

Review article

Controlled oral food challenges in children – when indicated, when superfluous?

The diagnostic work-up of suspected food allergy includes the skin prick test (SPT), the measurement of food specific immunoglobulin E (IgE) antibodies using serologic assays, and more recently the atopy patch test (APT). For specific serum IgE and the SPT, decision points have been established for some foods allowing prediction of clinical relevance in selected cases. The APT may be helpful, especially when considered in combination with defined levels of specific IgE. Controlled oral food challenges still remain the gold standard in the diagnostic work-up of children with suspected food allergy. Most food allergic children will lose their allergy over time. As there is no laboratory parameter, which can accurately predict when clinical tolerance has been developed, controlled oral food challenges are the measure of choice. In this article, the current knowledge of predictors for the outcome of oral food challenges is reviewed and proposals for the daily practical work-up in the case of suspected food related clinical symptoms are presented.

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Food allergy is among the most frequent allergic disorders, currently affecting 6–8% of children in countries with Western lifestyle. The prevalence appears to be increasing (1, 2). Atopic dermatitis (AD) is commonly associated with food allergy (3). The proportion of children with AD who also have clinically relevant food allergy is reported to be around 40% (4–6). The foods most commonly involved are cow's milk (CM), hen's egg (HE), peanut, tree nuts, soy, fish and wheat (5, 6). Clinical reactions to foodstuffs range from mild skin symptoms to life threatening anaphylactic reactions. Especially in peanut and tree nut allergy, severe reactions have been observed (7–9).

The diagnostic work-up of suspected food allergy includes the patients' history, skin prick testing (SPT) (10), the measurement of food specific immunoglobulin E (IgE) antibodies using serologic assays (11, 12), and more recently the atopy patch test (APT) (13–15). While a positive SPT seems to reflect early reactions (e.g. urtic-

aria) to food challenges (13), the APT has shown diagnostic efficacy for late phase clinical reactions (e.g. exacerbation of eczema) (13–15). To date there is no complementary or alternative diagnostic procedure, which can be recommended as a meaningful element in the diagnostic work-up of food allergy (16).

Double-blind, placebo-controlled food challenges (DBPCFC) represent the 'gold standard' for diagnosing food allergy, as none of the above parameters can accurately predict tolerance (6, 17–20). However, DBPCFC are time-consuming, expensive and troublesome for the patient, involving the risk of severe systemic reactions. A simple *in vivo* or *in vitro* test that could accurately diagnose food allergy and render oral food challenges unnecessary would therefore be of great value. In this article, we review the current knowledge of predictors for the outcome of oral food challenges and introduce proposals for the daily practical work-up in the case of suspected food related clinical symptoms.

Abbreviations: AD, atopic dermatitis; APT, atopy patch test; CM, cow's milk; DBPCFC, double-blind, placebo-controlled food challenge; eHF, extensively hydrolyzed formula; HE, hen's egg; IgE, immunoglobulin E; PPV, positive predictive value; SPT, skin prick test.

Specific serum IgE

Specific serum IgE plays a major role in IgE-dependent food allergy. Diagnostic decision points for specific serum

IgE have been established to predict symptomatic food allergy (11, 12, 21–25). They make it possible both to provide the predicted probability (in %) for a given specific IgE value, as well as providing the required IgE level for a chosen probability. However, predicted probabilities vary remarkably among authors and populations studied (Table 1).

For HE, the 95% decision point in the German population (13.0 kU/l) was comparable with the US level (7.0 kU/l) (21), confirming these results in a large number of children. For CM, no such predictive decision points could be obtained for the German children, while Sampson described in the US population a 95% predicted probability of 15 kU/l (21). A Spanish group investigating the role of specific IgE in infants with immediate reactions during a CM challenge found even 5 kU/l as a 95% positive predicted value (PPV) (23). So far, there are no explanations for these differences. For wheat and soy, predictive probabilities in the German population did not exceed 61 and 37%, respectively, which limits the value of this parameter for these food allergens (23). These results are in concordance with other study populations (26).

It is necessary to consider whether PPVs of 99% should be preferred to 95% in order to avoid unnecessary diets in one of 20 children. In our population, the 99% predictive cut-off value of 59.2 kU/l for HE was fulfilled by only seven of 151 positive challenges with HE (5%) (23). These numbers are quite low; however, one may argue that every single oral challenge, rendered superfluous in the

children with the highest specific IgE levels by using the 99% predicted probabilities eliminates the risk of severe side effects.

Children with AD frequently show very high total IgE levels and numerous sensitizations, often without clinical relevance. Therefore a higher ratio of specific IgE/total IgE may result in a higher probability of symptomatic food allergy. This hypothesis was recently investigated in our group, but the determination of the ratio of specific IgE/total IgE for diagnosing symptomatic food allergy offers no advantage of the ratio over specific IgE measurement alone for CM, HE, wheat or soy (27).

Conclusion

Decision points have to be studied for each food allergen separately. They are not established for many foods so far and vary between populations. For several foods, the predicted probability does not exceed 70%. Specific IgE decision points render controlled oral food challenges superfluous only in selected cases.

Skin prick tests

Skin prick tests have been used for decades to prove or exclude sensitization to allergens. For foods, the use of native allergens seems to be superior to commercially available extracts (28). Eigenmann and Sampson studied the SPT with such extracts of CM, HE, wheat, soy, and peanut in children and found 'cut-off' values of wheal sizes exceeding the upper 95% confidence interval of responses in tolerant subjects: 5 mm for CM, 4 mm for HE, 6 mm for peanut, 3 mm for wheat and soy (29). Another study reported higher 'cut-off' levels for the diagnostic capacity of children with food allergy: 8 mm for CM, 7 mm for HE, and 8 mm for peanut (30). In small children (below 2 years of age) 'cut-off' values may be lower (30).

We studied the predictive capacity of the SPT in comparison with specific serum IgE and found that the PPV for the SPT with native foods is slightly superior to the measurement of specific serum IgE for CM, HE and wheat (15). These findings are supported by a report from Australia, showing a higher sensitivity of the SPT than food specific serum IgE antibody testing (30). Like with food-specific IgE levels, decision points can be developed by calculating predicted probabilities. Our datasets from 385 children indicate that the 95% predicted probability for HE is 13.0 mm, the 99% value is 17.8 mm and 12.5 mm and 17.3 mm for CM, respectively (Table 2) (A. Verstege, A. Mehl, C. Rolinck-Werninghaus, M. Nocon, K. Beyer, B. Niggemann, unpublished data). In our population, no decision points could be determined for wheat and soy. These results are in accordance with those for specific serum IgE. Differences in SPT

Table 1. Diagnostic decision points with a 90–100% predicted probability of clinical reactivity

Study population	Age (years)	Number of challenges	Allergen	Specific IgE cut-off level (kU/l)	Predicted probability for positive reaction (%)	Reference
US	≤ 14	Total of 196	Cow's milk	32	95	(12)
			Hen's egg	6	95	
			Peanut	15	95	
US	≤ 14	62	Cow's milk	15	95	(21)
		75	Hen's egg	7	95	
		68	Peanut	14	95	
German	≤ 16	398	Cow's milk	*	95	(23)
		398	Cow's milk	*	99	
		227	Hen's egg	13	95	
		227		59	99	
German	≤ 1	186	Cow's milk	*	95	(23)
		186	Cow's milk	*	99	
		41	Hen's egg	11	95	
		41	Hen's egg	89	99	
Spanish	≤ 1	170	Cow's milk	5	95†	(22)
Spanish	≤ 2	81	Hen's egg	0.35	88†	(11)
French	≤ 16	363	Peanut	57	100‡	(44)
Korean	4–14	44	Buckwheat	0.35	100‡	(25)

*Calculations did not yield 95% predictive values.

†Efficiency.

‡Positive predictive value.

Table 2. Diagnostic decision points for skin prick test wheal diameter in different study populations

Study population	Age (years)	Number of challenges	Allergen	Skin prick test cut-off wheal diameter (mm)	Predicted probability for positive reaction (%)	Reference
Australian	≤ 16	339	Cow's milk	8	100*	(30, 45)
		121	Hen's egg	7	100*	
		95	Peanut	8	100*	
Australian	≤ 2	27	Cow's milk	6	100*	(30, 45)
		30	Hen's egg	5	100*	
		33	Peanut	4	100*	
		81	Hen's egg	3	91†	
Spanish	≤ 2	363	Peanut	16	100‡	(11)
French	≤ 16	165	Cow's milk	12.5	95	(44)
German	≤ 16	165	Cow's milk	17.3	99	(8)
		118	Hen's egg	13.0	95	
		118	Hen's egg	17.8	99	

*Specificity.

†Efficiency.

‡Positive predictive value.

\$Verstege A, Mehl A, Rolinck-Werninghaus C, Nown M, Beger H, Niggemann B (manuscript submitted).

decision values between authors may be due to different patient populations.

Conclusion

Like with food-specific serum IgE, decision points for the SPT have to be studied for each food allergen separately and they have not yet been established for many foods. Only in a few cases can controlled oral food challenges be avoided by using the SPT alone.

Combination with atopy patch tests

While the specific serum IgE and the SPT have a high sensitivity, but low specificity for predicting the outcome of oral food challenges, the APT offers a high specificity but low sensitivity (15). Combining these two test systems may therefore improve the predictive capacity. A recent study investigating 173 DBPCFCs performed in 98 children showed that the APT was the best single predictive test, and the combination of a positive APT with proof of specific IgE, or APT together with a positive SPT optimized the PPV to 100% in some foods (15). The combination of all three tests (IgE, SPT, and APT) did not further improve the diagnostic efficacy. In both CM and HE challenges the predictability of oral challenges depended on the level of specific IgE. For wheat allergy, the APT proved to be the most reliable test and the PPV of 94% could not be improved by a combination with other allergy tests. However, the APT is time consuming and the results are sometimes difficult to interpret. Moreover, irritative reactions frequently occur.

Conclusion

In selected cases of suspected CM and HE allergy, the combination of a positive APT together with defined levels of food-specific IgE may make DBPCFC superfluous.

Oral food challenges

It is generally accepted that controlled food challenges represent the 'gold standard' for diagnosing food allergy (6, 16–19, 31, 32). Aims of controlled oral food challenges are both to prove that a certain allergen plays a role for the individual clinical symptoms and to exclude food allergy in order to prevent the child being subjected to unnecessary or even harmful elimination diets.

However, there is still debate, about whether oral food challenges should be performed in an open or double-blind fashion. Fig. 1 offers a flow sheet for the decision-making process. Placebo challenges are indicated when, for example, day-to-day variations play a major role (as in children with AD) or subjective symptoms may play a role (such as abdominal discomfort, burning of the tongue or palpitations) (33). Children under 1 year of age will rarely report subjective symptoms. Therefore, these children might undergo open food challenges when AD does not play a role. The algorithm after de-blinding of DBPCFC is presented in Table 3.

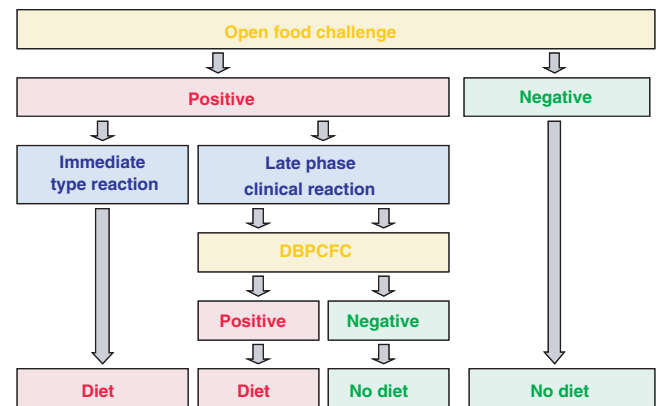


Figure 1. Flow sheet for deciding whether to perform open or double-blind oral challenges.

Table 3. Procedure after de-blinding of double-blind, placebo-controlled food challenge

Allergen	Placebo	Procedure
+	–	Elimination diet
+	+	Repeat challenge
–	–	No diet
–	+	No diet

Table 4. Clinical setting and subsequent diagnostic procedure

Highly suggestive history of an anaphylactic reaction (with IgE)	No oral food challenge
Questionable anaphylactic reaction (with or without IgE)	Open controlled challenge, inpatient
Specific serum IgE and/or SPT above decision point	No oral food challenge. Diet point
Special case: APT and specific IgE (defined level?) positive	No oral food challenge. Diet
Typical oral-allergy-syndrome plus corresponding sensitization	No oral food challenge. Diet
No improvement with elimination (or oligo-allergenic) diet	No oral food challenge. No diet
Introduction of new foods in highly sensitized infants (before exposure)	DBPCFC or open challenge†
Re-challenge after (long-term) avoidance of a food	DBPCFC or open challenge†
Expected late phase clinical reaction (e.g. AD)	DBPCFC
Subjective symptoms (e.g. abdominal discomfort)	DBPCFC

IgE, immunoglobulin E; SPT, skin prick test; APT, atopy patch test; AD, atopic dermatitis.

*Anaphylaxis = severe systemic reaction involving the cardio-vascular system.

†Decision on double-blind, placebo-controlled food challenge (DBPCFC) or open challenge according to the expectance of early or late phase clinical reactions.

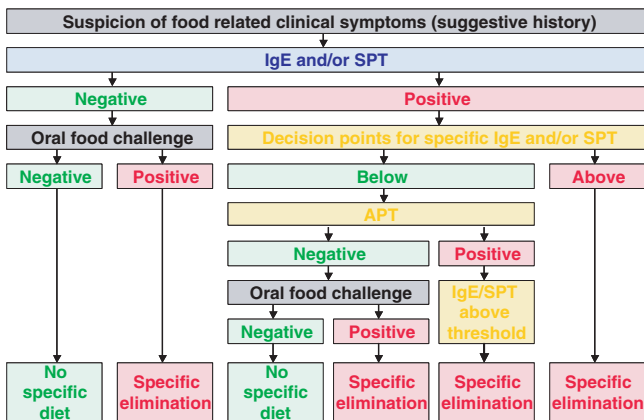


Figure 2. Flow sheet for the diagnostic work-up of suspected food-related clinical symptoms.

Indications for hospitalizing children for oral food challenges are e.g. life-threatening events in the past, or challenges with highly allergenic foods. Table 4 summarizes clinical settings and corresponding proposals for the resulting diagnostic step. Figure 2 provides a flow sheet showing how to proceed from the suspicion of food related symptoms to the final decision on recommending a therapeutic specific elimination diet. These diets should be prescribed under supervision of a trained dietician.

In addition to patients with a suggestive history we frequently see patients with elevated food-specific IgE levels before introduction of these foods into the child's diet. Sensitization might occur via breast-feeding or

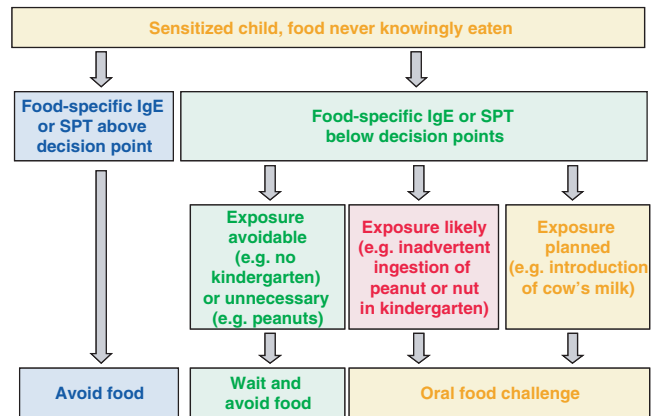


Figure 3. Flow sheet for the diagnostic procedure in sensitized infants, never having knowingly ingested the food.

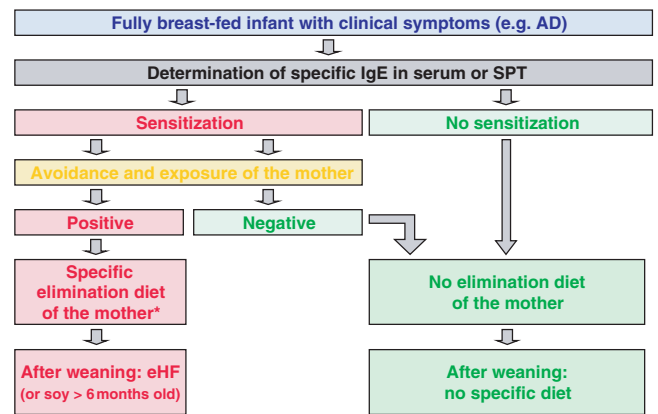


Figure 4. Algorithm for the diagnostic procedure in fully breast-fed infants with atopic dermatitis. *Only in rare cases a therapeutic elimination diet should be performed by the breast-feeding mother. In single cases breast-feeding has to be stopped. eHF, extensively hydrolyzed formula.

unrecognized exposure. Figure 3 proposes a diagnostic procedure for these sensitized children.

A special challenge is presented by food allergy in the fully breast-fed infant (Fig. 4): after proving sensitization of the infant by measuring specific serum IgE or performing an SPT, the diagnostic procedure includes short-term diagnostic elimination diets of the mother (e.g. 5–7 days) followed by re-introduction of the suspected food. Only in rare cases the mother should perform a therapeutic elimination diet. As such a diet may be harmful for the infants, a trained dietician should supervise it. Breast-feeding has to be stopped in single cases (34).

Conclusion

Oral food challenges remain the 'gold-standard' and can be performed open or as DBPCFC – the most important

thing is that they are carried out in a controlled manner. In sensitized infants with no risk of inadvertent exposure oral challenges are not mandatory. In selected cases, oral food challenges are superfluous because of preceding diagnostic steps with a high predictive capacity.

Indications for re-challenges

Some allergens such as peanuts and tree nuts are usually responsible for long-lasting allergic symptoms on exposure, although remission has been observed in about 20% of cases. Other food allergies have a good prognosis in childhood (35). This is especially true for CM and HE, with tolerance developing in about 80% of children after 3 years (36). Especially for allergens for which development of tolerance is likely, clinical relevance should be checked over time. Intervals of around 12–18 months may be a practical compromise in order to avoid unnecessary or even harmful elimination diets. For peanut and tree nuts far longer time intervals may be appropriate.

However, the results of the same *in vitro* tests carried out for the diagnostic work-up at the time of the first diagnosis or during re-evaluation of the patient differ in their diagnostic efficacy (37). There are still conflicting views on whether changes in specific serum IgE levels predict the development of clinical tolerance (38–40). Recent findings show a relationship between the decrease in food-specific IgE levels over a specific period between two challenges and the development of tolerance (40). A greater decrease in sIgE levels over a shorter period of time was indicative of a greater likelihood of developing tolerance. However, additional studies on larger patient populations may be necessary to further elucidate this aspect. In addition, peptide-specific IgE seems to be a valuable parameter in predicting the outcome of tolerance development (41–43).

Despite these advantages in food allergy diagnostic, controlled oral food challenges are still the only measure to establish clinical tolerance after some time of avoidance.

Conclusion

For food allergies typically manifesting early in life, the clinical relevance should be re-evaluated with oral food challenges after around 12–18 months. For tree nuts and peanuts longer intervals of approximately 3–5 years may be more meaningful. As predictive laboratory parameters are still under investigation, controlled oral food challenges are necessary to prove clinical tolerance after a period of avoidance.

Conclusions

Controlled oral food challenges remain the gold standard in the diagnostic work-up of children with suspected food allergy. In selected cases, decision points for specific serum IgE or SPT, especially when interpreted together with APTs, may make oral challenges superfluous. Several groups have established cut-off values but they vary considerably between allergens and between populations studied. For proving clinical tolerance after a period of avoidance, controlled oral food challenges are the measure of choice, as predictive laboratory parameters are still under development.

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