

Improving in-vitro tests for the diagnosis of food hypersensitivity

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Food hypersensitivity reactions affect up to 8% of children under 3 years of age and approximately 2.5% of the general United States population. Food allergic disorders may be subdivided into either IgE-mediated or cell-mediated reactions. The diagnostic 'gold standard' of 'symptomatic' food allergies remains the blinded oral food challenge because of the poor specificity of patient histories, skin testing and standard radioallergosorbent tests, and the outcomes of elimination diets. Little progress has been made in the development of in-vitro tests for the diagnosis of cell-mediated food hypersensitivities. However, new developments in in-vitro technologies have improved the capabilities of these tests to diagnose IgE-mediated reactivity and perhaps predict the development of future 'tolerance', i.e. 'outgrowing' the allergy. *Curr Opin Allergy Clin Immunol* 2:257–261. © 2002 Lippincott Williams & Wilkins.

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Abbreviation

RAST radioallergosorbent test

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Introduction

In the past decade the public and primary care physicians have become increasingly aware of food allergic disorders, especially in children. Food hypersensitivity reactions are most prevalent in young children, affecting up to 8% of children under 3 years of age and approximately 2.5% of the general population of the United States [1]. As depicted in Table 1, food allergic disorders can be subdivided into those that are of rapid onset and primarily IgE-mediated, those that are delayed in onset and primarily cell-mediated, and an intermediate group that are mediated by components of both IgE- and cell-mediated hypersensitivity reactions and are variable in their onset. The diagnosis of food allergy relies upon a careful history, selective skin tests or in-vitro measurement of food-specific IgE if an IgE-mediated disorder is suspected, an appropriate exclusion diet, and blinded oral food challenges.

At present, there is no evidence of any diagnostic value of food-specific IgG or IgG₄ antibody levels, food antigen–antibody complexes, evidence of lymphocyte activation (³H uptake, IL-2 production, leukocyte inhibitory factor production, etc.), or sublingual or intracutaneous provocation studies [2]. Food antigen-specific IgG (or IgG₄) antibodies are generally elevated in patients with food allergy affecting the gastrointestinal tract, but their specificities typically reflect the type of foods ingested, and are not indicative of a specific food-related pathogenesis [3]. Food antigen-specific lymphocyte activation also appears to reflect exposure and is not diagnostic of cell-mediated food hypersensitivity [4].

Table 1. Food hypersensitivity disorders: mechanistic classification

IgE-mediated – 'immediate' onset:	
Gastrointestinal	Oral allergy syndrome, gastrointestinal anaphylaxis
Cutaneous	Urticaria, angioedema, morbilliform rashes and flushing
Respiratory	Acute rhinoconjunctivitis, bronchospasm (wheezing)
Generalized	Anaphylactic shock
Mixed IgE- and cell-mediated – 'variable' onset:	
Gastrointestinal	Allergic eosinophilic esophagitis Allergic eosinophilic gastroenteritis
Cutaneous	Atopic dermatitis
Respiratory	Asthma
Cell-mediated – 'delayed' onset:	
Gastrointestinal	Food protein-induced enterocolitis Food protein-induced proctocolitis Food protein-induced enteropathy syndromes, celiac disease
Cutaneous	Contact dermatitis, dermatitis herpetiformis
Respiratory	Food-induced pulmonary hemosiderosis (Heiner's syndrome)

Skin-prick tests and radioallergosorbent tests (RASTs) have been utilized since the 1970s to detect evidence of IgE sensitivity to various foods. Skin-prick tests are highly reproducible [5] and are frequently utilized to screen patients with suspected IgE-mediated food allergies. As reported by Bock *et al.* [6], any food allergens eliciting a wheal at least 3 mm greater than the negative control are considered positive; all others are considered to be negative. Positive skin tests indicate the possibility that the patient has symptomatic reactivity to the specific food (overall positive predictive accuracy is less than 50%), whereas negative skin tests confirm the absence of IgE-mediated reactions (negative predictive accuracy is greater than 95%) if good quality food extracts are utilized [7–12]. Therefore, the skin-prick test may be considered an excellent means of excluding IgE-mediated food allergies, but is only ‘suggestive’ of the presence of clinical food allergies. RASTs and similar in-vitro assays (including enzyme-linked immunosorbent assays) for identifying food-specific IgE antibodies are also frequently used to screen for IgE-mediated food allergies. Although generally considered to be slightly less sensitive than skin tests, one study comparing the Phadebas RAST with double-blind, placebo-controlled food challenges [10] found skin-prick tests and RASTs to have similar sensitivity and specificity to the food challenge outcome when ‘Phadebas scores’ of three or greater were considered positive. More recently, the use of a quantitative measurement of food-specific IgE antibodies has been shown to be more predictive of symptomatic IgE-mediated food allergy.

In-vitro assays for the diagnosis of IgE-mediated food allergy

Several studies analyzing serum levels of food-specific IgE antibodies suggested that there was a direct correlation between the quantity of food-specific IgE and the likelihood that the patient would experience an allergic reaction after ingestion [13,14], and the likelihood that the patient would ‘outgrow’ their clinical reactivity [13,15,16]. In the past decade, a commercial test has become available that provides a quantitative measurement of allergen-specific IgE antibodies, the CAP-System fluorescent immunoassay (CAP-System FEIA; Pharmacia-Upjohn Diagnostics, Uppsala, Sweden) [17].

Utilizing the CAP-System fluorescent immunoassay to quantify food-specific IgE antibody concentrations in previously diagnosed food allergic patients (median age 5 years), we were able to establish ‘diagnostic decision points’ that were 95% or greater predictive of clinical reactivity to egg, milk, peanut and fish in a subset of children with atopic dermatitis [18]. As this patient group is known to have markedly elevated serum IgE levels, a

second prospective study was performed to determine the validity of these diagnostic decision points in a more representative group of children and adolescents referred for evaluation of food allergy. One hundred children (62% male; median age 3.8 years, range 0.4–14.3 years) were evaluated for food allergy [19•]. The diagnosis of ‘food allergy’ was established by ‘unequivocal’ history or oral food challenge. On the basis of the previously established 95% predictive ‘decision points’ for egg, milk, peanut and fish allergy, over 95% of food allergies diagnosed in that prospective study were correctly identified by quantifying serum food-specific IgE concentrations. Table 2 lists the recommended ‘diagnostic decision points’ for the major childhood food allergens based on the study. Food-specific IgE levels exceeding the ‘diagnostic decision point values’ indicate that the patient is greater than 95% likely to experience an allergic reaction if he or she ingests the specific food. For example, a physician would not need to perform an oral egg challenge on a child if the egg-specific IgE was 7 kU_A/l or greater, as it is more than 95% likely that the child would experience a positive reaction. If the egg-specific IgE was less than 7 kU_A/l but 0.35 kU_A/l or greater, the physician would need to perform some form of egg challenge to determine if the child was truly reactive to egg.

In young infants, especially those without atopic dermatitis, the ‘diagnostic decision points’ of food-specific IgE antibodies are likely to be lower than the values listed in Table 2. For example, Garcia-Ara *et al.* [20•] evaluated 170 infants under 1 year of age who were suspected of having milk allergy. The investigators found that 44% of the infants referred experienced ‘immediate’ reactivity to an open oral milk challenge. Utilizing an approach similar to that described above, they found that a serum milk-specific IgE level of 5 kU_A/l or greater was 95% predictive and 2.5 kU_A/l was 90% predictive of clinical reactivity to milk. The same group [21•] evaluated infants under 2 years of age with a history of reactivity to egg, and found that they were

Table 2. Food-specific IgE concentrations predictive of clinical reactivity [19•]

‘Decision point’ Allergen	[kU _A /l]	Sensitivity	Specificity	PPV	NPV
Egg	7	61	95	98	38
(Infants ≤ 2 years) ^a	2			95	95
Milk	15	57	94	95	53
(Infants ≤ 1 year) ^b	5			>95	
Peanut	14	57	100	100	36
Fish	20	25	100	100	89
Soybean	30	44	94	73	82
Wheat	26	61	92	74	87
Tree nuts ^c	~15	–	–	~95	

^aBoyano *et al.* [21•]. ^bGarcia-Ara *et al.* [20•]. ^cProposed but not yet confirmed values.

94% likely to react to egg if the serum-specific IgE levels to egg white were greater than 0.35 kU_A/l. Without a clear history of reactivity, a level of 2 kU_A/l or greater was more than 95% predictive of clinical reactivity. Further studies will be necessary with larger numbers of food-allergic children to determine more precise, age-related diagnostic decision points.

As noted in Table 2, the positive predictive values of the wheat and soy diagnostic decision points are less than 75%, suggesting that the allergens used in the test are suboptimal or have extensive cross-reactivity with other allergens. A recent study by Palosuo and coworkers [22•] determined that the presence of IgE antibodies to omega-5 gliadin, a water insoluble protein found in wheat, was more than 95% specific and predictive for patients with challenge-confirmed wheat allergy. The study suggested that the identification of the major allergenic protein in various foods is critical for more accurate laboratory diagnoses.

In-vitro assays for predicting the development of clinical tolerance in IgE-mediated food allergy

A number of studies suggested that the majority of young infants will 'outgrow' (become clinically tolerant to) their food allergies. Prospective studies from a number of countries indicated that approximately 2.5% of newborn infants experience hypersensitivity reactions to cows' milk in the first year of life [1], with IgE-mediated reactions accounting for approximately 60% of these reactions. Most infants with non-IgE-mediated cows milk allergy 'outgrow' their sensitivity by the third year of life [23], but approximately 25% of infants with IgE-mediated cows' milk allergy retain their sensitivity into the second decade, and approximately 35% develop allergic reactions to other foods [24]. Hypersensitivity reactions to egg occur in approximately 1.6% of young children [25], and to peanut in 0.5% of children in the UK [26] and the USA [27]. Approximately two-thirds of egg-allergic children 'outgrow' their egg allergy and 15–20% of young infants 'outgrow' their peanut allergy by 5 years of age [28••].

As noted above, a number of studies found that food-allergic patients with high levels of food allergen-specific IgE were more likely to react to the food upon challenge compared with patients with low levels of food-specific IgE, and suggested that these levels could be monitored to determine when a patient may be challenged to determine if the food allergy had been outgrown [13,14,16]. Crespo *et al.* [15] challenged 40 children with egg allergy after 2.5 years of egg elimination. The results of oral challenges were correlated with egg-specific serum IgE levels. A likelihood ratio of 6.3 was found if the egg-specific IgE was

1.2 kU_A/l, prompting the investigators to conclude that follow-up challenges could be delayed in children with serum egg-specific IgE concentrations greater than 1.2 kU_A/l, as it was highly likely that they would still be clinically reactive. Recent studies supported the notion that IgE levels can be monitored to assist the physician in determining when it may be worthwhile rechallenging a patient with food allergy. Such studies [19•,28••] suggested that if serum food-specific IgE levels fall to less than 1.5 kU_A/l for egg, less than 7 kU_A/l for milk, and less than 5 kU_A/l for peanut, provided the patient has not experienced an allergic reaction in the previous 2–3 years, they should be challenged to determine whether he or she has 'outgrown' their food allergy.

IgE (allergenic) and IgG (antigenic) binding to proteins occurs at sequential epitopes, i.e. antigenic determinants consisting of single segments of sequential amino acids along the polypeptide chain, or conformational epitopes, i.e. antigenic determinants consisting of amino acids from different parts of the protein sequence that have been brought together by protein folding. When mapping allergenic sequential epitopes on ovomucoid, it was noted that children who failed to 'outgrow' their egg allergy possessed IgE antibodies to sequential epitopes, whereas children who 'outgrew' their egg allergy did not [29]. It was shown that the latter group made IgE antibodies only to conformational epitopes. As extensive cooking is known to alter the three-dimensional structure of proteins, it also was suggested that egg-allergic patients with IgE antibodies primarily to conformational epitopes were likely to tolerate baked products containing small amounts of egg protein. This concept was supported by the report by Urisu *et al.* [30], who found that approximately half the children reacting to freeze-dried egg white did not react to cooked egg white. Similar results were seen when the conformation of ovomucoid was destroyed by digesting the protein with pepsin [31]. To determine whether this phenomenon was restricted to egg allergy, or whether it represented a more general mechanism related to food antigen processing by the gut-associated lymphoid tissue, IgE and IgG antibody binding sites were mapped on the major milk allergenic proteins [32•,33,34•,35]. In general, the caseins (α_{s1} -, α_{s2} -, κ - and β -caseins) lack a fixed tertiary structure, as seen with ovomucoid. Nevertheless, studies mapping the IgE-binding epitopes of the four caseins identified a number of sequential epitopes (termed 'informative' epitopes) that were recognized by IgE from children with persistent milk allergy and not by children who outgrew their milk allergy. In the initial study by Chatchatee *et al.* [32•] it was shown that children with persistent milk allergy developed IgE antibodies to the 'informative' epitopes at an early age, suggesting that the immunological response leading to

persistent milk allergy is established early in life. This finding also suggests that evaluating milk allergic infants for the presence of IgE antibodies to 'informative' epitopes could be used to distinguish infants with persistent or transient milk allergy in the first few years of life. These findings may also have implications for the dietary advice given to milk-allergic patients, as noted above for egg-allergic individuals. During food processing and cooking, the native structure and many conformational epitopes are modified or disrupted by heat and chemical treatments, eliminating IgE binding to conformational epitopes and exposing sequential (linear) epitopes. Therefore, it may not be necessary for children lacking IgE antibodies to informative sequential epitopes on cows' milk proteins to avoid all cooked-milk products. Further studies are underway to establish whether a less restrictive diet will influence the time required to 'outgrow' milk allergy in such patients.

In-vitro assays for the diagnosis of cell-mediated food allergy

As noted above, there are no in-vitro diagnostic studies that are predictive of food-induced cell-mediated hypersensitivities. The only possible exception to this statement is the use of serological assays in the diagnosis of celiac disease, which is an autoimmune disorder of the small intestine resulting from an inappropriate T-cell-mediated immune response against ingested gluten in individuals expressing the HLA-DQ2 or HLA-DQ8 heterodimer [36^{*}]. Tissue transglutaminase-catalyzed deamidation of gliadin peptides increases their potency for activating patient-derived, gliadin-specific T cells, suggesting that tissue transglutaminase plays a causative role in the onset of an inflammatory response to gluten-containing grains. The measurement of IgA anti-gliadin, anti-endomysial and anti-tissue transglutaminase antibodies has shown them to be very sensitive and specific indicators for the diagnosis of celiac disease, e.g. the enzyme-linked immunosorbent assay for tissue transglutaminase has 95% or greater sensitivity and specificity in celiac patients ingesting gluten-containing foods. Although a small bowel biopsy is still recommended to establish the diagnosis of celiac disease, these serological tests have dramatically reduced the need for second biopsies. In addition, these tests can be used to monitor the adequacy of the gluten-free diet, because the presence of antigen-specific IgA disappears after complete gluten elimination.

Conclusion

The 'gold standard' for diagnosing various food hypersensitivity disorders remains the oral food challenge. In the past few years, in-vitro quantitative laboratory tests have been developed that are more predictive of IgE-mediated food hypersensitivity and celiac disease. With the improved definition of IgE antibody interaction with

allergens at the molecular level, in-vitro tests may be capable of distinguishing patients with 'life long' food allergies from those who will outgrow their allergy and allow a more liberal diet in a subset of patients.

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