

Standardization of double-blind, placebo-controlled food challenges

At present, no international agreement on standardized protocols for use in double-blind placebo-controlled food challenge exists. There is a great need for such standardization, both for clinical and for scientific reasons.

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As early as 1995, the European Academy of Allergy and Clinical Immunology (EAACI) published the first position paper on food allergy, in which the current status of knowledge in the field was presented (1). This was followed in 1999 by a second position paper, by the same Interest Group on adverse reactions to foods, dealing with more controversial aspects of adverse reactions to foods (2). Lacking, however, was - and still is - a procedure manual ("Standard operating procedures") for the practical aspects of challenging patients with foods in a standardized, feasible, safe and comparable way.

Standardization is necessary for two reasons: the clinical reasons are obvious, securing the safety to the patients and ensuring the correct diagnosis, but scientific reasons are also important because, due to the different conditions for challenge (i.e. timing, source of foods, time interval, etc.) the present situation does not allow for comparison between data obtained from different research groups. There is a need for comparable data on, for example, the lowest dose of a food that can elicit a clinical reaction in the most sensitive patients (low effect level) but this is not available today.

Several parameters need to be evaluated and standardized (Table 1). The items can be divided in parameters which are patient-related and parameters that are related to the challenge procedure.

Patient-related parameters

PA1 – Selection of patients for challenge

The selection of patients for subsequent challenge today depends mainly on the decision of the physician in question, his settings, knowledge and preferences.

Therefore, in some centers, very sensitive patients are not challenged, due to the risk of severe systemic reactions. This selection hampers the determination of low effect levels and makes comparisons between centers impossible. In some centers children are not challenged, whereas in others, no challenges at all are performed. All these different approaches have advantages and disadvantages.

PA2 – Use of *in vitro* and *in vivo* tests for selection of patients for challenge

At present, there is no mutual agreement on which *in vitro* (specific IgE from different commercial sources) and *in vivo* (skin-prick tests with different commercial extracts or use of fresh foods for skin testing) should be available prior to challenge (3). Different centers require different tests prior to deciding on the further procedure. For example, in some centers, challenge is considered unnecessary if the level of specific IgE towards the food in question exceeds a certain level (4). Thus the threshold value (i.e. the amount of food that elicits the clinical reaction) cannot be determined.

PA3 – Nature of a suspected reaction

In infants and young children, double-blind, placebo-controlled food challenge (DBPCFC) is usually unnecessary if the open challenge is conducted and evaluated by professional staff, whereas it is mandatory in older children and in adults (1).

The actual challenge procedure may also be influenced by the nature of suspected reaction in a patient: for example, will repeated challenges be necessary to establish statistical significance in a patient presenting

with only subjective symptoms (no objective signs), when one active and one placebo challenge is normally sufficient in classical food allergy (5).

Finally, the disease state of a patient influences the decision as to whether it is possible to perform challenge; especially in atopic diseases with spontaneously fluctuating severity, e.g. atopic dermatitis or asthma, the prechallenge severity of disease is crucial. Patients must be challenged when disease severity is stable and at as low a level as possible.

Procedure-related parameters

PP1 – The source of food used for challenge

The food used for challenge should be chosen based on actual eating habits, e.g. whether the food is eaten cooked or raw. In some centers, freeze-dried extracts of foods are used, carrying the risk of losing important epitopes during processing of the extract (6). In some cases of very stable foods, the blinding procedure is simple without risk of losing important epitopes during preparation, whereas other foods are so labile that, for example, merely peeling an apple destroys the proteins responsible for the clinical reaction.

Masking of the food is also important. When freeze-dried foods are used in gelatine capsules for challenge, reactions in the mouth and upper respiratory tract are bypassed, possibly altering the dose-response curve in the patient.

The masking procedure is a crucial point both for securing preservation of the allergenicity of the food during preparation and for ensuring actual double-blind conditions, together with the palatability of the serving. Protocols using solid mixtures, semisolid mixtures and liquid mixtures have been developed, but have not in all cases been validated (5–10).

The challenge material used should be tested for preservation of the allergens and a negative DBPCFC should always be confirmed by a subsequent open challenge with the food. Examples of suboptimal mixtures used for DBPCFC resulting in false negative outcomes have been published and these mixtures should be avoided (1, 6).

PP2 – Starting dose used for challenge

The starting dose, i.e. the first dose of the food given to the patient, must be determined in every single case, based on information on the nature and severity of a reaction, the amount of food in question that is suspected to have elicited a reaction in the patient, and low effect levels of the food.

Care must be taken to avoid uncritically high starting doses, which carry the risk of eliciting severe reactions. Ideally, the first doses should be subclinical because this allows for establishment of the low effect level in the patient.

PP3 – Dose increment

At present, no consensus exists on how the food dose should be increased during challenge. In some protocols, doubling of the dose is used, whereas in others, threefold to even 10-fold increases are used. One important parameter for dose increment is, of course, the safety of the patient, but also feasibility, e.g. the length of the challenge or the total amount of challenge material to be ingested, is important.

PP4 – Time interval during challenges

Different protocols are also used for this parameter. In some cases where delayed reactions are suspected, timing must of course be adjusted to the actual situation, but even in classical reactions of immediate type, the time interval varies from 15 to 60 min. At present, it is not possible to determine which time interval is preferable. Whether the theoretical risk of inducing passive tolerance during a rapid challenge procedure exists remains to be elucidated.

Finally, classification of timing is important. In one center, the time to clinical reaction is determined from initiation of the challenge procedure. In fairly unsensitive patients reacting to large doses of the food in question, this gives rise to confusion between actual late phase reactors (reacting more than 24 h after the last challenge administered) and acute phase reactors (reacting a long time after initiation of the procedure but less than 30 min after administration of the last dose) (11).

The optimal timing between two challenge situations also remains to be established. In most centers, challenges are separated by at least 48 h. Whether a shorter time interval is possible remains to be established, but the patient should at least not be rechallenged prior to cessation of symptoms and signs elicited from the previous challenge.

PP5 – Top dose

The top dose of the food in question must be determined for every single food used for challenge. Top dose depends on the nature of the food, e.g. milk versus spices, and also on differences in eating habits in various regions of the world. The top dose should reflect the normal intake of the food.

PP6 – Number of placebo and verum challenges

As previously described (PA3), the number of repetitions of challenges is dependent on the nature of the reaction in the patient. It is generally considered sufficient to administer one verum and one placebo challenge in the case of patients with objectively measurable signs on challenge, whereas it is advisable to repeat the procedure in more doubtful cases (5). The decision on the number of challenges should be taken prior to initiation of challenge.

Table 1. Factors influencing challenge

Patient-related parameters	Procedure-related parameters
Nature of reaction	Source of food
Age of patient	Starting dose
Food in question	Increment
	Timing
	Top dose
	Blinding procedure
	Settings
	Requirements

PP7 – Statistical evaluation of the reactions

This topic will be dealt with elsewhere (Briggs et al., p. 83) in this volume. It is crucial to establish a common statistical procedure for evaluation of the patient's response. In many protocols, patients reacting to placebo are excluded from statistical evaluation, resulting in a risk of overestimation of the frequency of a given reaction to a food (12).

Statistical evaluation should be divided into statistics on the individual basis (e.g. the statistical change of finding the three active challenges among six, which is $0.05 (0.5 * 0.6 * 0.5 * 0.67 * 0.5 * 1)$) in patients with more dubious subjective symptoms and the statistical significance on group basis, where the number of patients reacting to verum should be adjusted against the number of patients reacting to placebo. A theoretical example is given in Table 2.

Evaluation of the challenge result

A successful challenge should establish or rule out clinical sensitivity of a given patient to a specific food. In patients sensitive to a given food, establishment of the threshold dose should be recorded, and patients

Table 2. 100 patients in an imaginary trial, all claiming to react with subjective symptoms only upon intake of aspartame

After DBPCFC (one active, one placebo):	
Patients reporting reaction to:	
Active only	25
Placebo only	25
Both active and placebo	25
No reactions	25
If placebo reactions are included:	No statistical significance
If placebo reactions are excluded:	50% reactors

should hereafter be divided, depending on sensitivity, into very sensitive patients and less sensitive patients, who react to higher, and avoidable, doses. Very sensitive patients should receive extensive training in avoiding the offending food and in many cases carrying epinephrine for autoinjection together with an alert bracelet.

Further group comparisons will make it possible to establish low effect levels in different patient groups. A negative DBPCFC must always be followed by an open feeding test.

Conclusions

At present, no international agreement on standardized protocols for use for DBPCFC has been established. There is a great need for such standardization and this is the reason for the establishment of the EAACI Task Force on Standardization of Challenge Procedures for DBPCFC, which currently is preparing a position paper on this topic.

In future, comparisons between results obtained in various centers from different parts of the world will then be made possible.

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