Standardization, validation and outcome of double-blind, placebo-controlled food challenges in children
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Download date: 07-11-2017
Chapter VIII  General Discussion
The DBPCFC is characterized by several cardinal features, such as randomization, the use of adequately blinded challenge materials, and the administration of placebos. Other important variables and considerations are the assessment of symptoms, incremental scales used, adequate top dose and safety of the procedure. Improved, standardized and validated practical protocols for the performing of DBPCFCs with regard to these parameters are needed for the medical profession to date, as has been outlined in chapter I.

In part I of this discussion, we focus on standardization and validation of some of these parameters of the DBPCFC, as well as the clinical relevance of our findings regarding placebo events (chapters II-IV).

In part II of this discussion, we discuss the practical, clinical and diagnostic implications, as well as the safety of the challenge outcomes in patients having their first exposure to allergenic foods (Chapters V and VI), and in patients with a history of anaphylaxis to food respectively (Chapter VII). Finally, recommendations for future research are discussed.

**Part I**

**Blinding**

Chapter II describes the first sensory laboratory validated recipes for use in DBPCFC. These recipes are available for use in other centres. While it is essential to guarantee blinded conditions during DBPCFCs, efforts to validate blinding of recipes for DBPCFCs, other than by volunteer panels, are more recent. The validation process in our study consisted of sensory testing for difference with regard to adequate blinding of the active food of the developed recipes. This process consisted of a two-step procedure, in which the recipes were first tested by a volunteer hospital panel, and subsequently, if no statistical differences were detected between placebo and active test food samples, by a professional panel of food tasters (Figure 1).

The professional panel decoded 10 of the 27 recipes tested by detecting significant differences between the samples. By obtaining these results we have clearly demonstrated that the use of a professional panel is mandatory for optimal results in sensory testing for difference with regard to blinding of the active (allergenic) food. Utilizing volunteer panels in a non-controlled environment is an important first step in testing challenge materials, but is not sufficient to guarantee optimal blinding. Validating recipes in a non-professional environment is likely to overestimate the blinding capacity, and thus validity of recipes, as is outlined in Chapter III. In this chapter, we stressed the use of food laboratories and professional panellists in validating recipes for DBPCFC.

Recently, also Ronteltap and Ballmer-Weber reported on the use of sensory testing of recipes in professional food laboratories. This method of validation of recipes has now become the standard, and is being used in recipe development in
Top dose in DBPCFCs
The major challenge in developing and validating recipes for use in DBPCFCs is to disguise sufficiently great amounts of allergenic foods in an acceptable volume\(^2,6\). The final discrete dose, or the administered cumulative dose should be high enough to prevent false negative test results. In general, it is stated that a maximum dose of 8–10g of dried food (which is equivalent to 60–100g of wet food) should be taken as a single, maximum dose\(^10\), or up to 15 – 20g of dried food as the cumulative dose. It is also stated that the top dose given should reflect a relevant amount of food\(^11\), or should reflect the normal daily intake of the food\(^10, 12,13\). Although these statements seem reasonable, they are not based on evidence, but on the assumption and individual observations that individual patients may react to amounts of allergenic food up to normal food servings.

However, the total and maximum amounts of active allergenic food we administered in DBPCFCs were smaller than the amount of a single food serving, and were mainly determined and limited by the maximum amount we could disguise in an acceptable volume of the validated recipes. In view of the results of our study, large amounts of allergenic foods are very difficult to disguise in acceptable volumes of test foods\(^2,6,14\), and the validity of high eliciting doses found in some studies may be questioned. For this reason Atkins et al.\(^14\) started food challenges in adults in a double blind manner for the lower doses, ending with open food challenges for the higher doses. For reasons of safety, in children age six and older having a negative double-blind challenge with egg, peanut or nuts, currently, we also have the DBPCFC followed by an open challenge, and not by gradual introduction.
at home as in younger children. It must be noted however, that, if reactions in these open food challenges occur, the validity of these observations remain to be assessed. Additional studies are needed to answer this question.

To date, there have been no studies specifically aimed at determining the top dose necessary to avoid false negative results of DBPCFC. Some studies describe the eliciting doses and the proportion of false negative results in detail\(^{1,3,8,14,15,18}\). In some of the previously mentioned studies, the (cumulative) eliciting dose is similar to or slightly higher than in our doses\(^{11}\), while in other studies doses were much higher than those we administered\(^{1,3,8,14,17,18}\). However, these data are only reliable if absolute blinding has been guaranteed. Thus, it is possible that some of the responses to high doses may be biased by lack of blinding. Adequate blinding techniques could possibly result in lower final required test doses than currently proposed. To date, it is unclear what the highest top dose is which is sufficient to rule out false negative test results.

Finally, it has not been determined whether single or cumulative doses are of greater importance in the DBPCFC. In the latter approach (cumulative dose) all doses administered are summed and calculated as influencing each other, whereas the first approach treats individual doses as independent events\(^{19}\). The validity of one approach or the other from a biological point of view depends on factors such as the time spacing of doses, and the matrix in which the allergen is masked\(^{19}\). We suggest that both doses should be considered.

**The diagnostic value of placebos**

Our study on the diagnostic significance of placebo events shows that placebo events present with a variety of symptoms, which may be classified as subjective or objective, and immediate or late onset\(^{20}\). The total number of placebo events in sensitized children (12.9\%) (Chapter IV), as well as the number of placebo events that reveals false positive test results (5.4\%), are relatively low. These relatively low figures could possibly lead to the mistaken conclusion, that the administration of placebos and hence DBPCFCs are of marginal importance in sensitized children, and that the diagnosis might as well have been established by an open challenge. However, the active test food challenge session from which the potential false positive rate is calculated can be considered as an open food challenge, with the notable difference, however, that patients and observers are blinded for the challenge order. Thus, they do not know whether the active test food is being given. We argue that in our study true open food challenges would have rendered a significantly higher percentage of false positive results. This is based on the studies by several other authors\(^{21-25}\). Venter et al.\(^{21}\) verified results of open food challenges in sensitized children by repeating positive open challenges by DBPCFCs. Remarkable differences were found in the proportions of test results. In children of 9 and 12 months of age, false positive rates of open food challenges
of 62% (5 out of 9 open challenges) can be calculated, and 50% (13 out of 25 open challenges) respectively. In six-year-old children, 3/6 (50%) children were overdiagnosed by open challenge as compared to DBPCFC22. In teenagers these proportions were 1/2 (50%) in 11-year-old children, and 4/7 (57%) in 15-year-old children23. It must be noted, that the results include both one day and one week challenges. In a recent paper by the same authors24, it was shown that, with regard to the one day challenges in children with immediate symptoms, 8 out of 11 open challenges could be confirmed by one day DBPCFCs, which represents a false positive diagnosis of 3/11 = 27% by the open food challenge test. Also, Brouwer et al25 found significantly high proportions of false positive diagnoses in children with atopic eczema, as is discussed in Chapter IV. Thus, from combining these data with the results of our study, the conclusion may be drawn that the most important contribution of the administration of placebos (in sensitized children) to the diagnostic accuracy of the DBPCFC is, that blinded administration of test food is made possible. Consequently, fewer events are observed during the active food challenge, because biased observations by patients and physicians are ruled out. It must be noted however, that these studies were population based21-24 and conducted in a primary health care setting25 respectively. In these populations, the proportions of self-perceived food allergy are higher than in tertiary care settings (7.2 – 14.2%)21,23, which may increase the number of false positive observations in open challenges. As our study was conducted in a tertiary referral centre, the expected differences between open challenges and DBPCFCs are expected to be lower. However, our data show that the use of placebos significantly enhances the diagnostic reliability of DBPCFCs in a tertiary care referred population.

Assessment of DBPCFCs

Another important aspect of the DBPCFC is the assessment of symptoms, and the related challenge endpoints. To our knowledge, to date, no other protocols providing detailed criteria for the assessment of symptoms in DBPCFCs and the assessment of the final outcome of DBPCFCs have been published (Chapter IV). With regard to assessment protocols, several features are important:

1. The diagnostic significance of placebo events, as discussed in the previous section;
2. History: DBPCFCs are assessed as positive when allergic symptoms occur following the active food challenge, or when symptoms from dietary history are reproduced, even if these symptoms are characterized as non-allergic symptoms (Figure 1, Chapter IV). This may implicate that subjective symptoms, as well as symptoms which are unlikely to cause food allergy, such as headache or an overall feeling of distress, if reproduced by DBPCFC, may be assessed as positive. However, in the individual patient, for scientific purposes, these latter observations can only be validated by repeated DBPCFCs according to the so-called N=1 trial.
This design is discussed later in this chapter. Safety may also be achieved by termination of the challenge when subjective symptoms occur (see below), and the use of prolonged time intervals between subsequent doses, if necessary in the individual patient; 3. Criteria to terminate a challenge (challenge endpoints): it is a matter of debate whether the challenge should be terminated in case of (repeated) subjective or objective symptoms, or in case of mild or more pronounced symptoms. Niggemann et al\textsuperscript{26}, for example, argue that objective symptoms should be induced to terminate a challenge. Considering both subjective and objective symptoms as valid will lead to an earlier termination of the test, which is likely to avoid more severe reactions. As in our clinic children with severe anaphylaxis in history are not excluded from challenge tests, we have decided to adhere to a challenge scheme giving optimal safety during DBPCFCs. This may be different for other centres, where severe reactors are excluded from food challenge testing. In our protocol, the challenge is terminated in case of objective symptoms, ongoing subjective symptoms for more than 30 minutes, or repeated transient subjective symptoms. In the latter situation, the same challenge dose is repeated. Also mild symptoms may be assessed as positive, since the purpose of the DBPCFC is not to reproduce severity of symptoms during DBPCFCs, but to demonstrate a causal relationship between the food and symptoms. The question can be raised if, for scientific purposes, results of DBPCFCs using different challenge endpoints may be compared\textsuperscript{19}, because earlier termination of a challenge session might result in a higher proportion of false positive test results. 4. The clinical relevance of late onset symptoms: Late onset symptoms may be particularly relevant in children with atopic dermatitis. In a position paper on eczematous reactions to food, late onset symptoms have recently been considered as valid\textsuperscript{27}. A rate of 25\% of late onset symptoms following food challenges in children with atopic dermatitis has been reported\textsuperscript{28, 29}. However, in these protocols, active and placebo challenges were interspersed, making assessment of placebo “reactions” difficult. In our study on placebo reactions (Chapter IV) it is shown that including late phase symptoms in the assessment of DBPCFCs enhances the proportion of placebo events significantly, as approximately as many late onset placebo events as immediate placebo events were observed. Significantly, we observed similar numbers of late onset symptoms following active food challenges and following placebo challenges (unpublished data). In our opinion, further studies are mandatory to elucidate the clinical relevance of these late onset symptoms. The DBPCFC: the best available test To date, the DBPCFC is the best available test in diagnosing food allergy. During recent international conferences on allergy, the question has been raised if other
diagnostic tools can replace the DBPCFC. Much work has been done on the diagnostic value of skin prick tests (SPTs) and specific IgE during the last 10-15 years. Current knowledge of the predictive value of specific IgE and SPTs has shown that increasingly higher values of food-specific IgE and increasing size of skin prick tests are associated with an increasing probability of clinical reactivity to food\textsuperscript{30}. Decision points with regard to immediate reactions to food have been established for cow’s milk, egg, and peanut above which 95% of patients were found to have positive challenge tests\textsuperscript{30,31}. In these patients many physicians consider the performance of DBPCFCs not necessary. However, many patients show sensitization levels below these decision points and thus need to be challenged, and different predictive values are being generated from emerging studies, which might represent nuances of diet, age, disease and challenge protocols\textsuperscript{29,32,33}. Recent data have shown that levels of specific IgE clearly increase with age\textsuperscript{34}. Furthermore, these decision points are determined on the basis of immediate reactions to foods, and have not been determined for late onset reactions to foods\textsuperscript{27}. Finally, it may be debated if a 5% chance of diagnostic error is acceptable, particularly if the diagnosis results in long term dietary avoidance for an individual patient. Thus, to date, the DBPCFC remains the best available test we have in diagnosing food allergy.

**Validation of the outcome of the DBPCFC**

The DBPCFC is considered the gold standard for the diagnosis of food allergy. However, this test is not perfect. As discussed before, false negative outcomes may occur, and as assessment protocols have not been validated yet, we might be unaware of false positive outcomes. The question is how to validate the outcome of a DBPCFC?

Reliable biomarkers could theoretically validate the outcome of DBPCFCs, but so far, no biomarkers have been identified, that distinguish between responders and non-responders\textsuperscript{35-37}. Recently, Clark et al\textsuperscript{38} showed that facial thermography as measured during a challenge might provide a sensitive method to determine the outcome of food challenge tests. A significant early rise in nasal temperature correlated with a positive challenge outcome. Such novel methods may aid interpretation of challenge outcomes in future, but need to be validated first.

Validation of a positive outcome of a DBPCFC in an individual patient, and thus the causative effect of the food, can be validated by repeated challenges\textsuperscript{13,38}. In a so-called “N of 1” trial (single patient randomized trial)\textsuperscript{39-41}, 3 placebo and 3 active food challenges are administered in a double-blind fashion and in a random order. In an N of 1 trial, in which 3 active and 3 placebo challenges are administered, a total of $6!/3!3! = 20$ different sequences can be made. Using this number of challenges, the chance that the patient guesses the right sequence of all possible sequences is 0.05. Additionally, in this procedure, the chance that
appropriate responses will occur to all six challenges by chance (in the worst case scenario, where the chance of reacting on any given test day is 50%), may be calculated as $0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 \times 0.5 = 0.015$, which is less than 0.05. In this model, appropriate responses are defined as symptoms on active challenge, and no symptoms on placebo challenge. Thus, positive test results in the individual patient are validated if a patient reacts to all 3 active challenge sessions, and not to one or more placebo challenges. This calculation may be used when there are no baseline symptoms. Alternatively, if baseline symptoms are unavoidable or cannot be reduced to zero, allergic reactions to the active challenges may be validated if statistically significant differences can be calculated between total mean or median symptoms scores during active challenges and placebo challenges. A stable baseline situation is of great importance to avoid placebo events in either situation, as this could make the test false negative.

However, in daily clinical practice, single patient randomized trials for every individual patient are not practical, too labour intensive and very time consuming, and may yield an unacceptable burden for the patient. Therefore, DBPCFCs are usually performed in patients once. Thus, when performing DBPCFCs only once, one should be aware that some positive results might be false positive. In practice, follow-up challenges are performed to verify the persistence or resolution of food allergy. Possible false positive challenge results may be refuted in these follow-up challenges. Also, equivocally positive DBPCFCs, in which the results remain questionable (usually mild) after the highest challenge dose may be repeated. Unequivocal negative DBPCFCs can be validated by a negative open challenge or a successful introduction of the challenged food into the diet of the patient. In the latter case patients should be monitored carefully for actual introduction of the food in normal servings into their diet. Equivocal negative DBPCFCs, in which late onset symptoms occur and are related to the introduction of the challenged food into the diet of the child, can either be validated by a subsequent period of elimination and renewed introduction, by repeated challenges, or by a blinded prolonged DBPCFC. In our experience, a subsequent period of elimination and a renewed introduction does usually not result in recurrence of symptoms (unpublished data).

**Part II**

**Practical implications of DBPCFCs in children having their first exposure to the challenged food**

Our finding in Chapter V in children having their first exposure to an allergenic food by DBPCFC, that a significant proportion (51%) of children reacts with allergic symptoms, is not new. The underlying reason for conducting this study was the need for practical guidelines in children at risk for food allergy regarding
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the introduction of allergenic foods at home as a first exposure. In every day allergy practice, as well as in the literature, allergic reactions to first exposure are common\textsuperscript{43-47}, but very unwanted. Therefore, guidelines with improved safety for home introduction of allergenic food are needed. Even if these reactions are not severe, and present as mild or moderate symptoms such as oedema, rash, diarrhoea, and/or vomiting, they are often experienced as very frightening by the parents of these infants. As a result, parents of children at risk for atopic disease are reluctant to introduce these foods into the diet of their children. As it is generally assumed that the lower the dose, the less severe the symptoms\textsuperscript{19}, the reason for the occurrence of relatively severe reactions at first exposure may be that the first dose administered by the parents at home is much too high in sensitive children. Our study showed that, without detailed instructions, parents would administer median doses which are approximately at least 8 times higher than the first doses of the incremental scales used in DBPCFCs, and for peanut even 25 times higher. The potential hazard that such quantities of allergenic foods may pose is further suggested by our finding, that even very small amounts of foods in their usual household form, such as 1 sip of milk, 1 bite of a sponge finger or muffin, 1 small cube of bread with peanut butter, contain considerable amounts of allergenic foods, comparable to doses 4 or higher of our incremental scales. Thus, detailed instructions on low-dose administration of allergenic foods are needed for introduction at home. We succeeded in designing such instructions because, when using the written instructions of the introduction schedule and the reference photograph (Appendix 1 and Figure 1, Chapter V), it seemed feasible by the parents to administer the median required amounts of food for all doses. As discussed in Chapter V, the introduction schedules we devised can be utilized by physicians and dieticians in children at risk for food allergy, but who do not, according to the physician’s assessment, warrant first exposure under medical supervision. We assume that when using these guidelines, safety is improved, as the incrementing amounts are based on the doses steps we administered in DBPCFCs in which severe reactions were absent. Future studies regarding the usage of these introduction schedules could validate the safety of these guidelines. It is a matter of debate in which children these guidelines are to be used. As stated in Chapter V, there is no consensus about which children who should introduce allergenic foods at home, and which children who should be challenged under medical supervision because of a significant risk for (severe) allergic reactions. As discussed in Chapter V, based on the literature, it could be argued that children with two or more of the following risk factors should not introduce allergenic foods at home as a first exposure: coexistent asthma or other significant comorbidity, adolescence or young adult age, introduction of peanuts or tree nuts, and distance to emergency medical care. Thus, these guidelines for first exposure to allergenic foods could be utilised for
those children not having two or more of these risk factors, but who are at risk for food allergy generally, and wish to introduce allergenic foods at home as safely as possible. Whether all atopic children should use these guidelines requires further study, and this would have major implications for health care delivery in the area of food allergy.

The guidelines for first exposure of major allergenic foods may become even more important because currently, our concept about the prevention of food allergy is changing\(^4^8\). Delay in the introduction of highly allergenic foods was generally regarded to be an effective preventive measure with respect to the development of atopic disease\(^4^9\). However, these recommendations on the prevention of food allergy with respect to the delayed introduction of major allergenic foods were merely based on only two, non-randomized, prospective studies\(^5^0,^5^1\). Additionally, a delayed introduction of allergenic foods might even increase the prevalence of atopic disease\(^5^2\). Thus, there are little epidemiological data to support this belief\(^5^3\).

As a result, depending on future study results, advice on timing of introduction of allergenic foods in young infants may change in the near future, promoting timely introduction of these common allergenic foods instead of delayed introduction. Studies show that it is an illusion to expect that a total avoidance of an allergenic food is feasible. Unintentional exposure and sensitisation may occur in utero\(^5^4\), through breast-feeding\(^5^5\), or by environment\(^5^6\). These mechanisms are supported by the observations that many children are sensitized to foods which they have never consumed before in their lives. Thus, primary prevention avoidance strategies result in low-level exposure rather than no exposure at all, because obviously, sensitization can not be prevented. In fact, low-dose, intermittent exposure may be the trigger for developing IgE-mediated food allergies\(^5^7\), and it is possible that the current practice of allergen avoidance may have contributed to the increased prevalence of food allergy\(^5^7\).

Unintentional exposure may also occur through the diet, despite efforts to totally avoid an allergenic food. In our study on avoidance of allergic foods in children adhering to a food allergen avoidance diet for allergy prevention (Chapter VI), we found that it was difficult to totally avoid allergenic foods. In only one third of the children, unintentional ingestion was thought to be unlikely following a thorough dietary history. Despite the attempt to adhere to dietary measures in all other children of the study population, unintentional ingestion could not be ruled out or was revealed by questioning. Additionally, cross-contamination with the allergenic food cannot be ruled out, even in the one third of children without unintentional ingestion. Thus, in all of these children, a low-level exposure and no-total avoidance by diet was very likely the result of the avoidance diet.
Practical implications of DBPCFCs in children with a history of anaphylaxis to food

In chapter VII, we have clearly shown that assessment of clinical reactivity to food by challenge testing in children with a history of anaphylaxis is not unnecessary or unsafe. In our study, a substantial proportion (29%) of children had a negative test result. To the great relief of the children and their parents, the diagnosis of anaphylaxis to food was removed from these children. These children would probably not have been aware of this, if they had not been challenged. Not unimportantly, these children could relinquish their Epinephrine self administration devices given for the food in question. As the impact of having a self administration device is enormous for the patient and his/her environment\textsuperscript{58}, the prescription of this device should be based on stringent diagnostic criteria, which, in the case of food allergy, should be obtained by double-blind challenge testing.

This figure is probably higher than many health care professionals had expected. In general, it is assumed that resolution of anaphylaxis is rare, but only few data exist on the natural history of anaphylaxis to food, as is discussed in chapter VII. This is probably due to the fear for severe reactions during DBPCFCs in children with anaphylaxis to food, and due to the statement, that food challenges are contraindicated in patients with a history of anaphylaxis\textsuperscript{60}, unless the patient is believed to have outgrown the food allergy\textsuperscript{60-62}. Therefore, DBPCFCs in children with a history of anaphylaxis are often not performed. In our study, no children had histories suggesting resolution, but nevertheless in a significant proportion of children the anaphylaxis had resolved.

There is no consensus on the long-term management with regard to the diagnostic work-up of anaphylaxis to foods to ascertain for resolution, except for the statement that children, who are believed to have outgrown their food allergy, may be challenged\textsuperscript{60-62}. This might be the case in, for example recent unintentional ingestion without subsequent reactions, as well as in cases of reduction or disappearance of sensitization. However, our data show, that re-evaluation of the initial diagnosis of anaphylaxis is worthwhile, even in the absence of such suspicion. These children should be referred to centres where DBPCFCs can be performed safely. Based on the results of our study it is not justified to formulate recommendations about regular time intervals following anaphylaxis on which DBPCFCs should be performed, as in our study, these prospective challenges were not performed at fixed time intervals following the last reaction. A different study design is warranted to answer this question.

We want to stress the fact that these children should only be challenged in centres experienced in performing high-risk food challenge tests. Aside from the elements of the challenge protocol which we feel contribute to the safety of the procedure, as described in Chapter VII, experienced staff is mandatory in making crucial clinical decisions while observing the patient. This is specifically important with respect
to decisions to terminate or continue the challenge, delaying the administration of the subsequent dose for safety reasons, and the administration of the required medical care. Of course, all necessary medical treatment should be available. Apart from the necessity of re-evaluation of anaphylaxis to food, it is important that all patients who have experienced anaphylaxis to food should be referred to a specialist physician knowledgeable about anaphylaxis. Patients should be referred to have the causative food identified, for education regarding avoidance strategies to avoid future anaphylactic reactions, as well as for the management of anaphylactic reactions. Additionally, dietary advice by a dietician knowledgeable about anaphylaxis to food, and information from consumers associations such as the Food Allergy and Anaphylaxis Network in the USA (www.foodallergy.org), the Anaphylaxis Network in the Netherlands (www.anafylaxis.net), or the Anaphylaxis Campaign in the UK (www.anaphylaxis.org.uk) is essential.

**Is there a sufficient basis for the use of the DBPCFC?**

The Health Council of the Netherlands stated that the DBPCFC is the diagnostic procedure of choice for diagnosing food allergy, and that this test should become available for diagnosing food allergy in primary care. Currently, many paediatricians and allergists are undertaking initiatives to initiate DBPCFCs, supported by workshops and educational sessions on DBPCFCs provided by paediatric departments of the UMCG and UMCU. Obviously, performing DBPCFCs seems feasible for many centres as soon as they are convinced about the necessity of this procedure. Similar initiatives in other countries could enhance the initiation of DBPCFCs.

However, not all physicians are convinced of the added diagnostic value of the DBPCFC as compared to open food challenge tests. Especially in case of a convincing history with immediate, objective reactions to food and sensitization to the food in question, many health care providers state that double-blind challenges are not necessary in these patients, and prefer open challenges in these cases. Others might even consider any oral food challenge unnecessary in these cases. However, there are no data to support these assertions. On the contrary, as discussed in Chapter IV and earlier in this chapter, studies have shown that open food challenge render many false positive results, even in case of immediate reactions in open food challenges. False positive open food challenges may be explained by a number of factors, the most important of which is bias due to lack of blinding, as is discussed in Chapter IV.

**Recommendations for future research with respect to the performance and validation of DBPCFCs**

In order to make the DBPCFC feasible for daily clinical practice, more specific practical standardized protocols are required. These protocols should include a
larger variety of validated challenge materials (recipes) for a broad range of foods, ready-to-use conversion of recipes to incremental scales to be administered, as well as broadly accepted guidelines for the assessment of symptoms, termination of challenges, and medical safety measures. For scientific purposes, adequate top doses could be determined by comparing results of open food challenges to DBPCFCs using different top doses, while using validated recipes to guarantee optimal blinding of such doses. Also, matrix effects on the clinical effect of the putative top dose should be studied. The clinical relevance of immediate vs. late onset symptoms, as well as subjective vs. objective symptoms should be validated by repeated challenges. The availability of biomarkers for the confirmation of allergic responses to challenge tests would be of great help in the avoidance of false positive test results. Indications for DBPCFCs could be studied in several subgroups of patients, such as in children younger than 3 years old, in non-sensitized children, and in children with immediate, objective symptoms in dietary history. This could be done by comparing results of open food challenges to those of DBPCFCs, by studying the clinical relevance of placebo events in DBPCFCs, and by examining the clinical relevance of the dietary history. Future studies regarding the use of introduction schedules at first exposure could validate the safety of these guidelines, and in which children there schedules are to be utilized. Finally, studies on the natural history of anaphylaxis to food prospectively utilizing DBPCFCs at different time points after such reactions are needed.
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