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Review article

Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology

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At present, the double blind placebo controlled food challenge (DBPCFC) represents the only way to establish or rule out an adverse reaction to a food in older children and adults, whereas an open challenge controlled by trained personnel is sufficient in infants and young children (1). The challenge procedure is not, however,

fully developed and no standardised procedure has so far been agreed upon, although a manual describing several of the issues has previously been published (2). For the safety and feasibility of the patient undergoing challenge there is a need for standardisation of the procedures. Standardization also allows for comparison of results between different centers and different populations in scientific protocols. This Position Paper gives advice on how the procedures can be performed, but since there are no direct comparative studies available in the literature directly comparing the various parameters (e.g. timing between two subsequent challenges or increment of the dose for challenge) we have not been able to recommend truly evidence based guidelines. It is also important to realize, that legislative aspects vary in different countries within Europe, and that the guidelines presented herein must be adjusted according to local legislation. Furthermore this guideline does not constitute a guideline for Ethics Committees to decide feasibility of DBPCFC in a scientific protocol.

There are several issues to be determined, prior to commencing a challenge in a patient. These can be divided into patient-related parameters, which are parameters concerning the actual patient in question and procedure-related parameters, which deal with the parameters independent of the patient in question (Table 1).

Selection of patients for challenge

Challenge should be performed either for establishment or exclusion of the diagnosis, for scientific reasons in clinical trials or for enabling determination of the sensitivity of the actual patient (threshold value) or for determining the allergenicity of foods. The determination of the sensitivity both enables tailor-made guidelines for the patient and opens the possibility of following sensitivity by repeated challenges especially in children with food allergies normally outgrown during childhood (cow's milk or hen's egg).

Table 1.

Patient related parameters	• age of the patient • clinical features of the suspected reaction • severity of the reaction • dosing (start dose, increment, top dose) • timing between challenges • regimen (in-patient or out-patient) • special considerations (concomitant factors) such as a possible influence of concomitant exercise (3) or intake of drugs such as β-blockers, ACE-inhibitors or aspirin (4), alcohol, antihistamines, corticosteroids
Procedure related parameters	• settings (trained personnel) • safety measures • informed consent procedures • blinding procedure • statistical evaluation

Patients should be investigated according to the EAACI guidelines (1) using case history combined with *in vivo* and *in vitro* testing supplemented with a elimination diet period prior to challenge when necessary. Based on the findings here, the patient-related parameters can be determined.

The guidelines in this position paper focus mainly on patients presenting classical immediate type allergic symptoms and signs (IgE-mediated type I allergy), as defined in EAACI position paper (1).

Inclusion criteria

Patients of any age with a history of adverse reaction to a food:

- For establishment or exclusion of the diagnosis of food intolerance/allergy
- For scientific reasons in clinical trials
- For determination of the threshold value or degree of sensitivity
- For assessment of tolerance. Once diagnosed, when a patient is suspected to have outgrown his clinical allergy – especially in children, whose food allergies normally outgrow during childhood, e.g. cow's milk or hen's egg allergies.

Patients without specific history of adverse reaction to a food:

- If any chronic symptom is suspected by the patient or the physician to be food-related
- If a patient is on an improper elimination diet - without history of adverse food reaction –, the food has to be reintroduced and there are reasons for suspecting that an adverse reaction is possible.
- If a sensitization to a food is diagnosed and tolerance is not known – for example, sensitization to cross-reactive foods that have not been eaten after the adverse reaction.

Eligible patients for DBPCFC include:

1. All patients with suspicion of an immediate, systemic allergic reaction to a food for establishment or exclusion of the diagnosis
2. in infants and children $\leq$ three years, an open challenge controlled and evaluated by a physician is most often sufficient.
3. Patients with pollen related oral allergy syndrome (5) as their only symptom should only undergo DBPCFC outside scientific protocols in selected cases; for example in cases with discrepancy between case history and outcome of *in vivo* and/or *in vitro* tests.

An open challenge may precede DBPCFC in older children and adults because a negative result herein renders DBPCFC unnecessary. Open challenges should not be applied in cases with a high probability of a

positive outcome or in cases with subjective and/or controversial symptoms only (6).

There are, however other types of patients, who also should be investigated in a standardised programme:

1. patients with isolated, late reactions such as a subgroup of patients with atopic eczema dermatitis syndrome (AEDS) (7–12). In the majority of AEDS patients with associated food hypersensitivity an immediate reaction is seen (eg exanthema, flushing, urticaria together with symptoms and signs from the respiratory and gastrointestinal tract), but data are accumulating on a subgroup of patients who only experience exacerbation of their eczema within 24–48 hours after challenge. In such patients, the challenge procedure should be adjusted to meet the demands concerning e.g. timing and settings (11–15).
2. patients with controversial symptoms often of subjective nature such as chronic fatigue syndrome, multiple chemical sensitivities, migraine or joint complaints, who are presenting symptoms which are not in accordance with classical atopic symptoms. Such patients should only be investigated in strict scientific protocols with special attention to the statistical evaluation of the outcome, see "Statistics section"(6).
3. patients with chronic urticaria, where a subgroup is reactive to additives or to high doses of special foods (e.g. tomatoes) (16–24). Standardised protocols for DBPCFC in these patients have so far not been fully developed, and the actual incidence of food dependent chronic urticaria remains to be established.
4. patients with isolated late reactions in the gut (25, 26). Also for this group of patients, special attention must be paid to the lack of knowledge of incidence and nature of reaction, since these patients have not been finally classified.

Specific guidelines for these four latter groups are not dealt with in this Position Paper. In these patients, the challenge procedures must be adjusted according to the nature and severity of the reactions. Detailed guidelines for such patients have so far not been developed within the EAACI. A detailed position paper which has just been published from the German Society of Allergology and Clinical Immunology for identification of the late reactions in AD is now being modified for the EAACI (13).

Challenge is thus performed when the diagnosis is not made by case history and outcome of in *vivo*/*in vitro* tests, in scientific protocols for research purposes, or when a patient is suspected to have outgrown his/her clinical allergy.

Exclusion criteria

1. Patients with a clear cut case history of anaphylaxis (or a severe systemic reaction) to one or more specific food items should not be challenged, provided the risk of misinterpretation of a positive skin prick test or specific IgE due to clinically insignificant cross reaction is considered and ruled out - this may be the case for instance in patients with a false positive specific IgE to peanut due to grass pollen sensitization (27). The potential risk to the patient must always be weighed against the risk of misinterpreting e.g. skin prick test results or positive findings in specific IgE.

We define Anaphylaxis according to EAACI 2002, comparable to class 3 to 4 in the Müller classification of reactions to bee or wasp (28).

2. In selected cases where positive test results makes challenge unnecessary as is the case in children with positive spt to egg and specific IgE (CAP) above a certain level from ≥ 0.35 KU_A/L to $17.5 \geq KU_A/L$, in which the probability of a positive challenge outcome exceeds 95%. At present, such a correlation has only been demonstrated in children with AEDS and allergy to selected foods (29–32). By omitting challenge, determination of the clinical sensitivity ("threshold") of the patient is not possible (33).
3. Patients with ongoing disease should not be challenged e.g. patients with acute infection, unstable angina pectoris or patients with seasonal allergy during the season. Patients with chronic atopic disease such as asthma or AEDS should only be challenged when disease activity is at a stable and low level. Pregnant women should not be challenged.
4. Patients taking medication which may enhance, mask, delay or prevent evaluation of a reaction or interfere with treatment of a reaction should not be challenged. Drugs include antihistamines, neuroleptics, oral steroid above 5 mg per day, aspirin and other NSAID's, ACE-inhibitors, beta-blockers and clinical experience and new drugs may extend the list. Medication such as short acting β_2-agonists, inhaled or topical steroids can normally be continued during challenge, but the amount used must be kept at a fixed level. Discontinuation of these drugs may interfere with the interpretation of the outcome of the challenge.

Types of challenge

Double blind challenge (DB)

- DB is the procedure generally recommended, especially if a positive challenge outcome is expected (for example, when studying an adverse reaction believed to be IgE-mediated, and the food skin test is positive).
- DB is the method of choice for scientific protocols.
- DB is the method of choice when studying late reactions or chronic symptoms, such as AEDS, isolated digestive late reactions, or chronic urticaria.

- DB is the only way to conveniently study subjective food-induced complains, such as acute subjective adverse reactions, chronic fatigue syndrome, multiple chemical sensitivities, migraine or joint complaints.

Open challenge

- A negative DB should always be followed by an open challenge.
- A positive open challenge could be sufficient when dealing with IgE-mediated acute reactions manifesting with objective signs.
- For practical reasons, an open challenge can be the first approach when the probability of a negative outcome is estimated to be very high (for example, when studying an adverse reaction believed to be IgE-mediated, and a properly performed food skin test is negative).
- In infants and children ≤3 years, an open, physician-controlled challenge is often sufficient for suspected immediate type reactions (unless a psychological reaction of the mother is expected).
- For patients with pollen-related OAS as their only symptom, an open challenge could be sufficient as regular procedure - due to difficulties in blinding fruits and vegetables conserving their allergenicity -. However, in these patients, DB are recommended for scientific protocols and other selected cases for example, discrepancies between clinical history and outcome of diagnostic tests.

Single Blind Challenge

- Single blind challenge carries the same difficulties for blinding foods as for DB, and introduces subjective biases of the observer. Therefore, with only a minor additional work (cross-over by an external technician), DB can be performed, and the result will be more robust. Therefore, our recommendation is to always use DB instead.

Settings

The personnel involved in challenge procedure must be specially trained in management of acute allergic reactions and equipment for resuscitation (including adrenaline for injection and oxygen) must be readily available.

In cases where a severe reaction is suspected, challenge should be performed in settings with immediate access to intensive care units.

A possible need for latex-free surroundings should be considered.

Placebo challenge and active challenge should ideally be separated by at least 24 hours, but when late reactions are not expected, both challenges can in many cases of classical type 1 allergy be performed on the same day.

If a reaction needing treatment occurs, the next challenge should not be performed until the symptoms have resolved and the quarantine period for the drugs used has expired.

Intravenous access should be available before initiation of challenges as a general rule, and always if a severe systemic reaction is expected. In small children, iv access is only necessary in selected cases, but if there is any doubt on the outcome (severity) of a challenge, it is advisable to place a cannula in advance.

Patients can be in most cases be challenged as out patients and discharged after an observation period of at least 2 hours after the last dose given, provided no reaction has occurred. The observation period must be adjusted to the expected symptoms and signs in the patient in question. The patient must be discharged with specific information and satisfactory arrangements for care if a late reaction (especially asthma) occurs. In some cases, "rescue medication" consisting of antihistamines, β-agonists and steroids may be given to the patient to take prn after contacting the physician.

If a patient experiences a severe reaction needing treatment (asthma, laryngeal oedema, severe urticaria), he/she should be kept under observation at the hospital overnight and treated accordingly.

A negative outcome of DBPCFC must always be followed by an open serving of the food in order to avoid possible false negative outcome of DBPCFC due to destruction of allergens during preparation of the challenge (34). For clinical purposes, a patient may thus be classified as positive, or likely positive (only positive in open challenge) whereas as in a scientific protocol a positive open challenge in a DBPCFC negative patient should be considered as a drop-out.

Procedure

If case history is suggestive of reactions in special situations only (reaction elicited only when exercising after eating (food dependent, exercise induced anaphylaxis (3) or with concomitant intake of a drugs (e.g. aspirin (4)) or intake of processed food (35–37)) challenges should first be performed without exercise/drug intake and if negative repeated with exercise/drug intake . Many of these reactions are, however, severe of nature and the use of pharmaceutical "facilitators" such as aspirine may enhance the severity of the reaction resulting in life-threatening situations. Such challenges should always be considered carefully.

The challenge protocol should be decided on beforehand. In cases of classical type 1 patients presenting objective signs a protocol using one active and one placebo is normally sufficient due to the low frequency of reactions to placebo in these patients (38–49). In more dubious cases and especially in cases patients presenting with subjective signs only a protocol with repeated challenges should be applied, either using three plus three challenges or three plus two challenges (50–53).

Table 2. Proposed starting dose for different foods (the actual starting dose must always be considered in the actual patient)

Food	Dose	Reference
Peanut	0,1 mg	(39, 56–58)
Milk	0,1 ml	(12, 31, 43, 59, 60)
Egg	1 mg	(31, 61, 62)
Cod	5 mg	(42)
Wheat	100 mg	(Personal communication)
Soy	1 mg	(31, 63)
Shrimp	5 mg	(64)
Hazelnut	0,1 mg	(45)

The starting dose, ie the amount of food in question administered to the patient as the first dose should be evaluated based on patient's case history and correlated to available data from the literature (Table 2). In published papers, 5% of patients react to less than 1 mg of peanut, whereas 15% of milk allergic patients react to less than 5 ml of cow's milk (43, 54). A computer model for assessment of threshold has recently been published demonstrating a possible threshold for a reaction in one in a hundred patients for milk, egg and peanut of 0,1 mg (55).

It is advisable to begin with a starting dose below the expected 'threshold dose', because this will enable determination of the actual sensitivity in the patient (low adverse effect level and no observed adverse effect level).

There is no correlation between the size of a skin prick test or the level of specific IgE and the clinical sensitivity in individual patients (33, 65).

Dosing and interval

A time interval of 15–30 minutes is in most cases suitable for investigation of IgE associated reactions unless using capsules. In published papers, symptoms most often occur 3 to 15 minutes after intake; especially the severe reactions always occur immediately - if the patient history claims a reaction developed later, time schedule should be adjusted accordingly (39, 42, 43, 45, 50, 56, 66, 67).

All patients follow the above incremental scheme if an acute reaction is suspected, patients with suspected isolated late reactions (e.g. exacerbation of AD) continue on another protocol with intake of normal daily amount the following day settings (11–15).

The increment may either be a doubling of the dose every 15–30 minutes until top dose has been reached or the patient react, or a increment using logarithmic mean ie 1, 3, 10, 30, 100 etc. No comparative studies comparing these two protocols are available. There is a theoretical risk of passive rush desensitization during the procedure, but evidence for such a phenomenon has not been published and is unlikely since this would result in a positive outcome of the open feeding following a negative DBPCFC. Such reactions have only been seen in cases, where the active substance was destroyed during the blinding procedure (34, 68). If too large increments, on the other hand, are used, the risk of severe reactions increases. Therefore, at the present state of knowledge, either doubling or logarithmic increment is recommended.

The top dose ie the maximal amount administered should normally be the normal daily intake in a serving of the food in question, adjusted for the age of the patient.

Preparation of food used for challenge

Data concerning the foods most often causing allergic reactions has previously been published (69).

Active and placebo challenges should be identical regarding taste, looks, smell, viscosity, texture, structure and volume. Assessment of possible differences between active and placebo should be evaluated by standard procedures such as duo-test and triangle-test, where differences in taste, texture, smell etc. are compared either in pairs or by ability for finding one different between three samples (70).

In infants and children liquid foods can be masked in extensive hydrolysed cow's milk based formulas or in amino acid formulas eventually with addition of flavouring agents or colourants. Items with a strong taste such as black currant juice or peppermint oil may help masking an unpleasant taste.

Different recipes for masking liquid and solid foods (peanut, soy, wheat, milk, egg, fish, hazelnut, almond, brazil nut, apple, carrot, celery, apricot, banana, zucchini, crustaceans) have been developed and are available on the EAACI homepage (http://www.eaaci.org or http://www.ig-food.org.)

It is of crucial importance to ensure presence and stability of the allergenicity of the food in the mixture. In cases with very stable foods such as peanut or cod (42, 71) stability in the serving is not a problem, whereas in other cases especially with foods of vegetable origin (apples) the stability is very low (72). The procedures must be adjusted according to the stability of the food in question (35, 37).

Only in cases of a suspected reaction to additives is masking in gelatine capsules recommended. Capsules should else wise be avoided, since reactions in mouth and throat are bypassed (OAS) and since the whole procedure is delayed due to the lag phase when the capsule is dissolved in the stomach.

Measures to avoid toxicity from the food administered should be taken (aflatoxins in brazil nuts, salmonella bacteria in eggs, and mites in flour).

Statistical considerations

Different approaches should be taken in patients presenting classical allergic symptoms with objective signs of a reaction on challenge and patients presenting subjective symptoms only. Furthermore, special attention should be

made to the statistical evaluation when investigating patients with controversial symptoms.

In classical type I allergy reacting with objectively measurable signs (e.g. a drop in FEV_1, sneezing or urticaria), reactions to placebo are relatively rare and a challenge procedure using one active and one placebo challenge is normally sufficient (40, 42, 61, 73).

In contrast, the frequency of reactions to placebo seen in patients reacting with subjective symptoms (OAS, migraine, itching) is higher (50, 53). Here, repeated challenges are normally necessary.

Two statistical approaches exist, necessitating different approaches in challenge procedure. This is especially true for patients only presenting subjective symptoms:

1. An approach considering the actual patient

The risk of a patient guessing the right sequence of challenges by chance is 50 per cent, if one active and one placebo is administered. Therefore repeated challenges must be used to ensure statistical significance. A protocol using three active and three placebo's has been published (51). The chance of a patient guessing the right sequence by chance is 0.05 ($0.5 \times 0.6 \times 0.5 \times 0.67 \times 0.5$).

Recently a new model has been proposed, where using five challenges in stead of six, where the patient is aware of the presence of either three active and two placebo challenges or vice versa (52). This approach holds the same statistical reliability as using six challenges.

2. An approach considering a cohort of patients

In several published papers patients reacting to placebo challenges are excluded from statistical analysis. This approach carries the risk of overestimating the actual frequency of patients with actual allergy. As a fictive example, the following outcome of a trial with 100 patients reacting with subjective symptoms only can be used for illustration:

1. Patients reacting both to active and to placebo	25
2. Patients reacting to active and not to placebo	25
3. Patients reacting to placebo and not to active	25
4. Patients reacting neither to active nor to placebo	25

It is evident, that using the whole cohort, no correlation between challenge and outcome is obtained. Excluding the patients reacting to placebo (1 and 3), however, results in a frequency of 50% in the remaining patients. The frequency of placebo reactors in a trial must therefore always be taken into consideration and the actual frequency reported.

In both cases, a statistical model has been developed (51). The use of such statistical evaluation of the outcome of a trial is highly recommended.

Documentation

All challenges should be documented. For comparative reasons, preformed and standardised documentation sheets should be used. Examples of such sheets are available at http://www.ig-food.org.

Conclusions

The present position paper reviews the present level of knowledge for performing double-blind, placebo controlled challenges. The use of the guidelines presented here will both increase safety and feasibility for the patient and staff involved in the challenge procedure and also, by using mutual protocols, enable comparisons between results obtained in different centres.

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