

Double-blind, placebo-controlled food challenge in adults in everyday clinical practice: a reappraisal of their limitations and real indications

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Purpose of review

The double-blind, placebo-controlled food challenge (DBPCFC) is widely considered as the ‘gold standard’ for the diagnosis of food allergy. However, in adult patients, this procedure is rather rarely performed outside the academic context. This review article aims to reappraise the pros and cons of DBPCFC and to elicit some critical thoughts and discussions about the real indications of this diagnostic procedure in adult patients in everyday practice.

Recent findings

There are many data showing that the DBPCFC poses a number of critical problems that are difficult to overcome in normal outpatient clinics and hospitals, and that are generally not addressed in most articles dealing with this issue.

Summary

Performing DBPCFC poses a number of practical problems and has several pitfalls, which make its routine use in normal clinical settings generally impossible. This review article shows that the need for this procedure in adult patients seems in effect very little and specifies new, more limited indications to its use in everyday practice. Further, it suggests a role for the open challenge, which lacks several of the disadvantages of DBPCFC.

Keywords

diagnosis, double-blind placebo-controlled food challenges, food allergy

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Introduction

Some diagnostic or therapeutic procedures are considered as essential by the broad clinical community and discussed in position papers, but are nonetheless largely absent in most clinical settings. The double-blind placebo-controlled food challenge (DBPCFC), which has been unanimously considered the ‘gold standard’ for the diagnosis of food allergy for a long time [1], is a typical example in this sense. There are situations in which such a procedure is really invaluable, for instance, to establish or exclude a diagnosis of food allergy in individuals whose symptoms are difficult to evaluate (e.g. if atopic dermatitis is present, especially in young children who are sensitized but do not eat the food in normal quantities; in case of chronic symptoms or late reactions, of reactions to complex foods in multisensitized/allergic patient, or of reactions to food combined with medication in which both might be the culprit; in patients strongly convinced that they are allergic based only on sensitization and on the opinion of a general practitioner/specialist/alternative circuit doctor, and in case of subjective food-induced

complaints), to detect the threshold dose of a certain allergen (i.e. the degree of sensitivity), or to assess tolerance [2]. However, the usefulness of DBPCFC as a routine means to diagnose food allergy in adults is much more questionable, especially in view of the enormous costs for both the hospital and the patient. The present article aims to elicit some critical thoughts and discussions about the real indications of DBPCFC in adult patients in everyday practice.

The diagnosis of allergy

In everyday practice, an IgE-mediated allergic status is suspected on the basis of a convincing clinical history associated with positive skin prick tests (SPTs) with relevant allergens, the demonstration of specific IgE, or both. In patients with suspect respiratory allergy, such diagnostic procedures (i.e. clinical history along with positive SPT, positive in-vitro test, or both) are considered sufficient to diagnose an allergic condition, and millions of people are presently prescribed drugs and specific immunotherapies on the basis of these data.

Nobody would carry out double-blind, placebo-controlled nasal, conjunctival, or bronchial provocations with specific seasonal airborne allergens on a routine basis to confirm a diagnosis of respiratory allergy in patients with unequivocal history and positive confirmatory skin tests, unless clinical data and diagnostic tests (either *in vivo* or *in vitro*) are totally discordant. The same holds true in patients with hymenoptera venom allergy.

In patients with suspected food allergy, the story is different. On the basis of the observation that the misperception of food allergy is widely present in the general population, patients' reports have to be considered unreliable even in the presence of an unequivocal clinical history, supported by positive SPT, and by elevated levels of serum-specific IgE. It has been claimed that the diagnosis has to be considered 'presumptive' until an objective allergic reaction has been reproduced and personally seen by a physician on DBPCFC [3]. Two exceptions to this rule are accepted or suggested: when unequivocal allergic symptoms occur following an isolated ingestion of a specific food or when serum food-specific IgE levels exceed certain 'decision point' values [3–15]. Regarding the first point, one wonders why an unequivocal history of allergic symptoms following the ingestion of the offending food together with other tolerated foods should be considered less reliable than an isolated ingestion. Regarding the latter point, it has to be considered that factors such as the age of the patients, type of reactions (either immediate or late), concomitant atopic disorders, duration of food allergy, and prevalence of that particular food allergy in the population considered may heavily influence the results of these studies making them probably valid only for the population in which they have been performed. Most studies have been in effect carried out in children and, unfortunately, resulting cutoff points varied from one centre (i.e. study population) to another, and specific IgE levels needed to gain sufficient sensitivity and specificity were frequently so high that the proportion of patients that could 'escape' DBPCFC was minimal. Further, the selection of a 95% cutoff level (as opposed to 90% or even 80%) as a decision point is arbitrary. Although largely subjective, expert clinical judgement will always be an important feature of diagnosis and a wise use of a weight-of-evidence approach will always retain merit. The attempts to use the wheal size obtained on SPT as a decision point [16–19] have had to face even bigger problems: the use of different extracts, different methods, and different reading times made any attempt to standardize these procedures impossible. Although the drawbacks of 'decision points studies' discussed above might seem to argue in favour of the use of DBPCFC as a diagnostic test, it has to be considered that most potential candidates to these

procedures seen in allergy clinics already have positive SPT and elevated specific IgE levels (as well as a suggestive clinical history) before studies of cutoffs of SPT or IgE are performed.

One further exception to the DBPCFC rule is that, because of safety reasons (i.e. the fear of possibly harmful reactions during DBPCFC), on the basis of a risk/benefit calculation, patients with histories of very severe allergic reactions are normally excluded from DBPCFC protocols [1,2]. This means that in patients with a history of severe allergic reactions, anamnesis, positive SPT, and serum-specific IgE are considered sufficient to diagnose food allergy reliably, irrespective of the fact that the specific food was ingested isolated or not, the wheal size exceeds a certain mean diameter, or specific IgE levels are high or low. As a result, individuals allergic to the same food (possibly to the same allergen protein), equally positive on SPT, and possibly with the same level of food-specific IgE are artificially divided into 'class A patients' (who are believed because they have a history of anaphylaxis and for whom the DBPCFC is considered superfluous) and 'class B patients' (whose history is not trusted because they experienced 'only', say, urticaria with angioedema but not anaphylaxis and for whom DBPCFC is considered an absolute need for diagnosis). In view of the poor correlation between the severity of reported reactions and the severity of reactions elicited during DBPCFC [12] and of the fact that, at least for peanuts and tree nuts allergy, the false positive rate (i.e. suggestive clinical history not proven on subsequent challenge) is less than 20%, suggesting that clinical history is reliable in most cases [20,21], one wonders whether all this is scientifically acceptable. Of course, adequate diagnosis is of utmost importance and there are reports showing that challenges can be safely done [22], but clearly the risks have to be weighed against the possible benefits.

Altogether, the existing guidelines and most published papers on this issue disregard the paramount importance of careful history taking, which is one of the main and most delicate duties of a well trained and experienced allergologist (physician). Regarding the sensitivity of available in-vivo and in-vitro tests with food allergens, it is certainly true that patients sensitized to labile allergen proteins may score negative on SPT or in-vitro assays with commercial food extracts (poor sensitivity), but in these cases, SPT with fresh foods are the solution. About the presumptive 'poor specificity' of in-vivo and in-vitro testing, it is well known that patients sensitized to cross-reacting allergens (but also other patients as well) may be found to score positive for some food sources in the absence of a clinical history; however, in most patients, a positive

clinical history with another food (equally positive on SPT or ImmunoCAP) will be the reason why these patients asked for medical advice. These aspects are further discussed. The fact remains that in all cases, history taking is of paramount importance and usually leads to suspect one or more specific foods to at least some of which sensitization can be subsequently demonstrated either by SPT or specific IgE.

Practical problems of double-blind, placebo-controlled food challenge

The DBPCFC poses a number of critical problems that are difficult to overcome in normal outpatients' clinics and hospitals, and that are generally not addressed in most articles dealing with this issue.

Setting

For safety reasons, food challenges should be performed in a hospital setting in which emergency care is immediately available as severe reactions have theoretically to be expected [1]. However, many (in some countries, most) allergists work outside hospitals; if all of them would refer their patients with a good indication to their colleagues working in clinics and hospitals in order to confirm their 'presumptive' diagnoses by DBPCFC, the latter would in no case be able to comply with all the requests. As a practical consequence, most patients with food allergy seen during everyday practice are left with a 'presumptive' diagnosis.

Further, the practical problem for DBPCFC in hospitals and clinics is that additional facilities and staff to blind adequately the foods are needed, which may really be a limiting factor.

Form of challenged food

Until recently, it was recommended that in DBPCFC the challenged food should be given in a lyophilized form [1]. However, hospitals rarely own a lyophilizer, and the number of foods marketed in a lyophilized form is very limited; even in the case that these are available, their reliability in terms of protein content, allergenicity, and possible premarketing processing is all but established. Nowadays more and more fresh foods are used in the recipes to match the actual eating experience of the patient. However, much more work needs to be done on the validation of food challenge materials. Standardization is another major issue, as the content in the single allergens may change within different batches of the same food [23].

Blinding

Validation of adequate blinding can be achieved by sensory testing in a professional food laboratory [24], a facility that is normally not present in hospitals and

clinics. Even when it is professionally performed, blinding the high challenging doses of nuts, peanuts, fish, shrimp, and so on may become a major problem, and can be accomplished only at the cost of feeding patients with an enormous amount of matrix in order to prevent unblinding [25]. This implicates that these challenge foods generally are not a good reflection of what is eaten in everyday life and caused the reaction. Further, notably, large amounts of foods may by themselves cause symptoms mimicking allergy, such as nausea or vomiting, leading to a wrong diagnosis (or to a falsely positive placebo reactivity) [25].

Matrix

For the active test food challenge, the suspected allergenic food is disguised in a food matrix (recipe) consisting of food components normally tolerated by the patient. Placebo and active test recipes should be as sensory equivalent as possible in terms of taste, smell, consistency, texture, and colour so that the active meal cannot be distinguished from placebo. Again, this cannot be achieved properly in all normal hospitals or clinical settings. Further, a matrix effect exists and has been described.

Psychological aspects

When they present at the clinic for the first time, many patients may have already spontaneously excluded the putative offending foods from their diets irrespective of the fact that they had a suggestive or nonsuggestive reaction; such decision will be much enforced if they see a positive SPT or an elevated IgE level to that particular food. Although in principle, it is important that these patients (particularly those with nonsuggestive reactions) learn/understand that they can tolerate the food and normalize therefore their diets and increase their quality of life (especially if nutritionally essential foods or foods difficult to avoid are involved), it is unlikely that they will change their mind after a negative DBPCFC. Hence, one wonders whether the procedure makes sense or is a waste of time in these patients. A negative open challenge would be a much clearer and believable demonstration of tolerance in such patients.

One further psychological aspect that deserves to be considered is that to obtain an informed consent for a food challenge (either double blind or open), which is mandatory in most European countries as well as in the USA, may pose a problem. In fact, even when patients are given careful explanations about the risks and the benefits of the procedure, if patients' clinical experience is corroborated by positive SPT, elevated levels of specific IgE, or both, most of them will decline because they do not understand why they should undergo a time-consuming and potentially dangerous diagnostic

procedure that will at best confirm what they already consider absolutely clear. Irrespective of the fact that they have got a right or wrong perception of their status, if they do not agree with an oral challenge, what kind of diagnosis should then be registered? 'Food allergy' (for safety reasons) or 'possible food allergy'? Notably, in the latter case, food allergy will be under diagnosed on a population level.

Costs

The DBPCFC is rather expensive for both the patients (in terms of loss of working hours or school days and of direct costs) and for the health service (both public and private) because 2 working days per food are needed. Further, if DBPCFC scores negative, a third day for an open challenge is required. Finally, because of its intrinsic complexity, the procedure demands many personnel and is time-consuming.

Which foods should be challenged?

Some patients, particularly those sensitized to cross-reacting plant-derived foods, may present with a number of equally offending (or potentially offending) foods. In these patients, the question is whether to challenge all candidate foods (which is practically unfeasible for the reasons discussed above) or to focus on the most important ones. However, in this latter case, who decides which are the 'most important' foods, and by which criteria? Should a potentially offending food be disregarded as a 'minor' one based on the patient's or the doctor's opinion?

Sensitivity and specificity issues

The DBPCFC shows a number of pitfalls that seem to make it all but the 'gold standard' that has been claimed up to now.

The 'false negative' double-blind, placebo-controlled food challenge

The prevalence of false negative results on DBPCFC has been estimated at between 2 and 5% [1]. Such false negative challenges have been ascribed to the administration of insufficient challenge material during the challenge or to some alteration of the relevant allergenic epitopes during lyophilization [1]. However, one aspect that has probably received too little attention so far is that the DBPCFC may not be able to reproduce the conditions that occurred when the reported allergic reaction took place. Some examples are as follows:

- (1) Sensitization to labile allergens. Patients with pollen allergy may develop allergy to plant-derived foods as a result of sensitization to cross-reactive allergens. Notably, such food allergies are by far the most frequent in adults. As allergen proteins involved in

these reactions (e.g. profilin and proteins homologous to Bet v 1) are extremely labile and easily destroyed by oxidation, heating, or handling, most allergenicity of offending foods may be lost during the procedures needed to prepare the meals for the DBPCFC [26]. As a consequence, the challenge procedures will score negative despite a clinical history of oral allergy syndrome, positive SPT with fresh foods, and elevated specific IgE. Although position papers claim that there is no indication to carry out DBPCFC in patients with oral allergy syndrome outside scientific protocols [2], systemic reactions possibly caused by profilins have been reported [27].

- (2) Matrix effect. Matrices used to mask foods during DBPCFC procedures may influence the release and absorption of allergens [28], causing the DBPCFC to score falsely negative.
- (3) Food-dependent, exercise-induced, urticaria/anaphylaxis (FDEIA). Some food-dependent, exercise-induced reactions may be triggered by such a small amount of exercise (e.g. hurrying to answer the telephone at home [29]) to prevent the patients' noticing the association with exercise. In these cases, the patient will probably report an association between symptoms and a particular food but not with exercise, and the DBPCFC will invariably score negative in spite of positive history, positive SPT, and positive specific IgE.
- (4) Aspirin and other nonsteroidal anti-inflammatory drugs. The patient might have a mild food allergy that has caused severe symptoms because 'facilitators' such as aspirin or other nonsteroidal anti-inflammatory drugs have been associated with the food [30–32]. If a specialist visit is performed some time after the adverse event (as is the case in most instances), the patient could not recall the association with anti-inflammatory drugs if these have been subsequently taken without any consequence, but will probably report correctly the foods eaten before the reactions occurred. Also, in this case, the DBPCFC will score negative in spite of positive history, SPT, and specific IgE.
- (5) Other augmentation factors. Although little actual proof exists of their relative importance, alcohol, warm baths or sauna, and gastrointestinal infections are some other cofactors that might have concurred in the reported allergic reactions and that cannot be reproduced during DBPCFC. Another cofactor that has recently emerged as possibly able to influence both sensitization and clinical expression of food allergy is antacid treatment. Antacids can delay digestion and prevent degradation of certain pepsin-sensitive allergen protein, thus allowing them to reach the intestinal tract in an unmodified form [33•].
- (6) Unexplained false negative challenges. In some cases, a negative DBPCFC is followed by an allergic reaction upon the subsequent reintroduction of the

same food in the absence of any of the conditions listed above [34,35].

- (7) Specific oral tolerance induction (SOTI). Recently, a series of studies of the so-called food-SOTI have appeared in the medical literature (reviewed in [36]) claiming that the repeated administration of small, increasing doses of the offending foods finally results in short-term tolerance. Something similar might occur also in some patients undergoing diagnostic challenges and causing a falsely negative DBPCFC.
- (8) Some final remarks. In case of a negative DBPCFC, it is recommended to do an open challenge, which often is positive. So, in a certain sense, this already indicates that a negative DBPCFC does not represent the final word of the diagnostic procedure. Thus, why not think of an open challenge first, and in case of doubt, a blinded one?

The 'false positive' double-blind, placebo-controlled food challenge

Very recently, a paper drew attention to possible placebo reactions in children submitted to DBPCFC. In that study [35], placebo-induced events occurred in 12.9% of 132 challenges carried out in 105 children, and 5.4% of positive active food challenges were revealed to be false positive by a positive placebo challenge. In adults, some clinical conditions characterized by spontaneous recurrence such as chronic urticaria or atopic dermatitis may be considered at risk for false positive DBPCFC. Needless to say, in most cases, the positive DBPCFC will probably contrast with negative SPT and absence of detectable levels of circulating specific IgE.

Medication withdrawal is another key issue; in some cases, if all medications are removed, symptoms may occur as a result of the absence of medication rather than as the result of the challenge material. Especially in atopic dermatitis in young children (in the absence of acute symptoms on food), skin lesions should be treated adequately and should be stable during maintenance therapy before an oral food challenge can be performed with a reliable outcome [37]. The history of tartrazine intolerance is another typical example in this sense. Tartrazine has been thought to be a provoker of asthma and chronic urticaria for years, but eventually some studies showed that very few tartrazine reactors really exist. Another important concept involves offending challenges on 1 vs. 2 separate days. The order effect may play a role in these cases.

The clinical history of adult patients with food allergy

Altogether, in adult patients, the proportion of IgE-mediated food allergies that cannot be properly diagnosed without a DBPCFC is very limited. Clinical history is clear-cut and highly suggestive in the large majority of

cases, irrespective of the fact that the offending food was ingested alone or associated with other foodstuff (e.g. 'the last two times I ate seafood, I became red and covered with wheals within 30 min and I had to rush to the emergency room' or, 'whenever I eat a fresh fruit, severe itching at the mouth and throat occurs within a couple of minutes', etc.). This underlines the capital importance of thorough and correct history taking as this is actually perhaps the most reliable and valuable, although often underappreciated, approach to the diagnosis. When history is not clear, skin tests and specific IgE measurements are helpful to re-evaluate clinical history. One has always to keep in mind that the patients are presenting at the clinic because they experienced a possible food-induced adverse reaction (a fact that is often disregarded as irrelevant).

On the contrary, the large majority of those who present with a history of a single episode of acute urticaria not associated with drugs or insect stings score invariably negative on SPT with food allergens and in many cases report that they have spontaneously reintroduced all the foods eaten before the urticaria episode began without any problem. Similarly, patients with chronic urticaria, although frequently convinced to have a food allergy at the first visit, are generally unable to report any association with specific foods or show normally any sign of food allergy on SPT or in-vitro tests. Thus, food challenges may not be necessary in the majority of cases.

Indications for double-blind, placebo-controlled food challenge in adults

In light of what has been discussed earlier, the clinical indications for DBPCFC in adult patients should be probably revised as follows:

- (1) In everyday practice:
 - (a) To establish/exclude food intolerance/allergy when discrepancies exist between clinical history and in-vivo, in-vitro tests, or both; that is, when history is clearly positive but both SPT and in-vitro tests are negative [38] or when history is unclear and SPT/CAP are clearly positive. Notably, in both instances, a much simpler and less time-consuming open food challenge (OFC) should work equally well, unless symptoms are protracted, chronic, or exclusively subjective.
 - (b) When anxiety prevents a patient from eating certain food with important nutritional value (but also in this case, an open challenge performed first might represent a proper choice).
 - (c) To establish/exclude allergy to foods that are positive in SPT/CAP and that the patients have not been eating or have ingested only in trace amounts for long periods.

- (2) For scientific reasons in clinical trials:
- (a) to confirm food allergy diagnosis in clinical research and in multicentre studies;
 - (b) to detect the threshold doses for allergenic foods [39].

The open food challenge: a possible alternative

When a challenge is absolutely needed to confirm the presence/absence of allergy to a certain food, the OFC should theoretically serve well. This is particularly true if a negative outcome or a positive response with objective symptoms is expected or if labile food allergens, as in fruits and vegetables, are involved. Although there is not much literature comparing OFC with DBPCFC, there are no reasons to believe that a patient with a history of urticaria/angioedema following the ingestion of a certain food may behave in a different way if submitted to OFC rather than to DBPCFC. The OFC lacks several of the drawbacks that characterize the DBPCFC. First, the challenge procedure can be easily performed in one session (1 day), also in hospital settings unable to purchase or prepare proper matrices, or lacking the facilities (i.e. a professional food laboratory) to prepare properly blinded doses of the food. Second, the food can be administered in the same form that it had when the presumptive adverse reaction occurred, thus avoiding the matrix effect. Third, the lack of blinding dramatically reduces the amount of challenge materials to be ingested to get a high dose, thus making the challenge more acceptable and less prone to false positive results (occurrence of nausea or vomiting induced by the ingestion of a too large amount of challenge material). All this is essential to convince patients that the food avoided for long time is well tolerated for them. Of course, the OFC does not overcome most of the problems associated with possible 'false negative' results discussed above, as well as the need for an emergency department or some patient-related factors such as the willingness to undergo the procedure or other psychological factors.

In our view, the OFC should be used first to evaluate tolerance or reactivity. If it scores negative or positive with objective symptoms, the diagnostic procedure can be considered as completed. If the OFC scores positive with only subjective symptoms, a DBPCFC is needed [with the exception of oral allergy syndrome (OAS) in pollen–food allergy syndrome].

Conclusion

Recently, after years of acceptance of DBPCFC as the only reliable means to diagnose food allergy, a critical reappraisal of this procedure has been started [14,40,41]. This has shed light on the fact that, although it is the 'gold

standard' in certain specific situations, the DBPCFC also has many pitfalls and is not the ideal procedure that has been considered for a long time. In fact, the high costs, the difficulty in making proper recipes, the need for highly trained personnel, and well equipped facilities have hampered widespread introduction of DBPCFC in daily practice. Furthermore, nothing is really standardized in DBPCFC: neither the quantity of allergen to be administered (presently, we are able to calculate, at best, the total protein content of each dose) nor the timings between the doses, nor the observation periods, nor the matrix whose possible influence is unknown in most cases. Time has come to say honestly that in the normal clinical practice it is not only impossible to submit the majority of adult patients with food allergy to DBPCFC but also that this procedure is unnecessary in most instances. In cases when oral challenges are needed, open challenges should be considered first.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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