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Review

Diagnosis and therapy of food allergy

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According to the recently revised nomenclature for allergy [1] the term "Food Hypersensitivity" is proposed to define a reaction on food exposure causing objectively reproducible symptoms or signs at a dose tolerated by normal subjects. Those reactions to food in which immunologic mechanisms are demonstrated comprise the term "Food Allergy". Immunologic reactions to food in which an immunoglobulin E (IgE)-mediated mechanism is established are defined as IgE-mediated food allergy. This review focuses on IgE-mediated allergic reactions to foods.

Keywords: Double-blind placebo-controlled / Elimination diet food allergy / Food challenge / Immunoglobulin E / Oral challenges / Review

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1 Diagnostic assessment

The aim of the diagnosis of food allergy is to objectively establish a causal relationship between food ingestion and the clinical symptoms reported by the patient and to identify the immune mechanism of the reaction. As stated by consensus and guidelines [2–4], the diagnostic evaluation of reported adverse reactions to food should include a detailed clinical history and physical examination, diagnostic tests for immunoglobulin E (IgE), elimination diets, and oral food challenges.

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Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; **IgE**, immunoglobulin E; **OAS**, oral allergy syndrome; **oFC**, open food challenge; **SBFC**, single blind food challenge; **SPT**, skin prick test

1.1 History and physical examination

The clinical history should include an accurate description of the adverse food event in order to determine precisely its clinical features and it should provide sufficient information that can be used in the design of a diagnostic oral challenge procedure, which, if positive, reproduces the reported reaction. The main issues of the food reaction to include in the clinical history comprise a description of the specific symptoms, the timing of the reaction, and food suspected of causing the reaction. Specific questions should address the food suspected of provoking the reaction, the amount and the food processing procedure, such as boiled or dry roasted, as the oral challenge should be designed employing the implicated food in the same way as reported by the patient [5, 6]. Symptoms produced by allergic reactions to foods may include, alone or in combination, gastrointestinal manifestations with oropharyngeal pruritus and/or local angioedema, acute gastric and abdominal pain, nausea, vomiting, and diarrhea. Skin symptoms are commonly pruritus, urticaria, angioedema, and worsening of atopic dermatitis. Airway symptoms may include rhinitis and/or asthma. Cardiovascular manifestations such as hypotension and anaphylactic shock may take place during a reaction. If one or more of these symptoms is present, information should be obtained regarding the time relationship and the reprodu-

cibility of the symptom with regard to the consumption of the suspected food and whether any other circumstances were involved. Associated factors, *e.g.*, ingestion of medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs), and exercise should also be identified [7]. It is worthy to ask about his/her history of other atopic diseases, such as asthma and atopic dermatitis, both of which are risk factors for food allergy [8, 9]. A comprehensive medical history should be obtained in patients suspected of having food allergy-induced respiratory tract symptoms or anaphylaxis [10]. The history should include questions about the timing of the reaction in relation to food ingestion, the minimum quantity of food required to cause symptoms, specific upper and lower respiratory signs and symptoms, and the reproducibility of the symptoms. A family history positive for allergy and/or asthma can be a useful historical point. When there is a history of an unexplained sudden asthma exacerbation, details about preceding food ingestion should be elicited. A history of a severe or anaphylactic reaction following the ingestion of a food may be sufficient to indicate a causal relationship. Finally, documentation of the specific treatment received and its response should be documented.

Diet diaries can be a useful supplement to a medical history, especially in chronic disorders. Moreover, elimination diets, which are typically implemented for 7–14 days, can be used both for diagnostic and therapeutic purposes. Their success depends on identifying the correct allergen and completely eliminating it in all forms from the diet. All efforts should be made to prevent complications from unnecessary dietary restrictions such as poor weight gain and failure to thrive [11].

In evaluating patients with suspected allergic reactions that may be induced by food allergy, the physical examination is mandatory. Helpful findings include the assessment of overall nutritional status, growth parameters, and any signs of allergic disease, especially atopic dermatitis. Moreover, this examination will help rule-out other conditions that may mimic food allergy [12]. Attention should be directed toward detecting the presence of atopic features, particularly dermatitis, asthma, and rhinitis [13]. If the patient has asthma, an objective evaluation of airway obstruction prior to an oral challenge is mandatory. No oral challenges should be carried out with a FEV1 lower than 80% of predicted because of the risk of severe asthma if the challenge is positive [14].

1.2 Diagnostic tests for IgE

When an IgE-mediated allergic reaction to food is suspected, skin testing and *in vitro* tests are useful in establishing if the patient possesses IgE antibodies to specific foods. These tests indicated the presence of an immune IgE-mediated response, but they do not establish *per se* the diagnosis of clinical allergy to food. Several studies using the double-blind, placebo-controlled, food challenges (DBPCFCs) to establish the diagnosis of clinical allergy revealed that only 40% of medical histories of food adverse reactions can be verified [15–18].

1.2.1 Skin testing

Percutaneous skin testing remains a primary tool in the diagnosis of food allergy [10]. While the patient is off antihistamines for an appropriate length of time, it is performed with an appropriate skin testing device (*e.g.*, lancet) which punctures the skin through a drop of a glycerinated food extract and appropriate positive (histamine) and negative controls (saline). Skin prick tests (SPTs) are judged positive if there is a mean wheal diameter of 3 mm or greater than those induce by the negative control. These tests have a negative predictive value generally greater than 95% (assuming the disorder being evaluated is IgE-mediated), however, the test has in general a relatively low specificity (approximately 50%). The positive predictive value is only 20–50%, depending on the history. Thus, a positive skin test merely indicates allergic sensitization. Positive tests cannot be considered absolute proof of clinically relevant hypersensitivity and must be interpreted in the context of the clinical history. Negative skin test responses essentially confirm the absence of IgE-mediated allergic reactivity (negative predictive accuracy of > 95%) and are very helpful in excluding IgE-mediated food allergies [19–26]. Fruits and other foods of vegetable origin are frequently reported by young and adult patients as the cause of allergy. However, as noted early in 1942 by Tuft and Blumstein [27], commercially prepared extracts from many fruits and vegetables frequently do not induce positive skin responses in clinically sensitive patients, because of the presence of labile proteins responsible for IgE-mediated sensitivity. Dreborg and Foucard [28] introduced the prick-prick technique with fresh fruits and vegetables which improved the ability of skin testing to detect immunological IgE-mediated hypersensitivity. In this procedure the skin is punctured after pricking the fresh food. In a study of 100 adults with a history of oral allergy syndrome (OAS) after ingestion of fruits and vegetables, Ortolani *et al.* [29] demonstrated that skin testing with the prick-prick technique was very sensitive for fruits and vegetables, such as carrot, celery, cherry, apple, tomato, orange, and peach. As observed during skin testing with commercial allergenic extracts, the accuracy of the results of the prick by prick technique with plant-derived foods to predict true clinical allergy is limited. In addition, the extensive immunologic cross-reactivity among different plant proteins implies that skin testing with different fresh fruits and vegetables may

produce a high number of positive skin responses which are not clinically relevant.

Intradermal skin tests with food extracts have an unacceptably high false-positive rate. These tests have been associated with systemic reactions and should not be used in the workup of food allergy. Finally, well-designed and medically supervised oral food challenges are critical for the confirmation of food allergy [10].

1.2.2 Food-specific IgE antibodies

In vitro tests for specific IgE (RAST) are also helpful in evaluating IgE-mediated food allergy. For example, quantitative measurements of food-specific IgE antibodies (*e.g.*, CAP System FEIA, Pharmacia-Upjohn Diagnostics) have been shown to be very useful in predicting symptomatic IgE-mediated food allergy. These tests for specific IgE antibody can be used while the patient is taking an antihistamine and do not depend on having an area of rash-free skin for testing. The general concepts for interpretation are the same as for prick skin tests: a negative result is reliable in ruling-out an IgE-mediated reaction to a particular food and while a positive result does not absolutely prove clinical reactivity, it can be very helpful in implicating a specific food allergy. To some extent, the greater the concentration of a food-specific IgE antibody, the higher the chance of true clinical reactivity. As mentioned above with skin testing, positive tests cannot be considered absolute proof of clinically relevant hypersensitivity and must be interpreted in the context of the clinical history [19 – 26].

1.2.3 Optimal performance of diagnostic tests for IgE for clinical food allergy

In the last years, it has become apparent that a global assessment of the performance (*e.g.*, receiver-operating characteristic plots) of the diagnostic tests for IgE could be useful in selecting the best cut off (optimal operating) point to differentiate actual food allergy. Sporik and colleagues [30] designed an investigation to determine the specificity of the allergen wheal diameter to help identify children who react on formal open food challenges (OFCs). Over a 9-year period, children referred to a tertiary allergy clinic for the evaluation of suspected food allergy were prospectively studied. Allergen skin prick testing to commercial extracts of cow milk, egg white, and peanut extracts was undertaken using a lancet technique. All children underwent OFSc to the relevant food(s) in a hospital clinic. Challenges were classified as positive if objective signs were seen; negative if the child could tolerate normal quantities of the food, daily, for one week; or inconclusive if none of the former criteria were met. Five hundred and fifty-five challenges were undertaken in 467 children (339 challenges to cow milk, 121 to egg, and 95 to peanut). Fifty-five percent of challenges were positive, 37% negative, and 8% inconclusive. For each food it was possible to identify a skin wheal diameter at, and above, which positive reactions occurred: egg: 7 mm; cow milk: 8 mm; peanut: 8 mm. These investigators proposed that the utilization of these measurements may reduce the need for formal food challenges in patients being assessed for allergic reactions to egg, cow milk, and peanut.

Another recent investigation compared the results of skin prick testing to *in vitro* measurements of specific IgE to food allergens [31]. These investigators reported SPT wheal diameters to cow milk, egg, and peanut above which infants and young children referred for investigation of suspected food allergy showed an adverse reaction on food challenge. These were termed the "100% diagnostic SPT levels". *In vivo* and *in vitro* measurements of IgE antibody levels to three common food allergens, cow milk, egg, and peanut, were compared in infants and young children with suspected food allergy, in order to reduce the need for food challenges. SPT (from 1992 to 1998) and CAP values (from 1999 to 2000) were performed in 820 children <2 years of age with suspected allergy to cow milk and/or egg and/or peanut. SPT levels previously shown to be diagnostic of challenge-proven allergy to cow's milk, egg, and peanut were used as the "100% diagnostic SPT levels" and compared with SPTs and CAP values associated with IgE-mediated food allergy. Statistical analysis showed a significant difference between the "100% diagnostic SPT levels" and positive SPT in identifying patients who did not require food challenge for cow milk ($P = 0.01$), egg ($P < 10–6$) and peanut ($P < 10–6$), and a significant difference between the "100% diagnostic SPT levels" and positive CAP ($P < 10–6$) for egg and peanut but not cow milk. Overall, 23% of the food challenges were avoided by the use of the "100% diagnostic skin prick test levels". The use of these levels compared with *in vitro* measurement of IgE antibody to cow milk, egg, and peanut reduced the need for food challenge in young children with suspected food allergy.

Two recent studies have attempted to define the risks of clinical reactions as they relate to food-specific IgE antibody (*i.e.*, Pharmacia Diagnostics termed the CAP-RAST FEIA that measures the antibody concentration as kU/L). In the initial study, stored sera from 196 children and adolescents (mean age 5.2 years, 60% male) with atopic dermatitis were analyzed for specific IgE antibodies to foods commonly causing allergy in children, and the results compared to blinded food challenges and "convincing" history of anaphylactic reactions [26]. When compared with the outcome of DBPCFCs, results of CAP System FEIA are generally comparable to those of SPTs in predicting symptomatic food hypersensitivity. Furthermore, by measuring the concentrations of food-specific IgE antibodies with the CAP System FEIA, it is possible to identify a subset of patients who are highly likely (>95%) to experience clinical reac-

tions to egg, milk, peanut, or fish. The performance characteristics of the CAP System FEIA for soy and wheat were poor. The follow-up to this study involved a prospective investigation in a patient population of children (median age = 3.8 years) with only about 60% having atopic dermatitis gave similar results [32]. Serum samples from 100 consecutive children and adolescents referred for evaluation of food allergy were analyzed for specific IgE antibodies to egg, milk, peanut, soy, wheat, and fish by using the Pharmacia CAP System FEIA. Food-specific IgE values were compared with history and the results of skin prick tests and food challenges to determine the efficacy of previously established 95% predictive decision points in identifying patients with increased probability of reacting during a specific food challenge. The diagnosis of food allergy was established by means of history or oral food challenge. On the basis of the previously established 95% predictive decision points for egg, milk, peanut, and fish allergy, greater than 95% of food allergies diagnosed in this prospective study were correctly identified by quantifying serum food-specific IgE concentrations. Previously established 95% predictive decision points of food-specific IgE antibody concentrations for four major food allergens were effective in predicting clinical reactivity. Therefore, these two studies demonstrate that quantification of food-specific IgE is a useful test for diagnosing symptomatic allergy to egg, milk, peanut, and fish in the pediatric population and could eliminate the need to perform double-blind, placebo-controlled food challenges in a significant number of children.

It has become apparent that adjustments in interpreting these diagnostic cutoff values must be made for disease and age. Forty patients with symptomatic immediate hypersensitivity to egg who did not have atopic dermatitis were evaluated to determine if they continued to remain clinically symptomatic [33]. Individual patients had specific IgE *in vitro* and positive PST to egg. All patients were on an egg elimination diet. During the follow-up period, an open egg re-challenge was performed along with a determination of egg white-specific IgE by CAP System. The egg white-specific IgE values were higher in the positive challenge group than in the negative challenge group ($P < 0.01$, Mann-Whitney test). There was a direct proportional relationship between the levels of egg white-specific IgE and the likelihood of positive challenge. Specific IgE values above 1.20 KUA/L could be adequate grounds for delaying the follow-up of egg challenge. Overall, the study showed that increasing concentrations of egg-specific IgE antibody indicated a higher likelihood of clinical reactivity on re-challenge. The likelihood ratios for a positive oral challenge with egg white IgE level equal to or above 0.35, 0.70, and 1.20 kU/L were 2.2, 3.0, and 6.3, respectively.

Another example of the adjustments for age and disease that are needed in the interpretation of these values was demonstrated in a study of infants with possible acute reactions to milk but without atopic dermatitis or gastrointestinal allergy [34]. A prospective study was carried out on 170 patients < 1 year old (mean, 4.8 months) with histories suggesting immediate hypersensitivity after ingestion of cow milk formula. Prick test with cow milk and its proteins (α-lactalbumin, β-lactoglobulin, and casein), determination of specific IgE antibodies with the CAP system FEIA for the same allergens as for the prick test, and a challenge test according to the diagnostic protocol were performed for all of the children. A study of validity of the prick test (cutoff point, 3 mm) and CAP system by using different cutoff points in the specific IgE values for cows' milk and its proteins were also analyzed. Prevalence of immediate symptomatic hypersensitivity to CMP in this study was 44%. When both the whole milk and its principal milk proteins were used in the prick test, the negative predictive value was very high, and a negative value excluded allergy in 97% of the patients. When the different cutoff points of the specific IgE for milk were analyzed, 2.5 KU(A)/L had a positive predictive value of 90% and 5 KU(A)/L had a positive predictive value of 95%. When diagnosing immediate hypersensitivity to CMP in infants, negative skin test responses exclude allergy in most of the patients. If the prick test response is positive, specific IgE levels for cows' milk may be helpful. If these values are 2.5 KU(A)/L or greater, the challenge test should not be performed because of its high positive predictive value (90%).

Comparing results of food-specific IgE by skin prick testing and *in vitro* measurements should help to provide better predictive information regarding whether or not to subject a patient with possible food allergy to an oral food challenge. Hopefully, there will be more published data in the future regarding predictive values for other food allergens and comparisons of *in vivo* and *in vitro* measures of food-specific IgE. This type of information will be useful to the clinician in the overall decision-making process with food-allergic patients.

1.3 Oral food challenges

Before carrying out any challenges the patient should be placed on an elimination diet of the suspected food for at least two weeks. In many cases the patient is already avoiding the food at the moment of consultation, especially in the case of several acute, clear-cut episodes. If the patient reports chronic symptoms with several possible culprit foods an elimination diet is advised. If a large number of foods is suspected it is practical to give the patient a list of "safe" foods to be taken and then introduce the suspected foods one by one every week watching for the appearance of symptoms. Whether the re-introduction of the food is carried out at home or in a clinical setting depends on the

severity of symptoms; nonacute reactions and symptoms probably not due to an IgE-mediated reaction may allow adding the food at home.

When there is a clinical suspicion of an allergic reaction to a food and the test for specific IgE antibody to the food is positive, an elimination diet may be implemented to see if there is a resolution of clinical symptoms. Confirming this association, however, can be difficult in many cases. Therefore, food challenges can be a useful and reliable procedure in the diagnostic evaluation of a patient with suspected food allergy. Open or single-blind food challenges are often utilized to screen foods unlikely to provoke food-induced allergic reactions. Of the different type of oral food challenge procedures, the DBPCFC is the best method and remains the gold standard to diagnose and confirm food allergy and other adverse food reactions [35]. An excellent publication has reviewed the combined clinical experience of six centers doing food challenges [2]. These challenges should be conducted in a medical clinic or hospital setting with available personnel and equipment for treating systemic anaphylaxis.

The DBPCFC is considered the state of the art for diagnosis of actual clinical reactivity after food ingestion. With the exception of severe reactions on ingestion of an isolated food it is the only method to exclude bias from patient and physician. Other modalities of oral challenge are performed in the clinical setting, OFCs in which the patient consumes the food without masking and single-blind challenges (SBFC) in which food masking only applies to the patient. In the diagnostic algorithm proposed by the European Academy of Allergy, Asthma, and Immunology, OFC are carried out prior to blinded challenges [3]. Patients having a positive OFC undergo a subsequent DBPCFC. If the result of the blinded challenge is negative, it must be confirmed by means of an open feeding under observation to rule out the rare false negative challenge result.

The design of all oral challenges with food is determined by the facts of the clinical history. The food for challenge should be administered in the same form as previously ingested, raw or processed. The initial dose should be a fraction of the minimum quantity to produce symptoms reported in the history. Successive increasing doses should reach a cumulative quantity equivalent to a normal amount of the food consumed in everyday life. The time interval between doses should be longer than that reported by the patient in the history and enough for symptoms to develop.

OFCs are very useful for evaluating reactions to many foods with a high probability of a negative outcome. SBFCs are time-saving and may prove useful for patients with a high subjective concern about their symptoms to refute doubtful histories. Double-blind challenges are the final procedure for diagnosis. Assignation for active food (verum) or placebo doses must be randomized by personnel not related to the administration of doses to ensure proper blinding. The number of placebo and verum doses is usually the same in most protocols. Masking may be carried out employing vehicles to hide the flavor, color, and texture of the food. It is preferable to use liquid or semisolid vehicles. Masking with capsules is effective but it may be misleading and dangerous; as no contact of the food with the oral mucosa is allowed, oral symptoms are not detected and severe symptoms may appear only after a high dose has been administered. Solid vehicles, such as fish for crustacean challenges may be good maskers of flavor and texture in some cases. After a negative outcome of a DBPCFC an open administration of the food in usual amounts under observation is mandatory to exclude any concern regarding preparation of the food. Causes of final positive open feedings after a negative DBPCFC include an insufficient amount of food administered in the challenge and loss of allergenic activity of the food due to preparation of the challenge. If capsules have been employed as the vehicle to evaluate oral symptoms by DBPCFC, the lack of contact of the food with the oral cavity during the challenge may produce false-negative results. Also, subjective aversive symptoms in some patients may cause a positive final OFC.

So far there are many different challenge protocols and sometimes it is not possible to compare the results of DBPCFC carried out in different centers. A recent study has developed and validated several recipes for milk, soy, egg raw and cooked, peanut, hazelnut, and wheat for DBPCFC in children [36]. Further studies are needed to develop validated protocols for adult patients and different foods. An important issue is the threshold dose, which should be safe and also the cumulative dose which should be enough as some patients need higher doses of a food to elicit a reaction.

2 Managing food allergy

Once an objective diagnosis is established, the treatment for food allergy is to strictly avoid the ingestion of the food. Patients, parents, and personnel in care of children should have precise instructions about the identification of the food in labels, as the many different names under which a food is labeled may not be recognized by consumers. An important difficulty is the minimum quantity of the food present in food products considered to be included in the label. Recently, the European Parliament in an amendment of a previous EU food-labeling directive has established that a number of foods considered as allergenic should always be labeled as present, independently of the quantity included in food products (Table 1) [37]. It is also mandatory to list all sub-ingredients and specify the source of

Table 1. Ingredients which must be on the label, following the EU regulations

Cereals containing gluten (*i. e.*, wheat, rye, barley, oats, spelt, kamut, or their hybridized strains and products thereof)
Crustaceans and products thereof
Eggs and products thereof
Fish and products thereof
Peanuts and products thereof
Soybeans and products thereof
Milk and products thereof (including lactose)
Nuts, *i. e.* almond (*Amygdalus communis* L.), hazelnut (*Corylus avellana*), walnut (*Juglans regia*), cashew (*Anacardium occidentale*), pecan nut (*Carya illinoiesis (Wangenh.) K. Koch*), Brazil nut (*Bertolletia excelsa*), pistachio nut (*Pistacia vera*), macadamia nut and Queensland nut (*Macadamia ternifolia*) and products thereof
Celery and products thereof
Mustard and products thereof
Sesame seeds and products thereof
Sulfur dioxide and sulfites at concentrations of more than 10 mg/kg or 10 mg/L expressed as SO_2

ingredients previously listed as "natural flavors". Highly sensitive individuals may react to minimum traces of the food due to cross-contamination of food products elaborated in production lines where traces of allergenic food may still be present. In some countries such as the UK, Australia, New Zealand, and Canada labeling includes the term "may contain" particularly for peanut and nuts.

Even with appropriate instructions, the risk of an accidental ingestion is present in high-risk situations, with food consumption out of home such as in restaurants, buffets, fairs, and summer camps. It also can happen when a local manufacturer changes the components of a food being consumed locally [38]. In a recent study analyzing the circumstances of a series of fatal reactions to food, most of them happened to individuals who were known to have food allergy, most subjects had active asthma and most individuals did not have epinephrine available at the time of the reaction [39]. In school settings, the patient and/or the caregivers should have precise instructions for treatment in the case of an allergic reaction. All patients with previous severe reactions to a food, especially asthmatic patients should receive or self-administer epinephrine immediately and should be treated as soon as possible in an emergency department. In the case of small children, unable to self-inject, teachers or personnel in charge should be instructed in the use of epinephrine, which should always be present in first-aid kits in schools. Children allergic to food should not be excluded of any school activity, therefore the school should be provided with written information of the food implicated and written instructions on what to do in case of a reaction [40, 41].

3 New therapies for food allergy

Over the past several years, there has been a significant amount of research in the area of potential new therapies for food allergy. Conventional subcutaneous allergen immunotherapy has been attempted for peanut allergy. In a double-blind placebo-controlled trial of rush (rapidly increasing doses) peanut immunotherapy, increased tolerance to oral feeding with peanut was observed in four of six patients receiving the active immunotherapy but in none of the six control patients. The rate of serious adverse reactions, however, was unacceptably high, even during the maintenance phase of immunotherapy (39%) [42]. This important clinical investigation suggested that immunomodulation might eventually be used to induce oral tolerance in food allergic patients if the overall safety profile was improved.

Some studies have addressed the use of immunotherapy with birch pollen extracts in birch-sensitive subjects with OAS to apple with promising results [43, 44]. Attempts at hyposensitization with food have demonstrated good results in some cases, but schedules are time-consuming and the patients must consume the food regularly to maintain the tolerance [45].

Allergen-specific IgE antibodies play a central role in the pathophysiology of atopic disorders, including food allergy. IgE binds to high affinity receptors on the surface of mast cells and basophils. Cross-linking of IgE molecules on the surface of mast cells by allergen leads to release of preformed mast cells mediators (early phase of allergic reaction) as well as synthesis of pro-inflammatory cytokines and chemokines that result in late phase reaction [46]. Humanized monoclonal anti-IgE antibodies bind to the constant region (third domain of the Fc region) of the IgE molecule and prevent its binding to the receptor on mast cells and basophils. In addition, anti-IgE downregulates the expression of the high affinity receptor on mast cells and decreases basophile histamine release [47]. In clinical trials of anti-IgE for the treatment of asthma and allergic rhinitis, symptomatic improvement was observed when circulating levels of IgE antibodies were significantly reduced [48, 49]. Recently, a multicenter, randomized, double-blind, placebo-controlled clinical trial evaluated humanized monoclonal anti-IgE antibody (Tannox 901) in the treatment of peanut anaphylaxis [50]. The investigators were interested in determining if treatment with anti-IgE therapy would reduce the sensitivity of patients with peanut allergy following the ingestion of peanuts. The study included 84 adolescents and adults (12 – 60 years) with a history of immediate hypersensitivity following peanut ingestion. The patients had histories of urticaria, angioedema, lower respiratory symptoms and hypotension and their reactions were confirmed by DBPCFCs. In addition, they had positive skin

tests to peanut, serum IgE levels between 30 and 1000 IU/mL and no prior exposure to monoclonal antibodies. The study design included four dose cohorts of 28 patients each randomized 3 : 1 (Tannox 901 : placebo), including 150, 300, and 450 mg of Tannox 901 or placebo. Injections were administered subcutaneously every four weeks for four doses. The primary endpoint was a change in the threshold dose of peanut that elicited symptoms during an oral food challenge 15 – 30 days after the last day of study drug. Tannox 901 increased the threshold sensitivity to peanut flour in a dose responsive manner. The effect was highly significant at the 450 mg dose level. The anti-IgE was well tolerated with no evidence of treatment-related systemic adverse events and no evidence of treatment-related laboratory abnormalities (*e.g.*, complete blood counts, urinalysis, blood chemistries). Local adverse events including mild erythema, burning, and edema were noted for at least one injection in 13 – 14 patients in each dose cohort. Finally, there was no evidence of anti-drug antibodies. An average accidental peanut exposure is believed to be approximately one to two peanuts or less (*i.e.*, approximately 325 – 650 mg of peanut). Thresholds achieved in the 300 and 450 mg dose groups, 2083 and 2805 mg, respectively (*i.e.*, 6 – 8 peanuts) should provide substantial protection for most patients. Moreover, 21% and 24% of patients at these respective dose levels were able to ingest at least eight grams of peanut (*i.e.*, 24 peanuts) before experiencing an allergic reaction. Keep in mind, this therapy has not been approved for actual clinical use on patients with peanut allergy. Further studies, including the investigation of other preparations of humanized monoclonal anti-IgE antibodies need to be conducted. If ultimately successful, anti-IgE could potentially be used for patients with any food allergy, although the protection against anaphylaxis would require continued therapy at regular time intervals indefinitely.

4 Opportunities and challenges

A better understanding of the predictive information that can be obtained from results of food-specific IgE by skin prick testing and *in vitro* measurements (*e.g.*, quantitative IgE antibody assays, recombinant food allergens) and how this information can be used in the clinical setting are excellent opportunities for the allergist [51, 52]. As demonstrated above, this data can provide better predictive information regarding whether or not to subject a patient to an oral food challenge, as well as the overall clinical decision making process with patients who have food allergy.

Recent investigations have utilized novel technologies to map allergenic epitopes of many of the major food allergens and have determined specific IgE-binding using individual patient serum samples [53 – 59]. Both conformational and sequential epitopes have been identified when epitopes from major food allergens (*e.g.*, cow milk and egg) have been evaluated. While individuals who possess IgE antibodies to sequential epitopes react to the food in any form, including well cooked or partially hydrolyzed, those with IgE antibodies primarily to conformational epitopes appear to tolerate small amounts of the food after extensive heating or partial hydrolysis because the tertiary structure of the protein is altered and the conformational epitopes are disrupted [60, 61]. Moreover, investigators have demonstrated that patients with egg and cow milk allergy who have IgE antibodies directed to sequential epitopes tend to have persistent allergy, as compared to those with IgE antibodies to conformational epitopes who tend to develop clinical tolerance to the food [62, 63]. Published data also suggest that the determination of epitope-specific binding might correlate with clinical reactivity better than quantitative IgE values to the whole protein [64]. Further utilization and development of this technology should eventually have specific clinical applications including more reliable screening methods for food allergy, identification of potential cross-reactivities based on homologous epitopes, prediction of the development of oral tolerance and severity of allergic reactions to specific foods.

The allergist must remain updated in regard to new therapies on the horizon for food allergy. Hopefully, confirmatory studies will be published regarding the use of anti-IgE in this disease process. In addition, experimental therapies, such as the use of recombinant peanut proteins in murine models of anaphylaxis, may potentially lead to immunotherapy strategies for food allergy in the future. Research applications utilizing recombinant food allergens are becoming more apparent in the literature. Li and co-workers [65] have reported on the long-term immunotherapy effect of heat-killed *Escherichia coli* (HKE) producing engineered (*i.e.*, mutated) Ara h1, 2, and 3 (HKE-MP 123) administered rectally in a murine model of peanut allergy. Peanut-allergic mice received either HKE-MP 123 (at three doses), HKE-containing vector alone or vehicle alone (*i.e.*, sham-treated group). Challenges with peanut were performed at designated time points. The medium and high dose HKE-MP 123-treated mice remained protected for up to 10 weeks after treatment accompanied by a reduction of plasma histamine levels compared to the sham-treated group. IgE levels were significantly lower in all HKE-MP 123-treated groups, especially in the high dose group. Furthermore, IL-4, IL-13, IL-5, and IL-10 production by spleen cells of the high-dose HKE-MP 123-treated mice were significantly decreased and INF-γ and TGF-β production were significantly increased compared with sham-treated mice at the time of the last challenge. These investigators concluded that treatment with per rectal HKE-MP 123 induced a long-term decrease of peanut allergy, which may be secondary to specific cytokine profile production

patterns. The allergist will need to be an expert on the potential therapeutic applications of these therapies in clinical practice.

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