

EDITORIAL

Are specific immunoglobulin E titres reliable for prediction of food allergy?

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Introduction

Food allergy in young children is frequently IgE mediated. Symptoms are most often elicited by cow's milk, hen's egg, peanuts and nuts, as well as wheat and soy. Common manifestations of food allergy include urticaria, flares of atopic dermatitis, respiratory symptoms such as acute asthma and/or rhino-conjunctivitis as well as multi-systemic symptoms of anaphylaxis [1, 2]. In most cases, the diagnosis is assessed by a clear clinical picture and positive IgE tests (i.e. positive skin prick tests (SPTs) and/or specific IgE titres). However, a significant percentage of children with IgE-mediated food allergy, especially those with atopic dermatitis, might have misleading positive tests because of sensitization in the absence of clinical food allergy [3, 4].

Standardized food challenges, in particular double-blind, placebo-controlled food challenges (DBPCFC), have greatly enhanced the accuracy of the diagnosis of food allergy in young children. Over time, numerous trials have used them as a gold standard for diagnosis, and they have become more common in clinical practice as well [5, 6]. In the hands of well-trained practicing allergists, these procedures are routine but remain rather time consuming (4–6 h for one food challenge). Consequently, only a limited number of well-selected foods might be tested by DBPCFC for each patient. In order to overcome these limitations, several investigators have examined the possibility of predicting which patients could be tolerant to foods by determination of cut-off values.

Predictors of allergy or tolerance acquisition

A suggestive history is the best predictor of food allergy at the time of diagnosis, or of tolerance acquisition during the follow-up. Indeed, the patient who has been naturally or accidentally exposed to a 'normal' amount of food without any reactions can be considered as tolerant and no further investigations are needed.

When allergy testing is needed, skin prick testing is the most rapid and cost-effective procedure. Several studies have examined cut-off values of mean weal diameters elicited by SPTs [7–9]. However, major caveats related to the methodology need to be pointed out. First, many different extracts are commonly used. Second, the method might vary from centre to centre. Finally, reading times might vary. Consequently, cut-off values by SPTs might be used in a given clinical setting but are very seldom applicable to others.

Unlike SPTs, serum-specific IgE titres can be measured by standardized methods (e.g. CAP FEIATM System, Pharmacia Diagnostics, Uppsala, Sweden; Magic LiteTM, ALK-ABELLÓ, Hørsholm, Denmark) using standardized allergens. In 1997,

based on retrospective data, Sampson and Ho [10] published a landmark study on specific IgE cut-off points to six common foods correlated to the outcome of DBPCFC. In 2001, the study was repeated in a prospective design on data from 100 consecutive patients with food allergy [11]. Their cut-off points in order to predict allergy were 7 kU/L to egg, 15 kU/L to milk, 14 kU/L to peanuts, 20 kU/L to fish, 65 kU/L to soy, and 80 kU/L to wheat. From this time on, many allergists did, at least in part, refer to these cut-off points in order to decide if a food challenge was necessary, or possibly potentially harmful to the patient. Boyano et al. [12] followed in 2001 with the publication of a prospective study on egg-allergic children. Open food challenges to hen's egg in 81 children were correlated to skin prick testing and serum-specific IgE titres. Similar to Sampson, they determined by receiver operating characteristics analysis the cut-off value of specific IgE. In their population, the 90% predictive value for egg was ≥ 0.35 kU/L. A further study examining egg allergy was published in 2003 by Osterballe and Bindslev-Jensen [13]. In their population, the 95% cut-off point was 1.5 kU/L (Table 1).

In this issue of *Clinical and Experimental Allergy*, Celik-Bilgili et al. [14] provide additional data on predictive value of specific IgE for the diagnosis of food allergy. This group of investigators conducted a retrospective study based on data from 501 children admitted to their wards for suspicion of food allergy. Eighty-eight percent of the patients suffered from atopic dermatitis (54% were scored as having mild atopic dermatitis). They were routinely challenged by DBPCFC to cow's milk, hen's egg, wheat and soy. Specific IgE values to the four foods were then correlated to the outcome of the challenges. In this population, the cut-off point for a 95% probability of allergy to cow's milk was 46 kU/L and for hen's egg 10 kU/L, values largely differing from those published previously.

The initial reports by Sampson were a great help to practicing allergists, although most of them were aware that these values did not constitute the ultimate and unique guideline for clinical practice. The other studies published thereafter and commented above might have shed some confusion, but have mostly highlighted the limitations inherent to cut-off values for the diagnosis of food allergy.

Subsequently, how shall we proceed? First, and all authors agree on this fact, the study populations were not similar. Sampson et al. studied a population that was older than in the three other reports and was in the majority referred for atopic dermatitis. Conversely, only 43% of the patients recruited by Boyano suffered from atopic dermatitis. Second, when looking at the outcome of the food challenges, Celik-Bilgili report a significant amount of late or combined early and late reactions (33%). The other studies cited above might not have been designed to observe late reactions. Third, the type of

Table 1. Summary of results from studies using specific IgE cut-off points for prediction of food allergy

Authors	Sampson [11]	Boyano et al. [12]	Osterballe and Bindslev-Jensen [13]	Celik-Bilgili et al. [14]
Study subject number	100	81	56	501
Presence of atopic dermatitis (%)	61	43	100	88
Age of study subjects	Median 3.8 years (range 3 months to 14 years)	Mean 16 months (range 11–24 months)	Median 2.2 years (range 0.5–4.9 years)	Median 13 months (range 1 month to 16.1 years)
CAP FEIA™ cut-off points for egg allergy (kU/L)	(95%) 7	(90%) 0.35	(95%) 1.5	(95%) 10
CAP FEIA™ cut-off points for milk allergy (kU/L)	(95%) 15	NA	NA	(95%) 46

food might greatly influence the outcome of the challenge. Celik-Bilgili used fresh whisked hen's egg while Sampson used dehydrated egg, Osterballe pasteurized egg and Boyano either raw or cooked eggs. Clinical reactions might be completely different according to the degree of allergen denaturation after egg processing or cooking [15, 16].

Be critical by using specific immunoglobulin E titres in order to predict food allergy!

Ideally, each practicing allergist should have their own data (unpublished and most often retrospective!) corresponding to the patients that they see. Additionally, each specific IgE titre should be compared with published values according to the age of the patient, the initial clinical picture, the time-point of determination (diagnosis or follow-up of tolerance acquisition), as well as the dynamic of IgE titres over time in the follow-up [17]. By using these criteria, and by carefully estimating their influence on the specific IgE titre, the values reported above can then be a real help to the practicing allergist.

In the future, measuring IgE to specific epitopes of food proteins might be of additional help for prediction of tolerance acquisition [18–21]. Altogether, these strategies might lead to a diminished number of DBPCFCs. However, I strongly believe that standardized food challenges will still be used in daily practice in the next 20 years.

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