

Food allergy diagnostics: scientific and unproven procedures

Kirsten Beyer^a and Suzanne S. Teuber^b

Purpose of review

The accurate diagnosis of food allergy is crucial not only for the right treatment but also for the avoidance of unnecessary diets. The diagnostic work-up of suspected food allergy includes the measurement of food-specific IgE antibodies using serologic assays, the skin prick test, elimination diets and oral provocation tests. In addition, some approaches are either under further rigorous investigation (the atopy patch test) or are already in widespread use, particularly by practitioners of alternative or complementary medicine, but are considered unproven. These diagnostic methods include specific IgG to foods, provocation/neutralization testing, kinesiology, cytotoxic tests and electrodermal testing. This review covers some of the most common scientifically validated and unproven approaches used in the diagnosis of food allergy.

Recent findings

For specific serum IgE and the SPT, decision points have been established for some foods, allowing prediction of clinical relevance. The APT may be helpful, especially when considered in combination with defined levels of specific IgE. In regard to other approaches, most scientific studies do refute the usefulness of these approaches.

Summary

In most patients, controlled oral food challenges remain the gold standard in the diagnostic work-up of suspected food allergy. The skin prick test and measurement of specific IgE antibodies to food extracts, individual allergens or allergenic peptides are helpful in the diagnostic approach. Food-specific IgG continues to be an unproven or experimental test. The other alternative and complementary techniques have no proven benefit and may endanger patients via misdiagnosis.

Keywords

atopy patch test, cytotoxic test, electrodermal testing, food-specific IgE, food-specific IgG, kinesiology, oral food challenge, provocation tests, skin prick test

Abbreviations

APT	atopy patch test
DBPCFC	double-blind, placebo-controlled food challenges
IBS	irritable bowel syndrome
SPT	skin prick test

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Introduction

In Westernized countries, food allergy is among the most common of the allergic disorders, resulting from an immune response to a food. About 6–8% of children and 2–3% of adults are affected. Moreover, the prevalence rate is higher in patients with atopic dermatitis, with around one-third of these children having a clinically relevant food allergy [1,2]. Cow's milk, hen's egg, peanut, tree nuts, fish, shell fish, soy and wheat are the most common offending foods. Clinical reactions to these foods range from mild skin symptoms to life-threatening anaphylactic reactions. However, the perception of food allergy in the public is different and around 20% of individuals describing a multitude of ailments and reactions believed them to be associated with food ingestion.

The diagnostic work-up of suspected food allergy starts with a detailed patient history and physical examination of the patient. The further work-up of the patient includes various in-vitro and in-vivo tests. In this article, we will cover the most recent literature on the most common approaches, such as the skin prick test (SPT), measurement of food-specific IgE antibodies, and oral provocation tests. The recently developed atopy patch test (APT) is also reviewed. Additional techniques in use, but especially by practitioners of alternative or complementary medicine, such as measurement of food-specific IgG or IgG4 antibodies, cytotoxic food tests, kinesiology, provocation/neutralization testing and electrodermal testing, will be critically reviewed.

Oral food challenges

Oral food challenge tests are performed in order to prove that allergens play a role for the individual clinical symptoms or to exclude food allergy in order to prevent the patient from unnecessary or even harmful elimination diets. Although oral challenges are still the most valuable diagnostic procedure, they are time-consuming, expensive and troublesome for the patient, and include the risk of severe anaphylactic reactions. However, Perry

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^aChildren's Hospital Charité, Humboldt University, Berlin, Germany and ^bUniversity of California, Davis, School of Medicine, Davis, California, USA

Correspondence to Kirsten Beyer, MD, Department of Pediatric Pneumology and Immunology, Children's Hospital Charité, Humboldt University, Augustenburger Platz 1, 13353 Berlin, Germany
Tel: +49-30-450559054; fax: +49-30-450566931;
e-mail: kirsten.beyer@charite.de

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et al. showed, in a retrospective chart review performed on children who underwent food challenges to milk, egg, peanut, soy and/or wheat in a university-based pediatric allergy clinic over a 7-year period, that the risks of oral food challenges are reasonable when challenges are performed under the guidance of an experienced practitioner in a properly equipped setting [3]. Oral food challenge tests should always be performed in a controlled manner. In general, double-blind, placebo-controlled food challenges (DBPCFC) represent the 'gold standard' for diagnosing food allergy [4–6]. DBPCFC are especially indicated if subjective symptoms or day-to-day variations of atopic dermatitis play a major role [7•]. However, children of less than 1 year of age will rarely report subjective symptoms. Therefore, these children might undergo open food challenges. Oral food challenge tests should be always done under medical supervision. Indications for hospitalizing patients for oral food challenges include life-threatening events in the past or challenges with highly allergenic foods.

The prognosis of food allergy is generally good, with the majority of children becoming tolerant over time. Therefore, children should be re-evaluated at regular time intervals. For cow's milk and hen's egg allergy, 12–18 months may be practical. However, for peanut and tree nut allergies that are not often outgrown, longer time intervals may be meaningful.

Measurement of specific serum IgE

Measurement of food-specific serum IgE plays a major role in IgE-mediated food allergy. Advances in technology have provided new laboratory tools for the quantitation of allergen-specific IgE antibodies in serum and on the surface of basophils. An excellent review by Hamilton *et al.* examines the evolution from qualitative IgE antibody assays of the late 1960s to the present-day, third-generation, automated and quantitative allergen-specific IgE assays [8••]. The latest technology trend is toward microarrays in which crude or purified native and recombinant allergens can be spotted in microdot arrays on chips to permit extensive panels of specific IgE measurements to be performed with small quantities of serum. They discuss the further requirements for optimization of these new techniques and their potential abuses [8••].

Recently, food allergen-specific IgE concentrations in the serum have been correlated with the outcome of oral food challenges in order to generate probability curves that depict the likelihood of patients with a particular food allergen-specific IgE level reacting to the food. Diagnostic decision points for food allergen-specific serum IgE concentration have been described for peanut, egg, milk and fish [9–14,15•,16•]. For other foods, such as

wheat and soy, diagnostic decision points could not be established [15•,17]. However, these diagnostic decision points vary remarkably among authors and populations studied [7•]. Especially, the age of patients appears to play an important role [14,15•]. Moreover, there are still conflicting views whether changes in specific serum IgE levels predict the development of clinical tolerance [18,19•,20,21••]. Vanto *et al.* followed prospectively 95 infants with immediate and 67 with delayed reactions to cow's milk up to the age of 4 years [19•]. Cow's milk allergy was assessed annually by cow's milk challenges. They were able to show that milk-specific IgE in the serum are useful prognostic indicators of the development of tolerance to cow's milk in infants with cow's milk allergy. Moreover, recent data showed a relationship between the decrease in food-specific IgE levels over a specific time period between two challenges and tolerance development [21••]. A greater decrease in specific IgE levels over a shorter period of time was indicative of a greater likelihood of developing tolerance. However, additional studies on larger patient populations may be necessary to elucidate this aspect. In addition, the use of peptide-specific IgE seems to be a valuable parameter in predicting the outcome of tolerance development [22–24]. In general, qualitative difference in epitope diversity might provide prognostic information about food-allergic patients [25•].

Whether the amount of total IgE should be taken into account in the interpretation of food-specific IgE levels has been recently evaluated. It was shown that the determination of the ratio of specific IgE:total IgE for diagnosing symptomatic food allergy offers no advantage for cow's milk, hen's egg, wheat or soy [26•].

Skin prick tests

For decades, sensitization to allergens has been measured using the SPT. Comparing results from different studies, the prick technique and the source of allergens used has to be taken into account. With foods, the use of native allergens seems to be superior to commercial extracts [27]. Similar to those for food-specific IgE, efforts have been made to develop diagnostic decision points for the wheal size diameters predicting the outcome of oral food challenge procedures. On the basis of 555 open food challenges in 467 children, Hill *et al.* showed recently that a food-specific SPT wheal diameter of at least 8 mm for cow's milk, 7 mm for hen's egg and 8 mm for peanut was '100% diagnostic' for allergic reactions using certain commercial extracts [28••]. In children of less than 2 years of age, the corresponding wheal diameters were 6, 5 and 4 mm, respectively [28••]. In a German population, 735 oral food challenges were retrospectively analyzed. Calculating 95% predicted probabilities using logistic regression, positive predictive decision points of 13 mm were determined for hen's egg and cow's milk, respectively.

In this study native allergens were used. Similar to the measurement of food-specific IgE, no decision points could be determined for soy, and only in a subset of patients for wheat (Verstege *et al.*, manuscript submitted). In another study, Vanto *et al.* prospectively followed 95 infants with immediate and 67 with delayed reactions to cow's milk up to the age of 4 years [19[•]]. Cow's milk allergy was assessed annually by cow's milk challenges. They were able to show that SPT and milk-specific IgE in the serum are useful prognostic indicators of the development of tolerance to cow's milk in infants with cow's milk allergy.

Atopy patch tests

The APT involves the epicutaneous application of intact protein allergens in a diagnostic patch test setting, with an evaluation of the induced eczematous skin lesions targeting the cellular component of the reaction. As reviewed 3 years ago in this *Journal*, the atopy patch test is developing into a potentially valuable additional tool in the diagnostic work-up of food allergy in infants and children with atopic dermatitis [29]. The combination of positive atopy patch tests together with defined levels of specific IgE appeared to make DBPCFC superfluous in some cases. Moreover, for wheat allergy, for which measurement of specific IgE and SPT gives unsatisfactory results, the APT proved to be the most reliable test, and the PPV of 94% could not be improved by a combination with other allergy tests [30]. Confirming previous studies, a European multicenter study showed that the APT had a higher specificity than SPT or specific serum IgE [31[•]]. In contrast, Hansen *et al.* showed recently that the APT with fresh whole egg extract was not able to increase the diagnostic accuracy in detecting egg-allergic children with atopic dermatitis compared with SPT [32]. However, the study comprised only a small number of patients, including control subjects. Similarly, Breuer *et al.* showed a poor reliability of the APT analyzing retrospectively 106 DBPCFCs to cow's milk, hen's egg, wheat and soy in 64 children with atopic dermatitis [33[•]]. In another study, Osterballe *et al.* showed similar results studying 486 unselected children of 3 years of age [34]. They concluded that the APT could not predict food hypersensitivity not predicted by SPT or specific IgE measurement. These controversial data might be explained by the fact that the APT is sometimes difficult to interpret, with non-specific reactions occurring frequently. As a number of apparently minor test modifications greatly influence the sensitivity, specificity and reproducibility of the APT, the European Task Force on Atopic Dermatitis (ETFAD) has recently developed a standardized APT technique [35[•]]. Moreover, the occlusion time seems to be very important for the test outcome. Rance was able to show that the sensitivity, positive predictive value and negative predictive value were all better for a 48-h than for a

24-h occlusion time [36[•]]. For now, the test appears to be very promising in specific circumstances, but additional refinements continue to be made.

Measurement of food-specific IgG or IgG4

Food-specific IgG or IgG4 panels are advertised as diagnostic instruments for food allergy, despite the fact that it is normal to produce specific IgG and IgG4 to commonly eaten foods without manifesting symptoms of food allergy. Several large commercial laboratories in the United States and Europe offer these tests to physicians and also directly to the patients. It is claimed that such antibodies can identify food intolerances that cause or contribute to chronic fatigue, nasal congestion, sinus problems, headache, hyperactivity, irritable bowel syndrome (IBS), arthritis and almost any somatic or mental symptom. As an example, in an unblinded, open study of patients with multiple subjective symptoms, patients improved after eliminating foods from their diet to which they had elevated IgG levels. However, this intervention did not include a sham group, nor was there subsequent correlation with DBPCFC; therefore, the placebo effect was likely extremely relevant [37]. In a previous review in this *Journal*, focusing on unproven diagnostic and therapeutic approaches to measurement of food-specific IgG, it was concluded that there was no evidence to support the diagnostic efficacy of food-specific IgG in any particular disorder, besides the rare syndrome of food-induced pulmonary hemosiderosis (Heiner's syndrome) [38]. Only a few additional studies have been published since then.

Atkinson *et al.* assessed the therapeutic potential of dietary elimination on the basis of the presence of IgG antibodies to food in 150 outpatients with IBS [39]. Patients were randomized to receive either a diet excluding all foods to which they had raised IgG antibodies or a sham diet excluding the same number of foods but not those to which they had antibodies. They were able to show that the true diet resulted in a statistically significant 10% greater reduction in symptom score than the sham diet and concluded that this technique is worthy of further biomedical research. The diets of the two groups were, however, not comparable.

In another study on 113 patients with IgE-mediated cow's milk allergy, Shek *et al.* were able to show that there was a significant positive correlation between IgE levels and levels of the other immunoglobulin isotypes for milk proteins [40[•]]. Although the production of IgA and IgG antibodies to cow's milk protein is a normal physiological response to the ingestion of milk [40[•]], the patients with cow's milk-induced IgE-mediated reactions in the study by Shek *et al.* produced significantly more of these antibodies than the controls [41]. However, these isotypes were unlikely to be pathogenic, since they

were found also in the control group of patients who tolerate cow's milk, with a great overlap in the levels of cow's milk-specific IgG or IgG₄ between patients and controls. We speculate that the increased levels of milk-specific antibodies in patients with cow's milk allergy may be a result of increased gut permeability, resulting in greater passage of antigen into the circulation and the formation of more antibodies. It also may be a reflection of the Th2 bias in allergic individuals, as Th2 cytokines such as IL-4 are more efficient inducers of immunoglobulin synthesis. However, as a diagnostic tool food-specific IgG or IgG₄ does not add any information. Taken together, measurement of food-specific IgG or IgG₄ in IgE-mediated food allergy does not add any information and is unnecessary. However, additional studies are desirable to investigate the role of food-specific IgG or IgG₄ in IBD.

Sublingual or intradermal provocation tests

Provocation testing to foods involves sublingual or intradermal 'provocation' by a test antigen, followed by an observation period, at which a local response is measured and *any* subjective symptoms are reported. We reported in the last review in this *Journal* [38] that two blinded, controlled studies have been published showing that these intradermal provocation tests rely on a placebo response [42,43]. Since then, no additional studies have been published. Therefore, these provocation tests should be considered as a disproven technique. Moreover, although adverse outcomes of such testing are rare, there are reports on severe adverse reactions following these procedures [44,45].

Kinesiology

Another frequently used alternative technique in the diagnosis of food allergy is applied kinesiology or muscle response testing. During this procedure, the patient holds a vial with a specific food item in one hand while the practitioner tests the muscle strength of the opposite arm by applying light pressure to the forearm. The diagnosis of food allergy or intolerance is based on the energy balances that manifest in the muscle response. We reviewed the literature on this technique 2 years ago [38] and concluded that the evidence suggests that this diagnostic modality is not validated when subjected to scrutiny. No further evidence has been reported since then; therefore, we still conclude that kinesiology as a diagnostic tool is no better than random guessing.

Cytotoxic test and equivalents

The cytotoxic test for food allergy is a blood test in which changes in the morphology of leucocytes are investigated. This original version of the cytotoxic food test became popular in the 1970s and 1980s [46]. In that version, a dried film of food extract on a slide was the substrate to

which a fresh drop of whole blood was added. Any morphologic change was considered positive. Although this test was shown to be non-reproducible [47], its core concept drives several current assays available using modern cellular approaches in a modified way [48]. Since our last review in this *Journal* [38], there are no additional published, peer-reviewed studies on this assay available. Despite the fact that its use is not supported by the literature available [49], the test is widely used by patients.

Electrodermal testing

Electrodermal testing involves placing the patient in a circuit with a machine that uses a galvanometer to measure skin conductance. A sealed glass vial of the food extract is put in contact with an aluminum plate within the circuit. If there is a drop in conductance, 'allergy' is diagnosed in view of the perturbation in the electromagnetic field. In our last review, we cited two double-blind, placebo-controlled studies of this technique [38]. In these studies, the testing could not distinguish between atopic and non-atopic participants [50], or between allergens and negative controls. A poor reproducibility of the method was noted in particular [51]. No additional peer-reviewed papers have been published so far. Therefore, we still conclude that electrodermal testing cannot be recommended for the diagnosis of food allergy, since it is without established scientific basis.

Conclusions

Controlled oral food challenges remain the most important diagnostic tools in suspected food allergy. In children of less than 1 year of age without atopic dermatitis, these challenges might be open; otherwise, DBPCFC are the gold standard. In selected cases, decision points for food-specific serum IgE or SPT wheal diameter may make oral challenges superfluous. The APT, which is continuing to undergo evaluation in the context of comparison with controlled oral food challenges, might provide additional information in patients with atopic dermatitis, if properly performed. Moreover, measurement of specific IgE over time could aid clinicians in prognosis and in timing subsequent food challenges, thereby decreasing the number of premature and unnecessary DBPCFC.

Despite the fact that alternative or experimental and unproven approaches are used widely in the diagnostic evaluation of food allergy, measurement of food-specific IgG or IgG₄ antibodies, sublingual or intradermal provocation tests, kinesiology, cytotoxic testing and electrodermal testing are not supported by current scientific evaluations. Therefore, these approaches cannot be recommended as a meaningful element in the diagnostic work-up of food allergy.

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