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Some Limitations in the Use of Specific IgE in the Diagnosis of Food Hypersensitivity

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The only accepted method for establishing a firm diagnosis of food hypersensitivity is double-blind, placebo-controlled food challenge (DBPCFC) or by open, controlled challenge in infants [1]. As DBPCFC constitutes the ultimate diagnostic tool, and a restricted diet the ultimate therapy for food hypersensitivity, it might be argued that all in vitro diagnostic methods should be considered as *nice to know* rather than *need to know* for the clinician [2]. A diagnosis based on challenges does not, however, elucidate underlying pathogenic mechanisms or guide the clinician towards an understanding of the natural history of the reaction.

In vitro diagnostic tests such as measurement of specific IgE against constituents in a food may help in shedding light on two aspects of the disease: (1) the causative agent, i.e., the offending food item, and (2) the pathophysiology of the hypersensitivity reaction.

In vitro diagnostic tests may be further subdivided into tests needing a clinical reaction to take place in the patient, and those where a clinical reaction (e.g. a challenge) is not necessary. The former group mainly serves to elucidate the pathophysiology of the hypersensitivity reaction, whereas the latter ideally – but so far not in reality – may render DBPCFC superfluous.

Basically, the following questions must be addressed before using any new diagnostic test [from 3]:

(1) Can the test diagnose the parameter in question with sufficient specificity and precision? Data for technical validation of the test should be available

Table 1. Some limitations in the use of measurement of specific IgE

Lack of important epitopes in the extract	Sensitivity of the test will be reduced
Cut-off level and normal range has never been established	Sensitivity and specificity reduced. Cut-off levels different for different foods?
Technical validation	Data on reproducibility not available
A new test is launched based on comparisons to the market leader	Every new test should be investigated in patients, validated by DBPCFC, and sensitivity, specificity and predictive values should be calculated for every single food
All foods are considered to be similar and, therefore, treated equally	Every food is unique. Data should be available for every single food regarding e.g. normal range, IgE classes, differences between children and adults
Cross-reactivity between related or non-related foods or groups of foods	Data generally not available on a possible clinical significance of a given serological cross-reaction

to the customer – a claim rarely fulfilled even in the best investigated tests such as some of the RASTs.

(2) Are abnormal values of the parameters associated with clinical disease, and has an age- and sex-related normal range been established? Since no single diagnostic test exists in allergology, the above claim cannot be thoroughly fulfilled in food hypersensitivity.

(3) Can other conditions (pathological or physiological) give rise to values outside the normal range? This criterium is particularly important in multiple allergy and in patients in pharmacotherapy, where drugs may interfere with the test (e.g. RAST in atopic dermatitis patients or skin prick test in patients taking antihistamines).

In food hypersensitivity, any new test *must* be validated against the 'gold standard', i.e., DBPCFC instead of against the most used test – the market leader – in the field [1, 2].

Although immunological reactions other than type I (via IgE) exist, the far most important in food hypersensitivity as well as the best studied are reactions mediated via binding of specific IgE antibodies situated on mast cells and basophils to epitopes on proteins in the offending food. There are, however, several pitfalls when using measurement of specific IgE in the diagnostic work-up (table 1). Some of these will be discussed below.

In all tests aiming at identifying the offending food item, an extract of the food allergen in question must be applied. If important components present in the native allergen material are missing in the extracts used for the in vitro assay, false negative results will emerge, lowering sensitivity of the test when compared to DBPCFC [4]. It is therefore of primary importance to ensure the use of allergenic material of optimal quality in the assay.

Since the documentation of most of the foods is limited or lacking, every allergen system should be evaluated as such, i.e., results from one allergen test system should never be transferred to other systems. No in vitro test for specific IgE will ever be better than the extracts employed. With many new and rare allergenic materials the lack of sera from a sufficient number of clinically well-characterized patients (by DBPCFC) sets an immanent limit to the development of properly validated in vitro tests for specific IgE. It is based on the relative levels of specific IgE towards constituents in a food not possible to deduct anything regarding which IgE specificity that bears the most clinical relevance – another argument for the use of extracts as close to the native food as possible.

In most cases of the foods where little or no documentation on the allergens is available, this is due to the lack of investigations of the food in a sufficient number of well-documented patients, verified by DBPCFC. Every allergen is unique, therefore it is never possible to recommend a test for use in every available allergen based on data on few foods.

Concerning the two most widely investigated test systems (CAP from Pharmacia Diagnostics and Magic Lite from ALK Abello/Ciba Corning), varying results have been obtained in different food allergen systems [reviewed in 2]. In the diagnosis of codfish allergy both tests demonstrate sensitivity and specificity above 99%, almost excluding the need for DBPCFC [5], whereas in the diagnosis of kiwi allergy, none of the tests demonstrate a sufficiently high sensitivity [6]. Concerning milk and egg allergy, only minor – but perhaps clinically very significant – differences in performance emerge in a comparative study that was recently published [6]. Several authors have tried to ascertain a 'level of discrimination' – or normal range – between allergic patients and controls, but even though it has been possible to improve the clinical sensitivity and specificity, there does not seem to exist an upper normal limit of specific IgE above which the patient is food-allergic and below which he is not. Consequently, most investigators have chosen a high sensitivity at the expense of a low specificity of the tests.

Many foods share allergenic determinants and therefore specific IgE molecules against an epitope on one food will also recognize similar epitopes on other related foods. Whether such a *serological* cross-reaction will also be reflected *clinically*, i.e., whether the patient will also be clinically hypersensible to the cross-reacting food, depends both on the nature of the food, especially the heat

Table 2. Examples of cross-reacting foods and their clinical significance

Food	Examples of serologically cross-reacting foods	Clinical significance
Cod	herring, plaice, mackerel	✓
Cow's milk	milk from goat, sheep, mare	✓
Cow's milk	beef	÷
Hen's egg	egg from turkey, duck, goose	✓
Hen's egg	chicken meat	÷
Peanut	soy, green pea, green bean	(✓)
Birch	hazelnut, almond, kiwi, apple	✓
Grass	wheat, rye, barley, corn	÷
Artemisia	celery, parsley, melon, vermouth	✓
Latex	banana	?

and acid stability, and on the way the particular food is prepared before being eaten. As is the case in the evaluation of the various test systems for specific IgE, where every single allergen must be evaluated separately, the same holds true for the cross-reactions. It is necessary to compare the serological response (specific IgE) to the clinical response (DBPCFC with the food in question) for every serologically cross-reacting food (table 2).

In conclusion, measurement of specific IgE is a valuable tool in the diagnosis of food allergy. The above limitations must, however, always be taken into consideration before ordering a test in a patient suspected of having food allergy. In the diagnostic work-up, a carefully taken case history together with skin prick testing with foods or high-quality extracts often result in a good basis for selecting patients for DBPCFC – and for the possibly offending food. Measurement of specific IgE will only add significantly to the process in the cases where skin prick testing cannot be performed or is considered inappropriate. On the other hand, when – if ever – high-quality tests based on DBPCFC patients and appropriate controls are launched, measurement of specific IgE will become a central diagnostic test in the diagnosis of food allergy.

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