

Proposals for standardization of oral food challenge tests in infants and children

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Adverse reactions to food have been reported for the last 2000 years (1). Adverse food reaction is the umbrella term referring to any untoward reaction following the ingestion of a food (or food additive). Adverse reactions to food can be categorized into two types: food allergy (food hypersensitivity) and food intolerance (1). Food allergy is based on an abnormal immunologic response, whereas food intolerance is the result of nonimmunologic mechanisms. In this paper we will refer solely to food allergy.

Food allergy is a common condition, which is believed to occur in about 1% to 6% of the pediatric population (1, 2). In children with atopic dermatitis, the frequency of a clinically relevant food allergy is suggested to be 33% (3).

Clinical symptoms of food allergy range from slight urticaria to severe eczematous exacerbations. Even fatal and near-fatal anaphylactic reactions to food have been reported in children (4).

Early, as well as late, phase reactions after single oral provocations are well known (5, 6). While immediate reactions are usually IgE-mediated and can quite easily be related to the suspected food in most cases, the latter are very difficult to identify

clinically (7). Specific IgE measurements often do not correlate with oral provocation tests (8). Recent studies suggest T-lymphocyte responses to play a role in IgE and non-IgE-mediated adverse reactions to food (8–12). It has been proposed that specific IgE were more often present in children exhibiting immediate reactions, and excessive lymphocyte proliferation more often positive in delayed reactions to cow's milk (11). Skepticism remains warranted until the data are reproduced by other groups (13).

For the diagnosis of food allergy, a detailed history as well as skin prick tests or specific IgE to the offending foods are mandatory prerequisites. However, only oral food challenges represent the "gold standard" for diagnosis of food allergy in these children (14–17).

Oral food challenge tests are indicated in infants and children if the parents or their physician suspect an adverse food reaction. Aims of oral challenge tests are (1) to detect and avoid specific foods and (2) to prove that specific food allergy is not responsible for symptoms and therefore avoid unjustified dietetic restrictions.

Even with "sophisticated" procedures, such as DBPCFC, it is sometimes difficult to assess the outcome of oral food challenges – especially in infants and small children. This especially holds true for late phase reactions. From a clinical point of view, late reactions are mostly eczematous reac-

This consensus statement is based on a workshop about "The standardization of food challenge tests in infants and children" held during the 4th Annual Meeting of ESPACI in Potsdam, April 22–25, 1993.

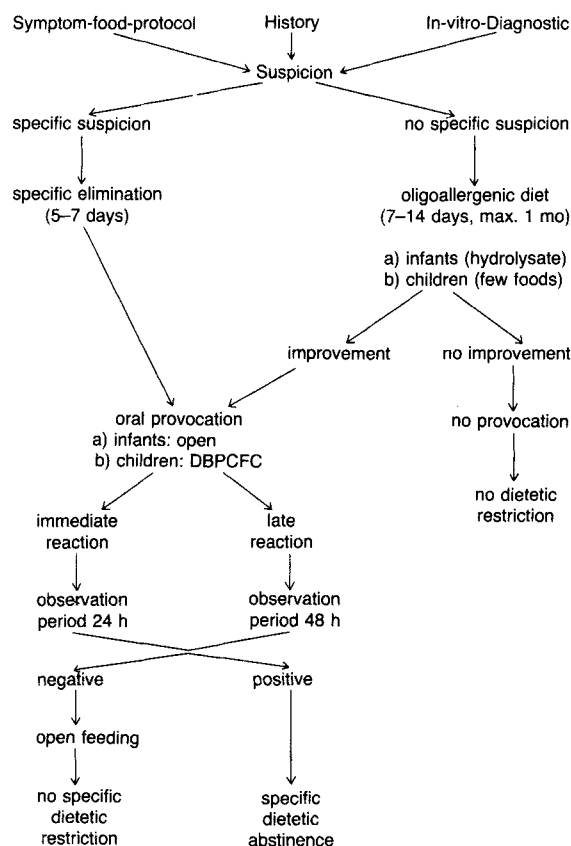


Fig. 1. Proposal for a standardized procedure for use with suspicion of food allergy.

tions (and to a lesser extent gastrointestinal ones). Controversy exists, whether there are isolated late reactions or if late reactions only occur in combination with early reactions.

Following, we will present proposals for a standardized procedure of oral food challenge tests in infants and children – with special emphasis on children with food sensitive atopic dermatitis.

Procedure for use with suspicion of food allergy

Fig. 1 shows a flow-sheet with a proposal for a standardized procedure on suspicion of food allergy – with special respect to the presence of specific or non-specific suspicion.

Practical instructions for DBPCFC

- Eliminate suspected food for at least 7 to 14 days before provocation. Maximum duration should be one month
- Withdraw systemic drugs (e.g. antihistamines) according to half-life; minimize local drugs (e.g. topical steroids)
- Make sure that correct “blinding” is given (e.g. by dietician)

- Use native (or dried) food in fluid (or capsules)
- Relation of placebo and verum episodes should be 1:1
- Give same amounts of verum and placebo
- Food should be given to patient in fasting state
- Increase doses every 15–30 min for fluid foods and every 30–60 min for capsules
- Total amount should correlate to age-related average “daily intake” – especially if late reactions are expected.
Use e.g. one egg, 250 ml of cow’s milk
- Challenges should be observed and supervised by professionals capable of dealing with anaphylaxis
- Chose observation period 24 hours for suspected immediate reactions, 48 hours for late reactions (e.g. all patients with atopic dermatitis)
- For the definition of late phase reaction, count time from highest dosage – not from first dosage
- Make sure that clinical monitoring is standardized (e.g. symptom-scores); optionally, monitoring by mediator measurements from effector cells is recommended
- Have emergency-set ready to use; personnel should be skilled to cope with the case of emergency
- Follow all doubtful and negative DBPCFC’s by open challenges with native food

Table 1 shows a proposal for a standardized protocol of titrated, blind oral food challenges for infants and children.

Comments

Oral challenges are mainly performed in liquid or by using capsules. Advantages of capsule provocations include the facts that they are easy to handle and that blind testing is thorough. Disadvantages of capsule provocations include a) “oral allergy syndrome” can be overlooked, b) dosage fit into capsules may not be high enough, c) the allergen is

Table 1. Proposal for a titrated protocol

*Base solution:
100 ml casein hydrolysate (14.7%) plus 1 g banana-flavour

*Mixture of 1:1 (verum and placebo)

Verum	Base	Total	Amount
0.1 ml +	0.1 ml =	0.2 ml	in a syringe covered with metal foil
1.0 ml +	1.0 ml =	2.0 ml	
3.0 ml +	3.0 ml =	6.0 ml	
10.0 ml +	10.0 ml =	20.0 ml	in a feeding bottle covered with metal foil or e.g. “Isostar”-bottle
30.0 ml +	30.0 ml =	60.0 ml	
100.0 ml +	100.0 ml =	200.0 ml	

* Placebo = 100% base-solution

usually not "native", and finally d) capsule provocations are not adequate for challenging infants. Challenges with food in liquid are therefore preferred in most cases – especially in infants and small children.

Natural food should be offered raw (or in the way the patient would normally eat it). The same food cooked or baked (e.g. milk in a cake) may be very well tolerated by the child without clinical symptoms, while the raw may elicit untoward effects. The nutrition in the natural food is therefore preferable for DBPCFC.

The "blind" effect can be best achieved by using a casein-hydrolysate and flavouring (e.g. banana-flavour). However, older children may not tolerate the strong and bitter taste of hydrolysates. Serving the solution cold can mitigate the unpleasant taste.

Breast-feeding during provocations may influence the outcome of oral food challenges. Due to the experience of cases in which false-positive challenge tests were most probably caused by the high allergen load of the mothers' diet (e.g. eggs, milk, sugar), the baseline diet of a feeding mother (as well as the child being tested) should be stable. Infants should receive a casein-hydrolysate, and older children and breast-feeding mothers an oligoallergenic diet consisting of the foods known to very rarely elicit allergic symptoms.

The interpretation of a positive oral challenge test is food intolerance, because a positive result does not automatically allow the use of the term "immunologically" or even "IgE-mediated" reaction. Assessing a positive challenge as "food-allergy" requires the proof of immunological methods, such as specific IgE (or lymphocyte responses), in combination with positive clinical reactions.

In view of the difficulties in assessing the outcome of oral food challenge tests, monitoring of challenge tests represents the key problem. Besides clinical parameters (e.g. symptom-scores), measurement of cell-specific mediators may be helpful in providing objective information on the outcome of oral challenges. Promising results have recently been achieved by determining peripheral blood eosinophils at baseline and immediately after clinical reaction and eosinophil cationic protein (ECP) at baseline and at 24 h after provocation. Measuring histamine in oral lavage fluid may be another approach in this respect.

All efforts to standardize oral food challenges are justified and needed, in order to prevent non-specific diets in cases with no proven food allergy, which may lead to a) unnecessary impairment of children, b) deficits in growth and development

and c) delay of effective therapeutic measures. Therapists should always take the full responsibility for treatment regimens. It is unacceptable, if responsibility is shifted towards the parents.

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