

Invited Review

Diagnosis of Food Allergy in Children: Toward a Standardization of Food Challenge

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ABSTRACT

Adverse reactions to food represent a common complaint in childhood; however, only a small proportion of children have proven clinically relevant food allergy. The foods most commonly involved in food allergy are cow's milk, hen's eggs, peanuts, tree nuts, seeds, soy, wheat, fish, and crustaceans. The diagnostic workup of suspected food allergy includes the patient's history, skin prick testing, the measurement of food-specific immunoglobulin E antibodies, and, more recently, the atopy patch test. Because none of these parameters can accurately predict tolerance, the gold standard for diagnosing food allergy is still the double-blind, placebo-controlled food challenge. Although numerous efforts have been made to standardize the procedure, there is a need for improvement. This review presents the current status of the indication and performance of

controlled oral food challenges in children with suspected food-related symptoms. It covers aspects of indications and contraindications, blinding, diet before the challenge, the practical performance, the handling of medication, the interpretation of test results, suitable locations for testing, safety considerations, and the procedure after a period of avoidance. Efforts to standardize oral food challenges to achieve the best possible decision on a diet are important to avoid an unnecessary diet that may be harmful to the child. *JPGN* 45:399–404, 2007. **Key Words:** Anaphylaxis—Atopic eczema—Double-blind, placebo-controlled food challenge—Immunoglobulin E. © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

INTRODUCTION

Adverse reactions to food represent one of the most common complaints in the general population (1) and in childhood (2); however, only 2% to 4% of these can be attributed to reproducible, immunoglobulin E–mediated food allergy (1,2). Atopic eczema (AE) is commonly associated with food allergy (3), and approximately 40% of children with AE are reported to have clinically relevant food allergy (4–6). Gastrointestinal symptoms and respiratory symptoms may also be caused by food allergy.

The foods most commonly involved in food allergy are cow's milk (CM), hen's egg (HE), peanuts, tree nuts, seeds, soy, wheat, fish, and crustaceans (5,6). Clinical reactions to foodstuffs mostly involve the skin (eg,

urticaria, flush, eczema), followed by gastrointestinal symptoms (eg, vomiting, diarrhea) and respiratory symptoms (eg, stridor, wheezing), and they range from mild symptoms to anaphylaxis. Especially in peanut and tree nut allergy, severe reactions have been observed (7–9).

The diagnostic workup of suspected food allergy includes the patient's history, skin prick testing (SPT) (10–13), and the measurement of food-specific immunoglobulin E (IgE) antibodies using serological assays (14–17). For IgE screening, group or panel tests may be helpful as a first step. More recently, the atopy patch test (APT) has been evaluated for its usefulness in diagnostic workup (18–21). For daily clinical practice, however, the APT adds little to the predictive value of standard SPT and IgE measurement in the diagnostic workup of suspected food-related symptoms (21). Regarding complementary or alternative medicine, no diagnostic procedure can be recommended as a meaningful element in the diagnostic workup of food allergy (22).

Double-blind, placebo-controlled food challenges (DBPCFCs) represent the gold standard for diagnosing food allergy because none of the aforementioned

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parameters can accurately predict tolerance (21,23,24). Although numerous efforts have been made to standardize the procedure (25–28), improvements are still necessary.

A unified approach in the diagnostic workup of infants and children with suspected food-induced disorders is necessary to overcome the intrinsic differences among the 3 main subspecialties involved in the care of young children with food allergies and intolerances (29). We present an overview of the status of the indication and performance of controlled oral food challenges in children with suspected food-related symptoms.

INDICATIONS FOR ORAL FOOD CHALLENGES

Figure 1 provides an algorithm for proceeding from the suspicion of food-related symptoms to the final decision to recommend a specific therapeutic elimination diet. The algorithm includes measurement of specific IgE or SPT in the decision-making process. The APT cannot generally be recommended for the daily clinical practice (21,30). Common clinical indications for oral food challenges and the corresponding procedure are shown in Table 1. Contraindications are a recent proven anaphylactic reaction to the food or poorly controlled bronchial asthma.

DECISION POINTS

Diagnostic decision points for specific serum IgE have been established to predict symptomatic food allergy (14–16,31–33). Predicted probabilities vary remarkably among authors and populations studied (34). For HE, the 95% decision point in the German population (13.0 kU/L) was comparable to the level in the United States (7.0 kU/L) (15). For CM, no such predictive decision points could be obtained for the German children, whereas Sampson et al (15) described a 95% predicted probability of 15 kU/L. A

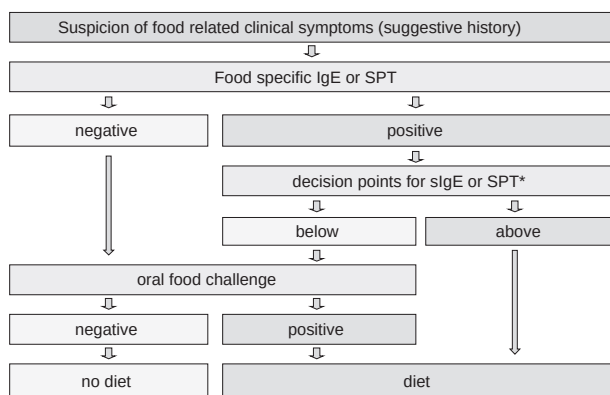


FIG. 1. How to proceed from the suspicion of food-related symptoms to the final decision on recommending a therapeutic specific elimination diet (21). *Diagnostic decision points appear to be population, age, and allergen dependent.

TABLE 1. Clinical indications for oral food challenges and the corresponding procedure

Challenge	Procedure
Anaphylaxis proven or highly probable (together with proof of specific IgE)	No oral food challenge; diet
Questionable anaphylaxis (with or without proof of IgE)	Open challenge; inpatient basis
Typical oral allergy syndrome with corresponding sensitization	No oral food challenge; diet?
No improvement of clinical symptoms under elimination (or oligo-allergenic) diet	No oral food challenge; no diet
Introduction of new foods in sensitized infants (before exposure)	DBPCFC or open challenge*
Rechallenge after (long-term) avoidance of a food (to investigate possible acquired tolerance)	DBPCFC or open challenge*
Expected late phase clinical reactions (eg, in children with atopic eczema)	DBPCFC
Subjective symptoms (eg, abdominal discomfort, nausea)	DBPCFC

* Depending on type of symptoms (eg, presence of atopic eczema).

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 predictive value (23). 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). In conclusion, decision points must be studied for each food allergen separately, and they render controlled oral food challenges superfluous in only selected cases.

OPEN OR BLIND ORAL FOOD CHALLENGES

Controlled oral food challenges are intended to prove that a certain allergen plays a role for the individual clinical symptoms or to exclude food allergy to prevent the child from being subjected to unnecessary or even harmful elimination diets. There is a debate about whether oral food challenges should be performed in an open or double-blind fashion. Figure 2 is a flowchart for the decision-making process. Placebo challenges are indicated if, for example, day-to-day variations play a major role (as in children with AE), or if there are subjective symptoms (eg, abdominal discomfort, burning of the tongue, palpitations) (35).

SPECIAL CONSIDERATIONS IN INFANTS

Children younger than 1 year of age will rarely report subjective symptoms. Therefore, these children may undergo open food challenges when AE does not play a role. This recommendation differs from the statement of the European Academy of Allergology and Clinical Immunology review, according to which open challenges

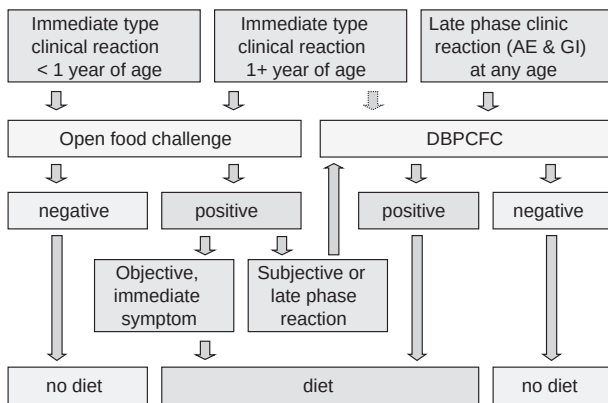


FIG. 2. Flowchart outlining whether to perform oral challenges in an open or double-blind fashion.

may be indicated in infants and children younger than 3 years of age (28).

Concerning decision points, subdividing children into groups younger or older than 1 year of age provided different predicted probabilities for specific serum IgE concentrations for HE: in children younger than 1 year of age, the decision point using a 95% predicted probability was 10.9 kU/L, whereas it was 13.2 kU/L for children older than 1 year of age (16). Similar findings were reported for SPT wheals, with a tendency toward smaller sizes in infants (13).

WHICH DIET BEFORE ORAL FOOD CHALLENGES?

If food is suspected to be responsible for a child's symptoms, then a diet should be started before the oral food challenge. Figure 3 shows a decision tree for the choice of the diet regimen before the oral food challenge. In an elimination diet, only the suspected food is elimi-

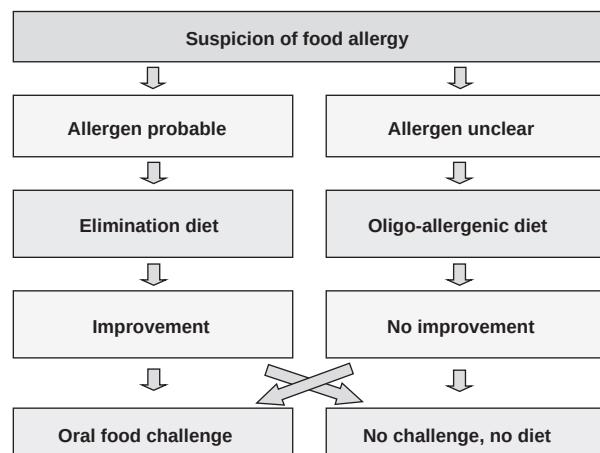


FIG. 3. Decision tree for choice of dietary regimen before an oral food challenge.

TABLE 2. Example of an oligo-allergenic diet in children

1 cereal (eg, rice)
1 meat (eg, lamb, turkey)
2 vegetables (eg, cauliflower, broccoli, cucumber)
1 fruit (eg, pear, banana)
Fat: limited to sunflower oil, milk-free margarine
Beverages: limited to water
Spices: limited to salt and sugar

nated from the child's diet. In contrast, an oligoallergenic diet includes only a few foods that rarely induce clinical symptoms in allergic individuals. An example of an oligoallergenic diet in children is shown in Table 2. A milk substitute should be used for infants and young children (eg, an extensively hydrolyzed CM formula or an amino acid formula). The duration of the diet before the oral challenge depends on the nature of the clinical symptoms: typical IgE-mediated symptoms only require 1 week, whereas 2 weeks may be more appropriate for atopic eczema or gastrointestinal symptoms.

For some food allergens, no nutritional problems will occur as a result of elimination, but during infancy and childhood an alternative hypoallergenic milk substitute is necessary in children with CM allergy. If the elimination diet or oligoallergenic diet has no effect on the symptoms of the child, then an oral food challenge is usually not necessary and a specific diet need not be implemented.

PRACTICAL PERFORMANCE

As many aspects as possible relating to oral food challenges should be standardized. Table 3 offers some practical proposals. Unfortunately, most recommendations cannot be based on comparative studies. Figure 4 shows an example for a block-wise approach to DBPCFCs. So as not to overlook clinical reactions that occur only after high doses, the final dose of the first day should be repeated on the second day. A titrated procedure is nearly always mandatory to avoid unnecessary severe clinical reactions. An example of volumes and amounts of protein has recently been published for the 4 most common cases: CM, HE, wheat, and soy (16). In addition, the child should be free from acute infections before starting the oral food challenge.

MEDICATION

Medication taken on a maintenance basis should be checked for possible masking of clinical symptoms. Systemic steroids represent a contraindication for any organ challenge testing. Systemic antihistamines should be completely withdrawn in accordance with their half-life. Topical steroids for the airways are usually no reason to discontinue testing; steroids in skin topical preparations should be tapered to the minimum dose

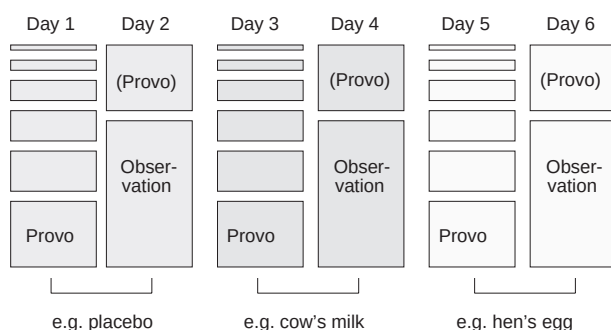
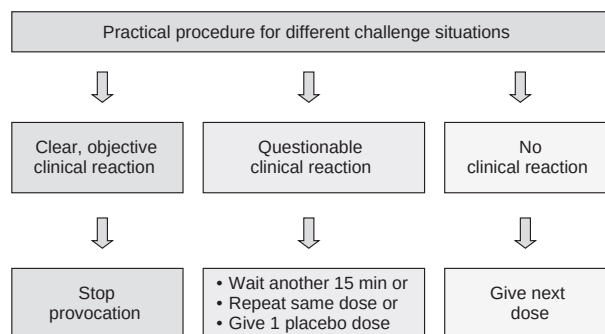
TABLE 3. *Circumstances to be standardized in the context of controlled oral food challenges*

In general
Eliminate suspected food for at least 7 (to 14) d (elimination diet) or for at least 7 (to 28) d (oligoallergenic diet) before provocation
Withdraw systemic drugs (eg, antihistamines) according to half-life
In the case of atopic eczema, reduce topical steroids to minimum and keep constant during challenge procedure
Use native (or freeze-dried) foods
Whenever possible, apply food in liquid form (capsules are not recommended)
Child should be well, and without febrile diseases
Foods should be administered in fasting state
Increase doses every 30 min (until highest dose or clinical reaction)
Total amount should roughly correlate to age-related daily intake
Choose observation period of 24 h for suspected immediate reactions and 48 h for late reactions
For definition of late reactions count from highest dose, not from first dose
Make sure clinical monitoring is standardized
Challenges should be observed and supervised by professionals capable of dealing with anaphylaxis
DBPCFC
Make sure blinding is applied (eg, by dietitian)
Relation of placebo and verum cases should be at least 1 placebo to 2 allergens
Give same amounts of verum and placebo

and should be kept constant throughout the challenge procedure.

INTERPRETATION OF TEST RESULTS

A clear and objective clinical reaction—especially if the time interval between ingestion and clinical reaction is short—may give grounds to assess an oral food challenge as positive. This is the case, for example, if generalized urticaria is observed. Objective means visible, measurable, or—even better—quantifiable clinical symptoms. Vomiting, although a clear and visible sign, may be of psychological origin, for example, if the child has an aversion to a food or recalls past clinical reactions. Therefore, before stopping an oral food challenge, vomiting should be observed as severe or

**FIG. 4.** Proposal for a block-wise approach to DBPCFCs.**FIG. 5.** Decision tree for various situations during oral food challenge procedure.

repetitive. A symptom that occurs a second or third time, and is therefore reproducible, is more likely to be a positive response to a given food. Cramping abdominal pain may be a warning of an impending anaphylactic reaction.

Another problem in assessing an oral food challenge as positive or negative is the occurrence of local urticaria around the mouth. Some children show symptoms of perioral contact urticaria (eg, if a drop of milk runs down the skin), but can tolerate the swallowed milk without overt clinical symptoms. The occurrence of a local contact urticaria should be followed by the next dose of the titrated oral food challenge.

The time interval between administering the food and observing the clinical reaction may influence the assessment of the challenge outcome. Certainly, the sooner the symptom is observed, the more likely this is to be a “true” positive reaction. Clinical reactions seen more than 48 hours after the challenge will not usually be assessed as causative.

Despite controlled (or even double-blind) conditions, it is sometimes difficult to decide whether clinical symptoms are clear enough for a “yes or no” decision. A decision tree for various situations during oral food challenge procedure is shown in Fig. 5.

An algorithm after debinding of DBPCFC is presented in Table 4 (34). Any diet, especially for important allergens such as CM, should be prescribed under the supervision of a trained dietitian to ensure that it is physiologically balanced.

LOCATION OF TESTING

Oral food challenges can be performed at home, in the general practitioner's office, on a day hospital admission, or on a full inpatient basis. Some oral challenges can be managed at home (eg, if the food has been eaten so far, the child is not sensitized to the food, symptoms are localized and not subjective). Any risk of a systemic reaction requires the presence of trained medical staff. Oral food challenges with possible mild systemic

TABLE 4. Procedure after deblinding of DBPCFC (32)

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

reactions may be carried out in the general practitioner's office, whereas in the case of possible severe reactions or foods with known high allergenicity, oral food challenges must be undertaken in a hospital setting. Day hospital admission is usually sufficient, but a full inpatient basis may be more appropriate if there are subjective symptoms, which are difficult to assess, or delayed symptoms.

SAFETY MEASURES

Oral food challenges should be performed in a setting suitable for the handling of any kind of side effects, including anaphylaxis. This covers the location, the presence of trained personnel, monitoring facilities, and suitable equipment for medical interventions. Intravenous access is a basic safety measure, but complications have been reported (9), which have ranged from local irritation through thrombophlebitis of the hand or arm to septic arthritis of the hip. The rate of severe complications connected with intravenous catheters was 0.3% in children with atopic eczema (9). *Staphylococcus aureus* was identified as the causative bacteria in blood cultures and was also found on the patient's skin. In our view, oral food challenges with a risk of systemic reactions require intravenous access; however, the indication for long-term venous access (eg, >4 days) should be well grounded.

PROCEDURE AFTER A PERIOD OF AVOIDANCE

Some allergens such as peanuts and tree nuts usually lead to long-lasting allergic symptoms on exposure, although remission has been observed in approximately 20% of cases. Other food allergies have a good prognosis in childhood (36). This is especially true for CM and HE, with tolerance developing in approximately 80% of children after 3 years (37). Especially if development of tolerance to an allergen is likely, clinical relevance should be checked over time. Intervals of approximately 12 to 18 months may be a practical compromise to avoid unnecessary or even harmful elimination diets. For peanuts and tree nuts, longer time intervals may be appropriate.

The results of the in vivo and in vitro tests carried out for the diagnostic workup may differ in terms of diagnostic efficacy between the first diagnosis and reevaluation of the patient (38). There are still conflicting views about whether changes in specific serum IgE

levels predict the development of clinical tolerance (31,39,40). Recent findings have shown a relationship between the decrease in food-specific IgE levels over a specific period between 2 challenges and the development of tolerance (40). A greater decrease in specific IgE levels over a shorter period of time was indicative of a greater likelihood of developing tolerance. Additional studies with larger patient populations are 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 diagnostics, controlled oral food challenges are the only measure to establish clinical tolerance in an individual patient after avoidance for some time.

CONCLUSIONS

Controlled oral food challenges remain the gold standard in the diagnostic workup of children with suspected food allergy. In most cases, they are best performed in a double-blind, placebo-controlled manner. Efforts should be made to standardize oral food challenges to reach the best possible decision and to avoid unnecessary diets, which may be harmful to the children.

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