

Article type : Review

Do we still need oral food challenges for the diagnosis of food allergy?

Philippe A. Eigenmann¹

¹University Hospitals of Geneva, Department of Child and Adolescent, Pediatric Allergy Unit, Geneva, Switzerland

Correspondence to:

Philippe A. Eigenmann, Pediatric Allergy Unit, University Hospitals of Geneva, 6, rue Willy-Donze, CH-1211 Geneva 14, Switzerland

Phone +41-22-372 4531 Fax +41-22-372 4779

E-mail: Philippe.Eigenmann@hcuge.ch

Eigenmann PA

Do we still need oral food challenges for the diagnosis of food allergy?

Pediatr Allergy Immunol 2018

Abstract

Food challenges are standard in the diagnosis in patients suspected of being allergic to food. However, their role is regularly questioned due to the time required to perform them, and to their cost and the inherent risk of severe reactions. Food

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12845

This article is protected by copyright. All rights reserved.

challenges have been challenged by recent advances defining threshold values for food-specific IgE helping to predict the probability of having symptoms to the suspected food. Also, identification of major allergens to various highly allergenic foods such as peanuts or tree nuts have contributed to an increased accuracy of IgE testing. Altogether, these new data have contributed to a better definition of the role of oral food challenges in the diagnosis of food allergy. Oral food challenges are not outdated, and remain the gold standard in the diagnosis of food allergy.

Keywords: food allergy, oral food challenges, in-vitro testing, IgE, skin prick testing

Reprints requests:

Philippe A. Eigenmann, Pediatric Allergy Unit, University Hospitals of Geneva, 6, rue Willy-Donze, CH-1211 Geneva 14, Switzerland

Potential conflict of interests:

The author received speaker's honoraria and research support from ThermoFisher Scientific.

The oral food challenge is an essential procedure in the diagnosis of food allergy, but food allergy diagnosis has much evolved in the last years. It is therefore legitimate to question *“Do we still need oral food challenges for the diagnosis of food allergy?”*, but shouldn't we really reformulate the question to *“How do we currently most rationally use oral food challenges?”*. Oral food challenges are only part of the more complex procedure leading to the diagnosis of food allergy, a procedure involving various steps well known by the clinician.

The whole diagnostic process is initially based on the patient's history, which is the cornerstone of further diagnostic workup. The clear value of thorough history is well established (1), and which will, in the peculiar case of food allergy, lead us towards three possible options: (i) either dismisses the diagnosis of food allergy most often for the much more common diagnosis of food intolerance, or for "symptoms due to a non-food related cause". If symptoms are suggestive of food allergy, the history will be most helpful to distinguish between symptoms (ii) related to IgE, or (iii) related to non-IgE-mediated food allergy.

History alone does not allow diagnosing food allergy (Table 1). Nevertheless, clinical histories potentially suggestive of food allergy cannot always be confirmed by the complete diagnostic workup. Kajosaari et al have shown, 25 years ago in a cohort of finish children, that only half of the history is confirmed by oral food challenges (2). More recently, the meta-analysis on epidemiology of food allergy has shown that if 25% of the general population self-report food allergy, the diagnosis is only confirmed in 4 to 5% of the population. The highest rate is found in the age group of the 11 to 17 years old with 5.7 percent (confidence interval of 0.1 to 5 percent) (3).

IgE sensitization versus food allergy

The next diagnostic step after taking the clinical history, most often involves skin prick tests and/or measurement of serum specific IgE. The major challenge with both of these tests is to distinguish between sensitization and clinical allergy (4). Indeed, the most challenging patient is the one with a questionable but non excluding history and with positive tests due to sensitization, possibly due to cross-reactivity, but without any clinical relevance. We have shown among others some years ago, that a

history and a positive skin prick test was confirmed by food challenges to egg in 69% and to wheat in 49% in the cohort we had examined (5). Similarly, two years later, Sporik et al. have shown that only approximately 55% of positive histories and skin prick tests to cow's milk, egg or peanut could be confirmed by challenge (6). Likewise to skin prick test, specific IgE measurement discloses the same clinical reliability with approximately half of the patients being finally diagnosed food allergic by food challenge (7). More recently, Nwaru et al. have shown that diagnosis of food allergy based on suggestive symptoms and positive IgE tests were only in part confirmed by than the gold-standard provided by the food challenge (8). Nevertheless, it needs to be mentioned that oral food challenges were not part of the routine tools in the diagnosis of food allergy for many years, and still are not considered as potential options in many clinical settings. This leads to many patients being falsely diagnosed based on history, sometimes combined to IgE tests, alone.

Atopic eczema and food allergy

The role of food allergy in eczema has been most controversial for years. Diagnosing food allergy in patients with atopic eczema has always been a very challenging clinical situation (9). Indeed, many of these patients are sensitized to common foods, but have recurrent non-allergic flares of their eczema. This has led to over diagnosis of food allergy in a large percentage of children sensitized to common foods such as milk, egg or nuts. In the 1980's, the first publications showing that double-blind placebo-controlled food challenges were an objective tool for diagnosing food allergy in atopic eczema patients strongly improved the reliability of the diagnosis (10,11). These studies led to major progress in the care of patient with atopic eczema, but also introduced a large misunderstanding in the medical community in relation to the design of oral food challenges. While the clinical situation of patients suffering from

eczema with flares mostly not related to foods justified the use of placebo-controlled food challenges, this procedure was perceived as compulsory for all oral food challenges, and not only atopic eczema or randomized clinical trials. As many clinical settings were not able, due to organizational or time constraints, to use double-blind placebo-controlled food challenges, oral food challenges were largely dismissed. As a second misunderstanding, there was a general perception that oral food challenges were a dangerous procedure with a high risk of life threatening reactions (12). As a result, despite the standardization of oral food challenge being a major step forward in the diagnosis of food allergy, the procedure has been dismissed by many clinicians due to the constraints inherent to the procedure.

Less food challenges due to predictive specific IgE values?

There has always been the feeling that the higher the specific IgE value, the better the diagnostic accuracy of the test. In the early 2000s, Sampson and Ho proposed cutoff values to predict the probability of the diagnosis of food allergy (13,14). In these seminal studies and in various studies performed in other populations (15–18), it was quickly recognized that these values largely rely on the food tested, as well as on various population-related parameters. Clinicians initially relying on definite cut-off values, progressively changed their vision of cut-off values by including them more largely in their diagnostic decision criteria for food allergy, oral food challenges still remaining the gold-standard and a necessary step for diagnosis in a large number of patients (19). A further decisive step in progressing for a reliable diagnosis of food allergy was then made with the characterization of food major allergens in various foods and the measurement of specific IgE to these various allergens by component resolved diagnosis (20,21).

Similarly to the studies published earlier on whole food allergen extracts, studies have been performed for the diagnosis of food allergy using specific IgE values to major allergens. The most frequently studied foods have been peanuts, with Ara h 2 being identified as the major allergen implicated in anaphylactic reaction to the food (22). Also, hazelnut allergy has been studied and patients with elevated Cor a 9 and Cor a 14 were found to be most reliable for diagnosing hazelnut allergy (23). Further studies have explored cutoff values for cashew nuts, milk, as well as egg. In addition to cutoff values predicting the probability of a positive oral food challenge, another major information provided by component resolved diagnostic testing has been to distinguish between primary anaphylactic and pollen-related food allergy (20).

So where are we now?

Since we now have reliable IgE tests with cutoff values suggestive of clinical reactivity, do we still need and use food challenges? Clearly, oral food challenges are still and even more often performed than 20 years ago. The demand for an accurate diagnosis of food allergy has increased in the general population, most probably due to a better understanding of what food allergy is. The fear of severe reactions related to foods has also increased in the public, thus it has become more important to identify patients at risk. It has become a major challenge to most of our patients to have the possibility to have a normal life despite many of them eating out at school or at friends' houses, as patients and parents are well aware of the decreased quality of life induced by the diagnosis of food allergy (24,25). They need to be spared of this social handicap if the diagnosis is not correct or the food allergy has been outgrown. Also, a large cost is associated to a diagnosis of food allergy,

not only related to the regular purchase of adrenaline self-injecting devices but also due to the global social cost of the disease (26). Finally, while there is still a quest for an efficient and safe treatment of food allergy, many of our patients naturally outgrow the disease and food challenges are the adequate procedure to follow-up their food allergies. Food challenges can be tailored to specific clinical situations, which will improve its acceptance to health providers and patients (Table 2)

In conclusion, while there are many challenges remaining, we feel that we have largely progressed in defining the correct indications of oral food challenges, mostly by combining history, the cornerstone of the diagnostic procedure, to well chosen IgE tests (Figure 1).

Table 1:

Clinical vignettes portraying the diagnostic value of specific diagnostic steps

	history	IgE tests	oral food challenges
- 8 month old with severe atopic eczema	(+)	++	+++ (DBPCFC)
- 20 months old with repeated immediate reactions after eating nuts	+++	+++	(+)
follow-up at 3 years of age of previous patient	++	+++	+++ (open challenges)
- 12 years old with seasonal respiratory allergies, and oral, skin and gastrointestinal reactions to various nuts and fruits	+++	+++	++ (consider DBPCFC)
- 12 months old with recurrent diarrhea, vomiting and poor weight gain	+++	-	+++ (open)

DBPCFC: Double-blind, placebo-controlled, food challenges

Table 2:

Main criticisms to oral food challenges in a clinical setting and how to overcome them

	Possible solution
- Food challenges are dangerous	Only a minority of patients have really a risk of a severe reaction. Is the challenge necessary for diagnosis? Can it be postponed? If the OFC is indicated start with very low doses. Do it in a safe environment with skilled health personnel. Postpone timing of subsequent dose if you have a questionable reaction.
- Food challenges are time consuming	Design your challenge with the minimal number of doses necessary (27). In clearly symptom-free, low risk OFC, consider reducing the intervals between doses.
- Food challenges are expensive	Only if they are done without a clear clinical indication. Otherwise, the benefit brought to the patient is clearly in favor of a food challenge. Consider reducing timing and doses to restrain costs.
- Food challenges are complex	Similarly to all other medical procedures, the first few challenges are complex to organize. Due OFC on a regular base. DBCFC can also be done in an office setting, this has been described 30 years ago (28).
- The procedure is useless, the foods are not introduced at home	When discussing the indication to do the OFC with patients/parents always ask if they are interested to introduce the food. Do challenges with the food in a form which will be consumed by the patient (29).

References

1. Du Toit G, Santos A, Roberts G et al. The diagnosis of IgE-mediated food allergy in childhood. *Pediatr Allergy Immunol* 2009; **20**:309–319.
2. Kajosaari M. Food allergy in finnish children aged 1 to 6 years. *Acta Pediatr Scand* 1982; **71**:815–819.
3. Nwaru BI, Hickstein L, Panesar SS et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69**:62–75.
4. Roberts G, Ollert M, Aalberse R et al. A new framework for the interpretation of IgE sensitization tests. *Allergy* 2016; **71**:1540–1551.
5. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. *Pediatr Allergy Immunol* 1998; **9**:186–191.
6. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000; **30**:1541–1546.
7. Perry TT, Matsui EC, Kay Conover-Walker M et al. The relationship of allergen-specific IgE levels and oral food challenge outcome. *J Allergy Clin Immunol* 2004; **114**:144–149.
8. Nwaru BI, Hickstein L, Panesar SS et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69**:992–1007.
9. Mastroiilli C, Caffarelli C, Hoffmann-Sommergruber K. Food allergy and atopic dermatitis: prediction, progression and prevention. *Pediatr Allergy Immunol* 2017; **published on line**:n/a-n/a.
10. Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: evaluation of 113 patients. *J Pediatr* 1985; **107**:669–675.
11. Bock SA, Atkins FM. Patterns of food hypersensitivity during sixteen years of double-blind, placebo-controlled food challenges. *J Pediatr* 1990; **117**:561–567.
12. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U et al. Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004; **59**:690–697.
13. Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; **100**:444–451.
14. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; **107**:891–896.

15. Boyano MT, Garcia-Ara C, Diaz-Pena JM et al. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001; **31**:1464–1469.
16. Osterballe M, Bindslev-Jensen C. Threshold levels in food challenge and specific IgE in patients with egg allergy: is there a relationship? *J Allergy Clin Immunol* 2003; **112**:196–201.
17. Celik-Bilgili S, Mehl A, Verstege A et al. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005; **35**:268–273.
18. Benhamou AH, Zamora SA, Eigenmann PA. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatr Allergy Immunol* 2008; **19**:173–179.
19. Eigenmann PA. Are specific immunoglobulin E titres reliable for prediction of food allergy? *Clin Exp Allergy* 2005; **35**:247–249.
20. Borres MP, Ebisawa M, Eigenmann PA. Use of allergen components begins a new era in pediatric allergology. *Pediatr Allergy Immunol* 2011; **22**:454–461.
21. Matricardi PM, Kleine-Tebbe J, Hoffmann HJ et al. EAACI Molecular Allergy User's Guide. *Pediatr Allergy Immunol* 2016; **27 Suppl 23**:1–250.
22. Nicolaou N, Poorafshar M, Murray C et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010; **125**:191-7 e1-13.
23. Masthoff LJN, Mattsson L, Zuidmeer-Jonghean L et al. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. *J Allergy Clin Immunol* 2013; **132**:393–399.
24. Avery NJ, King RM, Knight S et al. Assessment of quality of life in children with peanut allergy. *Pediatr Allergy Immunol* 2003; **14**:378–382.
25. Cummings AJ, Knibb RC, Erlewyn-Lajeunesse M et al. Management of nut allergy influences quality of life and anxiety in children and their mothers. *Pediatr Allergy Immunol* 2010; **21**:586–594.
26. Gupta R, Holdford D, Bilaver L et al. The economic impact of childhood food allergy in the United States. *JAMA Pediatr* 2013; **167**:1026–1031.
27. Hourihane JO, Allen KJ, Shreffler WG et al. Peanut Allergen Threshold Study (PATs): Novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J Allergy Clin Immunol* 2017; **139**:1583–1590.
28. Bock SA, Sampson HA, Atkins FM et al. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol* 1988; **82**:986–997.
29. Eigenmann PA, Caubet J-C, Zamora SA. Continuing food-avoidance diets after negative food challenges. *Pediatr Allergy Immunol* 2006; **17**:601–605.

Figure legends

Figure 1: Diagnostic flow leading to the decision of performing an oral food challenge

