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Invited review article

Recent advances in component resolved diagnosis in food allergy

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CRD, component resolved diagnostics; DBPCFC, double-blind placebo-controlled food challenge; EoE, eosinophilic esophagitis; FDEIA, food-depend-exercise-induced allergic reaction/anaphylaxis; IgE, immunoglobulin E; IgE-ab, IgE-antibody; LTP, lipid transfer proteins; MA, molecular allergology; OIT, oral immunotherapy; OAS, oral allergy syndrome; OFC, oral food challenge; PFS, pollen-food allergy syndrome; PR, pathogenesis-related; SPT, skin prick test

ABSTRACT

Due to the high prevalence of food allergic diseases globally there are increasing demands in clinical practice for managing IgE-mediated conditions. During the last decade, component resolved diagnostics has been introduced into the field of clinical allergology, providing information that cannot be obtained from extract-based tests. Component resolved data facilitate more precise diagnosis of allergic diseases and identify sensitizations attributable to cross-reactivity. Furthermore it assists risk assessment in clinical practice as sensitization to some allergenic molecules is related to persistence of clinical symptoms and systemic rather than local reactions. The information may also aid the clinician in prescription of oral immunotherapy (OIT) in patients with severe symptoms, and in giving advice on food allergen avoidance or on the need to perform food challenges. The use of allergen components is rapidly evolving and increases our possibility to treat food allergic patients with a more individual approach. Using molecular allergology, we can already now better diagnose, prognose and grade the food allergy. In summary, daily routine molecular allergy diagnostics offers a number of benefits that give us a higher diagnostic precision and allow for better management of the patient.
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Introduction

Component resolved diagnosis (CRD) provides a major step in improving the accuracy of diagnosing IgE-mediated food allergy. We are living in an era of exciting research and growth in the field of food allergy. With this CRD concept, allergology is experiencing a technological revolution, which is transforming into a rapid change in clinical practice. Our traditional way of diagnosing is challenged by this new concept. Our tools, based on sometimes poorly standardized and highly variable allergenic preparations become clearly defined and allow more analyses in depth.[1] The ability to identify and characterize single allergens at a molecular level is increasing our knowledge as to the mechanism of sensitization to foods. The increasing availability of food allergen components allow for a comprehensive review of the pattern of sensitization. Studies regarding structural similarity between food allergens help to explain cross-reactivity between allergens which may be clinically relevant. Certain pan allergen molecules can indicate broad cross-sensitization and underlie particular pollen-food or plant food syndrome.[2]

The relatively high prevalence of food allergy has led to increased diagnostic testing. CRD can be utilized both in the initial diagnostic workup and to follow specific IgE levels over time to determine when patients may be resolving their allergy and

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evaluated by food challenge. Sensitization to allergen components can either be measured by simplex or multiplex testing.[3]

This review is meant to be a general overview of IgE testing for food allergy with focus on recent advances of component testing.

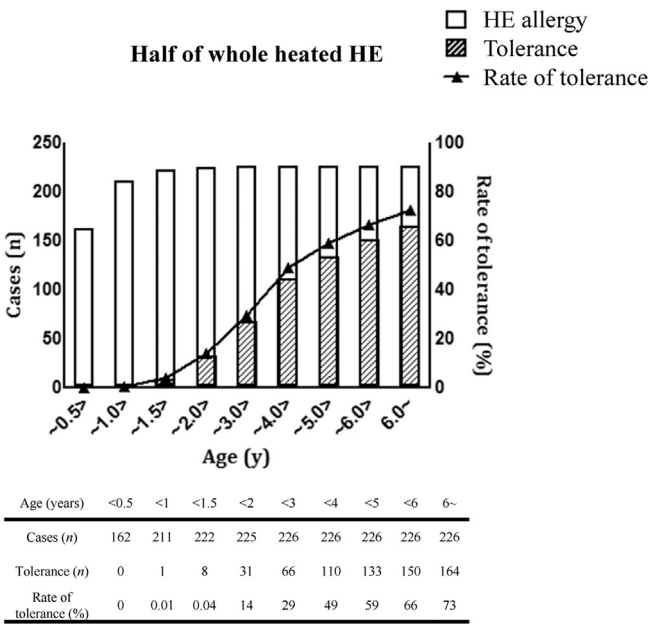
Egg (Table 1)

Egg white is the most important source of allergens in egg, and contains almost 80 non-allergenic and allergenic proteins.[4] Allergens that have been identified to be important and for which the clinician can test are ovomucoid (Gal d 1), ovalbumin (Gal d 2), ovotransferrin/conalbumin (Gal d 3), and lysozyme (Gal d 4).[5] Ovomucoid has been shown to be the dominant allergen in egg white. It has unique characteristics, such as stability to heating and cleavage by proteases and it appears to be allergenic in minute amounts. Ohtani *et al.* has recently shown that high levels of IgE to ovomucoid in egg allergic children is associated with delayed tolerance development (Fig. 1).[6] They investigated tolerance development in a group of 226 Japanese children allergic to hen's egg and found that those experiencing delayed tolerance developments had higher IgE levels of ovomucoid compared with children who developed tolerance early (Fig. 2).

Egg white IgE testing is in general mostly recommended for primary diagnosis of egg allergy because it combines the most common major allergens recognized in egg allergy (ovomucoid and ovalbumin). Molecular diagnosis has been shown to be helpful in a more fin-tuned diagnosis of egg allergy. Three different clinical situations can be distinguished. First scenario is when the individual is sensitized to egg white but is able to eat egg without symptoms. Second situation is when the patient is allergic to raw or partially raw egg only. Thirdly, when the patient is allergic to all forms of egg, which is the most severe form.

Ando *et al.* showed that a concentration of IgE antibodies against ovomucoid higher than 10.8 kU_A/l (positive decision point) indicated a high risk of reacting to heated (as well as raw) egg.[7] At the same time, a concentration below approximately 1 kU_A/l (negative decision point) means there is a low risk of reaction to heated egg, although the patient may well react to raw egg.

Benhamou Senouf *et al.* have recently shown in a similar study but with different patients' characteristics, a cut-off value for ovomucoid of 6.9 kU_A/L with a 95% specificity.[8] Also, they were able to show that a cut-off of 4.1 kU_A/L can be used for egg white in order to distinguish between allergy to all forms of egg, and sensitization in absence of allergy.



Age (years)	<0.5	<1	<1.5	<2	<3	<4	<5	<6	6~
Cases (*n*)	162	211	222	225	226	226	226	226	226
Tolerance (*n*)	0	1	8	31	66	110	133	150	164
Rate of tolerance (%)	0	0.01	0.04	14	29	49	59	66	73

Fig. 1. Tolerance acquisition of hen's egg allergy with aging. White bars represent number of HE allergy patients and black bars represent number of patients who tolerated half of whole heated HE. Filled triangles represent rate of tolerance.

Similarly, the heat-labile egg white allergen ovalbumin can help distinguishing between various patterns of clinical reactivity to egg.[9]

Sequential IgE testing starting with egg white, followed by ovomucoid, will significantly increase the sensitivity of diagnostic testing compared to testing egg white only, although with a decrease in specificity.[8]

Wright *et al.* tried to identify the component as potential biomarkers of sustained unresponsiveness in oral immunotherapy and

Table 1
Clinical characteristics of food allergen components (egg, milk, and wheat).

Antigen	Component to food allergens	Author	Published year	Results	Ref #
Egg	Gal d 1 (ovomucoid)	Ando *et al.*	2008	OVM-sIgE was a good marker for reacting to heated egg.	7
		Ohtani *et al.*	2015	High levels of OVM-sIgE was associated with persistent egg allergy	6
		Benhamou *et al.*	2015	OVM was best to distinguish between allergy to raw only, and allergy to all forms of egg.	8
	Gal d 2 (ovalbumin)	Benhamou *et al.*	2015	OVA was the best test for the diagnosis of allergy to raw and cooked egg	8
Milk	Bos d 4 (alpha-lactoglobulin) Bos d 5 (beta-lactoglobulin)	Ahrens *et al.*	2012	Low levels of IgE to milk allergen components (casein, Bos d 4, Bos d 5) predicted outgrowth of milk allergy	16
	Bos d 8 (caseins)	Kuitinen *et al.*	2015	High baseline IgE levels to milk components (casein, Bos d 4, Bos d 5) predict less successful milk oral immunotherapy	20
	Bos d 8 (caseins)	Boyano-Martínez *et al.*	2009	High levels of casein-sIgE was associated with persistent milk allergy	14
		Caubet *et al.*	2013	Casein-sIgE predict clinical reactivity to baked milk	19
		Yanagida *et al.*	2015	Casein-sIgE were significantly reduced during low-dose-induction OIT	21
Wheat	Gliadin	Kotaniemi-Syrjänen *et al.*	2010	high levels of IgE to gliadins was correlated with persistent wheat allergy and the development of asthma in children	33
	Omega-5 gliadin	Ebisawa *et al.*	2011	Omega-5 gliadin was useful diagnostic marker in immediate type of wheat allergy	38
		Nilsson *et al.*	2015	High levels of omega-5 gliadin-sIgE was associated with severity of reaction during wheat challenge	31
	Omega-5 gliadin HMW-glutenin	Morita *et al.*	2009	Omega-5 gliadin and HMW-glutenin were causative antigens in WDEIA	34
	Lipid transfer protein (LTP)	Palacin *et al.*	2007	Wheat lipid transfer protein was assosiated with Baker's asthma	44
	Alpha-amylase inhibitors	Pastorello *et al.*	2007	Alpha-amylase inhibitors and lipid transfer protein were associated with immediate type of wheat allergy	46

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