminations.

Intradermal testing to food is not recommended in the diagnosis algorithm of food allergy, because of the high rate of false-positive results, and the high risk of systemic life-threatening reactions [17,18].

Atopy patch tests (ATPs) involve the topical application of a food-containing solution to the skin for 48 hours. Currently, there are no standardized reagents, application methods, or guidelines for interpretation of APTs. Although ATP is not routinely recommended for investigating patients with suspected food allergy, it can be useful in assessing the relevance of food triggers in pediatric patients suffering from eosinophilic esophagitis [19].

In vitro testing

In vitro evaluation, or the determination of food-specific serum IgE (sIgE), prevails when *in vivo* testing is contraindicated or ineffective (extended dermatitis, dermographism, severe atopic dermatitis, medication that inhibits cutaneous reactivity). Radioallergosorbent tests (RASTs) and fluorescence enzyme immunoassay (FEIA) tests are in vitro assays used to identify food-specific IgE antibodies in the serum [20].

Serum IgE testing is an important adjunct tool in accurate identification of causal food allergens [21]. Testing to large panels of food allergens disregarding the clinical history is not recommended, as false positive results can lead to unnecessary dietary elimination of safe food, and subsequently to unjustified nutritional deficiencies [22]. Thus, selecting in vitro testing for sensitization to food should be based on medical history.

The negative and positive predictive accuracy of *in vitro* testing varies within wide ranges, with a few exceptions. Clinical studies have provided predictive thresholds for certain food (egg, milk, peanuts, nuts, and fish) [23,24,25,26,27]. These cut-offs correlate with clinical reactivity with a positive predictive value greater than 95% (Table II), which proves their utility in determining whether an open food challenge is warranted, and also to accurately advise patients.

Overall, higher sIgE levels are more likely to indicate clinical reactivity. However, the predictive value of sIgE levels varies within wide ranges and with different factors (population, age, time since last ingestion of suspected food, other associated disorders) [27,28,29,30]. A negative result does not exclude the diagnosis. Arguing in favor of reintroduction of food based solely on negative sIgE results is not recommended because of the risk of systemic life-threatening allergic reactions.

Both in vivo and in vitro testing only detect sensitization, not clinical allergy; they cannot predict prognosis or severity of subsequent reactions. It is of utmost importance that results be interpreted within the framework of the patient's clinical history.

Table II. Relevance of SPT and sIgE in the diagnosis of food allergy.

Skin prick test
- Sensitivity >80%
- Specificity ≈ 50%

Among the cases with increased possibility of disease and positive STPs with a mean wheal diameter of ≥ 3 mm:
- Negative Predictive Value ≈ 90%
- Positive Predictive Value ≈ 50%

Illergen	Age	Wheal	Probability of Reaction
Milk	3 years	8 mm	≈ 1
Egg	3 years	8 mm	≈ 100%
Peanuts	3 years	8 m	≈ 100%

Food specific IgEs[2]
- Sensitivity of sIgE = 60-95%
- Specificity of sIgE = 30-95%

sIgE levels associated with 9% PP

Egg	≥7 IU/mL
Egg (infants ≤2years)	≥2 IU/ml
Milk	≥15IU/ml
Milk (infants ≤2years)	≥5 U/ml
Peanuts	≥15 IU/ml
Peanuts (infants ≤2years)	≥15 IU/ml
Nuts	
Fish	≥20 I/ml

[2]a level of 0,35 kU/l indicates sensitization

Factors that dictate the impact of sensitization on the severity of the food allergy reaction (such as ingested amount, concomitance of other atopic diseases, asthma, general health) are currently the subject of study and interpretation. A recent study published in the *Journal of Allergy and Clinical Immunology* revealed that 1.6-10.1 mg of hazelnut, peanut or celery protein, and 27.3 mg of fish and 2.5 g of shrimp protein are needed to trigger allergic reaction in highly sensitized patients. This discovery is a new step in understanding food allergies and could also contribute to improving food labeling [31].

In certain situations, as is the case of allergy to cow's milk, in dynamic results of *in vivo* and *in vitro* tests to sensitization along with the clinical context are factors with prognostic role in the natural history of the disease and provide important information on when to reintroduce the food into the diet [32,33].

Other tests detecting sensitization include the basophil activation test (BAT), which evaluates the in vitro basophilic activation by specific allergens. According to a recently published study, BAT effectively discriminates between allergy and tolerance in peanut-sensitized children, showing 97% accuracy, 95% positive predictive value, and 98% negative predictive value [34]. Therefore, BAT promises to bring real improvement in diagnosing food allergy.

Component-resolved diagnosis

The last decade brought about a "refining" of food allergy diagnosis by identifying clinically relevant allergenic fractions. Molecular-based allergy diagnostics also referred to as component-resolved diagnostics (CRD), uses purified native or recombinant allergens to detect IgE sensitivity to individual allergen molecules [35].

This method of investigation is not routinely recommended in diagnosing food allergy. However, it proved to increase the accuracy of food allergy diagnosis and establish sensitization patterns with particular prognostic outcomes in a relatively small number of foods.

Recent studies propose Arah2 (storage proteins found in peanuts), as well as Cor a 9 and Cor a 14 (hazelnuts) as the most common allergens to be associated with clinical reactivity, whereas Arah 8 (Bet v1 related) is more likely to cause mild, local reactions or to be tolerated [36,37,38,39,40]. These findings suggest that component-resolved diagnosis has the potential to enhance diagnostic accuracy by discriminating between clinically significant and irrelevant sIgE results, as well as to enhance therapeutic approach by excluding the need for unnecessary open food challenges. Although the search for other clinically relevant molecules is needed and on going, studies are limited and inconsistencies exist. Thus, in certain geographic areas, such as the Mediterranean area, Arah 9 proved to be the major allergen, while a number of studies brought inconsistent CRD results across different parts of the world [41,42,43]. Further studies are needed to define the clinical utility of component resolved diagnosis.

Elimination diets are used in the management of patients suffering from food allergies, as well as a part of evaluation for food allergy, and refer to the avoidance of incriminated food. Therefore, elimination diets target different aspects in clinical practice:

• removing one or several suspect food from a patient's diet is sometimes useful in determining if they are causing or exacerbating a condition;

• prescribing an "oligo-antigenic" diet in which food that is commonly-involved in allergic disorders is removed temporarily from the diet may be useful in the evaluation of patients with chronic conditions, such as atopic dermatitis or chronic urticaria, in which food allergy is suspected, but no specific food can be incriminated;

• elemental diets, such as extensively-hydrolyzed or amino acid-based formulas, are used by some allergy specialists in the evaluation of disorders associated with multiple food sensitivities, such as eosinophilic esophagitis. Such diets should only be prescribed with great caution, particularly in infants and children, to avoid nutritional deficiencies;

• complete removal of the suspected trophallergen is recommended prior to food challenges, to ensure that the specific food is not interfering with the ability to appreciate a reaction [44,45].

Although elimination diets can be used as an adjunctive mean of diagnosing food allergy, they cannot confirm the diagnosis on their own.

Supervised food challenges are structured protocols in which the patient ingests the suspected food under a clinician's supervision. They are sometimes required for the definitive diagnosis of food allergy, with **double-blind placebo-controlled food challenge** (DBPCFC) being the most accurate form of challenge. Food is selected for testing based upon the history and the results of skin and/or in vitro testing. DBPCFC is currently the "golden standard" in the diagnosis of food allergy [46]. It helps identify the causative agent, the amount of food needed for a reaction / tolerated dose, and establish the significance of existence of co-factors (e.g. exercise in patients with food dependent anaphylaxis, induced by exercise). Challenge tests are often the only way to confirm the clinical relevance of sensitization. At the same time, they are time-consuming, resource-intensive and produce the risk of inducing systemic, severe allergic reaction.

Conclusions

Food allergy is a common health problem, which demonstrates a significant socioeconomic impact, especially in pediatric population. A reliable diagnosis of food allergy is crucial to avoid the unnecessary exclusion diets and to formulate personalized dietary recommendations. Recent years have brought considerable progress in clarifying the diagnostic algorithm in food allergy. Clinical reactivity

can be effectively predicted in patients with a relevant history and in whom a certain level of *in vivo* and/or *in vitro* sensitization is documented. However, in some cases, oral provocation tests may still be required to establish or exclude the diagnosis of food allergy. The characterization of the biology and cross-reactivity patterns of food allergens has allowed a shift of the *in vitro* diagnosis of IgE-mediated hypersensitivity to food from an extract-based approach to an allergen-specific or "component-resolved" diagnosis. The latter has brought new insights in the approach of food allergic patient; it helped increase the accuracy of food allergy diagnosis and to establish sensitization patterns with particular prognostic outcomes in peanut, hazelnut, milk and egg allergy. Molecular based diagnosis is a topic of major interest in the search for an improved diagnostic of food allergy, and the research of other clinically relevant molecules is needed and ongoing. Molecular based diagnosis is a topic of major interest in the clinical search for an enhanced diagnosis of food allergy, and further research to discover other relevant molecules is needed.

References

1. Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol. 2010;126(4):798-806.e13.

2. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008-1025.

3. Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy. 2001;56(9):813-824.

4. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ, et al. Diagnosing and managing common food allergies: a systematic review. JAMA. 2010;303(18):1848-1856.

5. Simons FE, Ardusso LR, Bilo MB, Dimov V, Ebisawa M, El-Gamal YM, et al. 2012 Update: World Allergy Organization Guidelines for the assessment and management of anaphylaxis. Curr Opin Allergy Clin Immunol. 2012;12:389-399.

6. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World Allergy Organization anaphylaxis guidelines: summary. J Allergy Clin Immunol. 2011;127:587-593.

7. Allen KJ, Koplin JJ. The epidemiology of IgE-mediated food allergy and anaphylaxis. Immunol Allergy Clin North Am. 2012;32:35-50.

8. Maleki SJ. Food processing: effects on allergenicity. Curr Opin Allergy Clin Immunol. 2004;4:241-245.

9. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. J Allergy Clin Immunol. 2008;122:342-347.

10. Commins SP, Platts-Mills TA. Anaphylaxis syndromes related to a new mammalian cross-reactive carbohydrate determinant. J Allergy Clin Immunol. 2009;124:652-657.

11. Commins SP, Platts-Mills TA. Allergenicity of carbohydrates and their role in anaphylactic events. Curr Allergy Asthma Rep. 2010;10:29-33.

12. Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. J Allergy Clin Immunol. 1984;74:26–33.

13. Roberts G, Lack G. Diagnosing peanut allergy with skin prick and specific IgE testing. J Allergy Clin Immunol. 2005;115:1291-1296.

14. 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. 2000,30:1540-1546.

15. Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K, et al. The predictive value of the skin prick test weal size for the outcome of oral food challenges. Clin Exp Allergy. 2005;35(9):1220-1226.

16, Peters RL, Gurrin LC, Allen KJ. The predictive value of skin prick testing for challenge-proven food allergy: a systematic review. Pediatr Allergy Immunol. 2012;23:347-352.

17. Bernstein IL, Li JT, Bernstein DI, Hamilton R, Spector SL, Tan R, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008;100(3 suppl 3):S1-S148.

18. Bock SA, Lee WY, Remigio L, Holst A, May CD. Appraisal of skin tests with food extracts for diagnosis of food hypersensitivity. Clin Allergy. 1978;8:559-564.

19. Spergel JM, Brown-Whitehorn TF, Cianferoni A, Shuker M, Wang ML, Verma R, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. J Allergy Clin Immunol. 2012;130:461-467.

20. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 suppl):S1-S58.

21. Fleischer DM, Burks AW. Pitfalls in food allergy diagnosis: serum IgE testing. J Pediatr. 2015;166(1):8-10.

22. Fleischer DM, Bock SA, Spears GC, Wilson CG, Miyazawa NK, Gleason MC, et al. Oral food challenges in children with a diagnosis of food allergy. J Pediatr. 2011;158:578-583.

23. Boyano Martinez T, Garcia-Ara C, Diaz-Pena JM, Munoz FM, Garcia Sanchez G, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. Clin Exp Allergy 2001;31:1464-1469.

24. Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM, Martin-Munoz F, Reche-Frutos M, Martin-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cows' milk protein in the infant. J Allergy Clin Immunol. 2001;107:185-190.

25. Garcia-Ara MC, Boyano-Martinez MT, Diaz-Pena JM, Martin-Munoz MF, Martin-Esteban M. Cow's milk-specific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. Clin Exp Allergy. 2004;34:866-870.

26. Perry TT, Matsui EC, Kay Conover-Walker M, Wood RA. The relationship of allergen-specific IgE levels and oral food challenge outcome. J Allergy Clin Immunol. 2004;114:144-149.

27. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. J Allergy Clin Immunol. 2001;107:891-896.

28. 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;100:444-451.

29. Boyano-Martinez T, Garcia-Ara C, Diaz-Pena JM, Martin-Esteban M. Prediction of tolerance on the basis of quantification of egg white-specific IgE antibodies in children with egg allergy. J Allergy Clin Immunol. 2002;110:304-309.

30. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. Clin Exp Allergy. 2005;35:268-273.

31. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, Defernez M, Sperrin M, Mackie AR, et al. How much is too much? Threshold dose distributions for 5 food allergens. J Allergy Clin Immunol. 2015;135(4):964-971.

32. Patel BY, Volcheck GW Food Allergy: Common Causes, Diagnosis, and Treatment. Mayo Clin Proc. 2015;90(10):1411-1419.

33. Saarinen KM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. J Allergy Clin Immunol. 2005;116(4):869-875.

34. Santos AF, Douiri A, Bécares N, Wu SY, Stephens A, Radulovic S, et al. Basophil activation test discriminates between allergy and tolerance in peanut-sensitized children. J Allergy Clin Immunol. 2014;134(3):645–652.

35. Valenta R, Lidholm J, Niederberger V, Hayek B, Kraft D, Gronlund H. The recombinant allergen-based concept of component-resolved diagnostics and immunotherapy (CRD and CRIT). Clin Exp Allergy. 1999;29:896-904.

36. Dang TD, Tang M, Choo S, Licciardi PV, Koplin JJ, Martin PE, et al. Increasing the accuracy of peanut allergy diagnosis by using Ara h 2. J Allergy Clin Immunol. 2012;129:1056-1063.

37. Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. J Allergy Clin Immunol. 2010;125:191-197.

38. Lieberman P, Glaumann S, Batelson S, Borres MP, Sampson HA, Nilsson C. The utility of peanut components in the diagnosis of IgE-mediated peanut allergy among distinct populations. J Allergy Clin Immunol Pract. 2013;1:75-82.

39. Asarnoj A, Moverare R, Ostblom E, Poorafshar M, Lilja G, Hedlin G, et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. Allergy. 2010;65:1189-1195.

40. Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, Lidholm J, Andersson K, Akkerdaas JH, et al. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. J Allergy Clin Immunol. 2013;132:393-399.

41. Vereda A, van Hage M, Ahlstedt S, Ibañez MD, Cuesta-Herranz J, van Odijk J, et al. Peanut allergy: Clinical and immunologic differences among patients from 3 different geographic regions. J Allergy Clin Immunol. 2011;127:603-607.

42. Ott H, Baron JM, Heise R, Ocklenburg C, Stanzel S, Merk HF, et al. Clinical usefulness of microarray-based IgE detection in children with suspected food allergy. Allergy. 2008;63:1521-1528.

43. Nicolaou N, Custovic A. Molecular diagnosis of peanut and legume allergy. Curr Opin Allergy Clin Immunol. 2011;11:222-228.

44. Sicherer SH. Food allergy: when and how to perform oral food challenges. Pediatr Allergy Immunol. 1999;10:226-234.

45. David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. Arch Dis Child. 1984;59:983-986.

46. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130:1260-1274.