SPECIAL REPORT

Dutch guideline on food allergy

M.S. van Maaren[1]*, A.E.J. Dubois[2]

[1]Department of Allergology, Erasmus MC, Rotterdam, the Netherlands, [2]Department of Paediatric Pulmonology and Pediatric Allergy, Beatrix Children's Hospital, University Medical Centre Groningen, Groningen Research Institute for Asthma and COPD, University of Groningen, Groningen, the Netherlands, *corresponding author: tel.: +31 (0)10-7040100, email: m.vanmaaren@erasmusmc.nl

LIST OF THE AUTHORS OF THIS GUIDELINE

M.S. van Maaren, MD, Internist allergist (chair); Prof. Dr. A.E.J. Dubois, MD, PhD, Internist allergist; Prof. Dr. A. Knulst, MD, PhD, Dermatologist; Prof. Dr. S.G.M.A. Pasmans, MD, PhD, Paediatric dermatology; Dr. C.M.F. (Frank) Kneepkens, MD, PhD, Paediatric gastroenterologist; Dr. J.H. Oudshoorn, MD, PhD, Paediatric gastroenterologist; Y. Meijer, MD, Paediatric allergist; M. Stadermann, MD, Paediatric allergist; M. Gorissen, MD, Paediatric allergist; Dr. G.J. Braunstahl, MD, PhD, Pulmonologist; J.P.M. van der Valk, MD, PhD student; Dr. Ir. J. Ruinemans-Koerts, Clinical chemist; Dr. B.J. Vlieg-Boerstra, PhD RD, Senior research dietitian; B.J. Beusekamp, Dietitian; Mrs. S. Visser, Dietitian; F. Timmermans, BEng, Representative Patient Organisation; E. Botjes, MA, Vice president EFA; V.R. Krones, MSc, Administrative support (Qualicura)

ABSTRACT

The diagnosis of food allergy is established in cases where an immediate allergic reaction has occurred in the last year to a clearly identifiable allergenic food combined with sensitisation to this allergenic food. In all other cases, a food challenge test is required to establish or reject the diagnosis of food allergy. Although the double-blind placebo-controlled food challenge (DBPCFC) test is considered the gold standard, false-positive and false-negative outcomes occur. The incidence of false-positive outcomes is unknown because the results of DBPCFC tests cannot be further confirmed by other tests. If possible, it is important to perform double-blind challenges with recipes that have been validated for blinding and to use challenge procedures that have been proven safe in clinical practice, in order to reduce the risk of unwanted false-positive and false-negative outcomes and severe challenge reactions. The national guideline of the Dutch Society of Allergology describes when challenges are indicated and contraindicated, how food challenges are best conducted and how patients could best be managed and followed-up after the challenge tests have been completed.

KEYWORDS

Double blind placebo controlled food challenge, Dutch guideline, food allergy

INTRODUCTION

If the patient's history concerning the ingestion of a particular allergenic food or information about the symptoms following ingestion or the time interval between ingestion and the beginning of the symptoms are lacking, not clear cut or not specific for an allergic reaction, determination of specific immunoglobulin E (IgE) may help to rule out an allergic cause. Absence of specific IgE in these cases indicates that the patients are probably not allergic to the ingested food because the specificity of this sensitisation test is very high. If, on the other hand, the patient has specific IgE to an allergen, the chance the patient is allergic to this allergen is more likely but yet not confirmed because the sensitivity of this test is in itself very low. This is because many people have specific IgE that is of no clinical relevance. In these cases a challenge test is the only way to ascertain the clinical relevance. The double-blind placebo controlled challenge (DBPCFC) is the best test available to establish the diagnosis of food allergy. Although the DBPCFC is the gold standard, false-positive, false-negative and inconclusive results, and undesired severe reactions do occur. A false-positive result indicates that the patient reacts convincingly during the challenge but is not allergic to the challenged food.

A false-negative result indicates that the patient does not react during the challenge but is allergic. Whether the test result is false-negative or false-positive will only be known if patients report that they reacted during (re)introduction of the challenged food or that they did not react following accidental ingestion. Because patients have reported such reactions and because placebo reactions have been documented during placebo-controlled challenges, it is known that these unwanted results do exist. However, the incidence of these undesired results is not known.

A false-positive challenge test has a negative impact on the quality of life.[1] A patient who avoids food has a poorer quality of life and may have a diet that lacks essential nutrients.[2] Additionally, increasing scientific evidence suggests that delayed introduction of foods or unnecessary avoidance may increase the risk of acute allergic reactions on (re)introduction to these foods in atopic children.[3] The danger of a false-negative test is obvious: the patient runs the risk of an allergic reaction during introduction when they may not be carrying emergency medication.

By adjusting the number of challenge steps, the start dose and last dose, the time intervals and the stop criteria for termination of the challenge test or the proportion of open to double challenges, the numbers of false-positive results, false-negative results and undesired reactions change. The goal of this guideline is to explain how to minimise the risk of these adverse results while keeping the challenge test acceptable as a routine test.

PLACE OF SENSITISATION TESTS IN DIAGNOSING FOOD ALLERGY

Sensitisation tests aim to detect specific IgE directed against an allergen. Specific IgE can be determined indirectly by a skin prick test or directly by a serological test. The result of a sensitisation test can be compared with the results of the gold standard, the DBPCFC. In this way the specificity and sensitivity can be determined. In general, the sensitivity of specific IgE tests with allergens is low, especially when the results are not combined with information from the patient's history.

Allergenic foods contain a mixture of different allergens. Skin prick tests with food or specific determinations of IgE give no information on which allergen the patient is sensitive to in this mixture. The individual allergens that are present in one food are called components by the manufacturer of a test to determine specific IgE to increasing numbers of individual allergens. This test is called component resolved diagnosis. With this test, one can discriminate between food-specific allergens that are associated with systemic reactions and some highly cross-reactive food-plant allergens such as those belonging to the pathogen-related family of proteins 10 (PR10) and profilins that are associated with tolerance or relatively mild symptoms as itchy mouth confined to the oral cavity and throat (so called 'oral allergy complaints'). As a result, component resolved diagnosis testing has a higher specificity and sensitivity when used to diagnose allergy to foods that contain both types of allergens such as peanut and tree nuts, as compared with skin prick tests and serological tests with these foods, but not in e.g. milk that contains milk specific components.[4]

The cut-off values of serological tests that can predict the negative or positive outcome of the food challenge test are of more clinical use than sensitivity and specificity of tests. If these positive and negative predictive values (PPV and NPV) can predict the outcome of the challenge test with high probability, a challenge test may not always be needed to establish presence or absence of allergy. If one could predict the negative outcome of a challenge test with 100% certainty in patients that have specific IgE equal or below a certain cut-off value, challenges may no longer be needed in these patients. An NPV of 95% indicates that 5% of the patients who have a value equal to or below the cut-off value would react in a food challenge test. Advising patients who have a 5% chance of being allergic to introduce food based on a sensitisation test alone is usually not acceptable because some of them run a risk of a severe reaction in an unsupervised setting.

High specific IgE cut-off values associated with a post-test probability of a positive outcome of a challenge test of 100% are desirable but are likely to be applicable to only a relatively small number of patients. If a PPV of 95% is considered acceptable, a larger proportion of challenge tests would be redundant. However, even more modest cut-off values associated with correspondingly more modest PPVs have been found to differ between populations of different ages, and even from different centres. There are many possible explanations for these differences including differences in age and sex composition, geographical region, proportion of sensitised patients, all of which may influence prevalence and thus PPV. Moreover, the prevalence of food allergy can vary over time and therefore cut-off values associated with certain PPVs may change.

As mentioned above, a new approach to serological testing is the component resolved diagnosis test, or determination of specific IgE to single allergens contained in foods. This has proved most successful in peanut allergy. Positive specific IgE tests to Ara h2, a major peanut specific allergen, is associated with an increased risk of clinical peanut allergy and, to a lesser extent, an increased risk of relatively severe reactions to peanuts. In several studies, PPVs of specific IgE against Ara h2 may be associated with PPVs as high as 95%. As expected, the cut-off value of Ara h2 with a PPV of 95% differs from one study to another. Published specific IgE cut-off values to different

allergens associated with high PPVs are thus of limited generalisability and as a result cannot currently replace challenge tests.[5-7]

Aside from establishing the diagnosis of food allergy, the challenge test gives the patient some experience in recognising symptoms and improves health-related quality of life. Reactions and the amount of food protein eliciting them may not be extrapolated to accidental reactions because in real life other factors are operational that can influence the threshold level, such as the way the consumed food has been processed and the matrix in which it is present, the use of medication, the presence or absence of illness and co-factors such as exertion and alcohol.

The Dutch guideline Task Force advises not to replace food challenges by sensitisation tests or component resolved diagnosis testing to establish the diagnosis of food allergy in patients who have never eaten the tested food, who did not react with convincing symptoms, who reacted more than one year before presentation, or who did not react to a clearly identifiable allergenic food.

INDICATIONS AND CONTRAINDICATIONS

Challenge tests are indicated in the following cases:

- To establish the diagnosis of food allergy
- To evaluate if a patient has outgrown a food allergy that was established in the past
- To establish the clinical relevance of specific IgE to an allergenic food if patient history is indeterminate
- To educate a patient on which symptoms he may expect if he accidentally ingests the food and how to respond.

Absolute contraindications are:

- Uncontrolled asthma
- Unstable angina pectoris
- Severe chronic lung disease
- Pregnancy
- Fever.

Relative contraindications are present when factors associated with severe reactions or complications during challenge tests that negatively interfere with the treatment of a reaction or that hamper the interpretation of the challenge test are operational. There is no direct medical evidence that these factors truly prohibit a challenge procedure because in challenge studies patients who have a medical condition or use medication that could negatively affect the severity or treatment of a reaction (beta-agonists, ACE inhibitors and NSAIDs) or interpretation of the challenge test (systemic corticosteroids and antihistamines) are always excluded. Indirect evidence concerning potential risk factors of severe reactions during challenge tests are derived from studies of patients seen in the emergency room because of anaphylactic reactions or who have been treated with allergen immunotherapy and reacted severely to a subcutaneous injection.[8,9] Because risk-augmenting medication can often temporarily be stopped or switched, or unfavourable conditions may often be treated prior to challenge or are of a temporary nature, it is rarely acceptable to undertake an oral food challenge when such risk factors are present, even if direct evidence of the increase in risk is lacking.

If an unfavourable condition persists or medication cannot be stopped or switched, it is advised to consult or refer to a centre where an allergist who has extensive experience with food challenges under difficult circumstances and with high-risk challenges can supervise the procedure. Official criteria for these 'allergy specialist centres' have not been formalised, but the Task Force considers centres that meet the following criteria as such:

- Challenges are supervised by recognised allergists/ paediatric allergists
- In these centres large numbers of challenge tests are performed
- The food challenge procedures are protocolised
- Tasks and responsibilities before, during and after the challenge test are clearly assigned
- All amenities are present to treat anaphylaxis including intensive care facilities.

OPEN VS DOUBLE-BLIND CHALLENGES

The challenge test can be done in an open (open food challenge: OFC) or double-blind fashion (double-blind placebo-controlled challenge: DBPCFC). In an open challenge test the food may be administered in its native form. In a double-blind challenge, the challenge material is administered incrementally on two occasions. On one day, the food to be tested is given while being masked in a matrix food (for example in a slice of cake or drink), while on the other day only a matched placebo is given. The order of the days is randomised so that neither the patient nor anyone in contact with the patient knows on which day the placebo or the suspected food is given.

Studies in which DBPCFCs are performed show that placebo reactions occur regularly. Generally these reactions consist of subjective symptoms or symptoms that appear more than two hours after the end of procedure, but sometimes they also consist of acute reactions with objective symptoms. In clinical practice, if we only use OFCs the outcome would be that a small unknown percentage of challenges ending with acute objective symptoms would be considered positive while actually being false-positive. Consequently some patients would be

incorrectly diagnosed as being allergic. If open challenges ending with subjective symptoms are also considered positive, it would result in a considerably larger percentage of false positive results.

The potential negative influence of several of these factors can be minimised by blinding the procedure. The result from the administration of the suspected food is compared with that of the placebo before making the diagnosis. The test is considered positive if the patient reacts to the suspected food with symptoms constituting the agreed stop criteria and clearly more severe than to the placebo. Patients not reacting on either test day or with atypical or relatively mild reactions on the placebo day are considered test negative.[10-12]

It is advised to choose an open challenge test if it is very likely that the patient is not allergic. If subjective or late symptoms are to be expected, if the patient has eczema, if the patients fears a severe reaction, or symptoms following an ingestion are different from what would be usually expected (e.g. urticaria instead of oral allergy complaints after eating an apple) the double-blind food challenge should always be the first choice.

RISK OF SEVERE REACTIONS AND SAFETY PRECAUTIONS

The percentage of a near-fatal or fatal anaphylaxis during oral food challenges is probably negligible in daily practice. In the literature no fatal reactions have been documented. The percentage of severe allergic reactions published in the literature reaches a maximum of 10% depending on how a severe reaction is defined and the characteristics of the patients who are challenged. It is believed that the percentage of anaphylaxis in the clinics where the members of the Task Force work is much lower than 10%. This low percentage is likely due to the fact that challenges are performed with carefully selected patients by skilled and experienced personnel, and with procedures and up-dosing schedules that have been proven safe and reliable in clinical practice.

In the Netherlands, allergists tend to categorise challenge tests into high- and low-risk challenges and take extra precautions when a high-risk challenge is performed. Despite this fact, no consistent predictors of a severe reaction during a challenge can be derived from published food challenge studies.[13,14] All authorities agree that any patient with a previous life-threatening reaction to a food is a high-risk patient unless there is evidence of tolerance subsequent to the severe reaction. Nevertheless the majority of high-risk patients have only experienced mild reactions, and the Task Force felt the need for uniform criteria that would discern high- and low-risk challenges in patients without previous life-threatening reactions. Criteria were thus derived from retrospective studies in which the characteristics of patients visiting an emergency room because of accidental (near) fatal anaphylaxis were analysed.[15] Patients in these studies have similar characteristics in different studies and these criteria are the same as those used to decide who needs to be prescribed an epinephrine auto-injector.[16]

The following criteria apply for high-risk challenges:

- If any combination of two of the following is present:
  - Challenges with adolescents and young adults (≥ 12 years of age)
  - Challenges in patients with asthma or a previous asthmatic reaction to the food to be challenged
  - Challenge in a patient who has reacted to traces of the food to be challenged
  - A challenge test with a peanut or tree nut.
- A challenge test with a food to which the patient reacted severely in the past regardless the degree of sensitisation.

As a result of these criteria, a challenge test with a peanut or tree nut is a high-risk test if only one other criteria applies, while a challenge test involving other foods is considered high risk if two criteria are applicable. Challenge tests with fruit are considered low risk even if two risk factors are applicable. Challenge tests with a food to which the patient has had an anaphylactic reaction in the past are always considered high risk even if no other criterion is applicable and even if a fruit is challenged.

If these criteria are used in daily practice, the chance of severe reactions during low-risk challenge tests is probably low but can never be completely excluded. For this reason the setting in which the challenge is performed must always be suitable to care for patients who have an anaphylactic shock and the supervising personal should always be prepared for such an event. Furthermore it is advised to only perform high-risk challenge tests in allergy specialist centres as indicated above.

RECIPES AND LOGISTICS OF CHALLENGE MATERIAL

To guarantee that the challenged food has been blinded appropriately, recipes should be used that have been validated for blinding. To validate recipes is a labour intensive procedure and in most studies that use 'double-blind' challenge tests the recipes used are not validated. The recipes that are validated are summarised in the full text version of the guideline as are the other requirements for these recipes to make them acceptable to use them in challenge tests.[17]

Recipes that are validated for blinding for double-blind challenge tests are available for the following allergenic

foods: cow's milk, hen's egg, soy milk, hazelnuts, peanut, cashew nut and wheat. Unfortunately, there are none for fish, shell fish, legumes other than soy and peanut, and seeds. These allergenic foods can thus only be challenged in an open fashion. Open challenges are usually best performed with food in its native form.[18-20]

CHALLENGE DOSING SCHEDULE

The optimal challenge schedule meets the following criteria:

- The challenge procedure should be performed in half a working day so that sufficient observation time is left.
- The lowest dose administered is about the same as the lowest threshold dose on which an allergic patient is able to react to prevent large numbers of patients reacting (severely) to the first dose.
- The highest dose is similar to the amount of food an adult or child could consume at one time in daily life to prevent false-negative results due to an inadequate final dose.
- The incremental doses and time intervals in between two following doses should be chosen in such a way to prevent severe reactions because the time interval is too short or a dose gap is too large.

The first-mentioned criterion could conflict with the last if a safe procedure cannot be completed within office hours. Fortunately, a lot of experience has been acquired with recipes and up-dosing schedules that meet the criteria above. An interval between doses of 30 minutes has proven to be safe and practical, even though there is evidence showing that many patients probably react to cumulative rather than discrete doses. One of the limitations of the schedules currently in use may be that the last dose is not always high enough to rule out false-negative outcomes.

Dosing schedules that have proven to be safe and practical have been shown to be quite similar for different foods when each dose step is expressed as the amount of protein of the allergenic food. As a result the same up-dosing schedule is advised for both open and double blind challenges independent of the food challenged. The ideal incremental dose sequence is mentioned in the full text version as are the adjustments that could be made depending on the food that needs to be challenged.[17,21-23]

Even when the last dose is similar to an age-appropriate portion of the food, false-negative results are possible. This is known because some patients fail to successfully introduce the food because of reactions during introduction. The reasons for this are only partially known and include occurrence of enhancing co-factors during introduction, induction of short lived tolerance by the challenge procedure and matrix effects. Therefore, open challenges should be carried out to confirm negative DBPCFCs and are especially important following high-risk negative double-blind challenges or those where the final dose was less than a possible daily portion, or when the double-blind test is unexpectedly negative.

STOP CRITERIA AND INTERPRETATION

It is generally felt that early termination of challenges with minimal symptoms will result in a greater number of false-positive test results. Conversely, late termination of challenges with clear objective symptoms will result in a greater number of severe reactions. Stop criteria for termination of the challenge test should be defined in such a way that the number of false-positive results and severe reactions can be kept to a minimum. Unfortunately it is not known which stop criteria are optimal because no studies exist in which the challenge tests with different stop criteria are compared. Therefore stop criteria are generally based on consensus and optimal stop criteria appropriate to the goals of the test centre should be ascertained in daily practice. Currently, it is deemed that objective stop criteria result in the lowest number of false-negative results and are still safe when used in studies. However, in daily practice it may not always be feasible to continue challenges until objective symptoms occur.

In 2012 the PRACTALL Task Force published a set of stop criteria that are advocated by the American and European Societies of Allergology. The Task Force of the present guideline adopted and translated these stop criteria into Dutch to promote their implementation. Using uniform stop criteria will promote the comparability of the results of challenge tests wherever they are performed. The symptoms in the PRACTALL list are ordered according to organ system, e.g. gastrointestinal or lower airways, and the severity of the symptoms is graded (mild, moderate, severe).

The PRACTALL stop criteria are not absolute. Based on the presence of a certain combination of specific symptoms and their severity it is more or less likely that the cause of the symptoms is allergic. This advice on when to stop and when to continue leaves room for the supervising allergist to decide if the challenge test day is positive or not (yet). If symptoms occur that are not enough to terminate the challenge it is advised to extend the time interval or to repeat the last administered dose. If an OFC ends with subjective, mild or moderate objective symptoms, or with other symptoms than what would be expected from the patient's medical history, it is advised to perform a DBPCFC to confirm the allergy.[8,24]

FOLLOW-UP AFTER THE CHALLENGE

Performing challenge testing is only of value if such tests are followed up by successful reintroduction of foods which tested negatively or continued elimination of the challenged foods following positive tests. In case of a positive challenge result, the challenge is successful if the patient manages to avoid the food he reacted to and/or is capable of treating him/herself adequately following accidental exposures while maintaining a diet that is still varied and not lacking in essential nutrients. A negative challenge is successful if the patient manages to (re)introduce the food into the diet. From five published studies in which patients were asked by means of a questionnaire or an interview if they had introduced the tested food permanently it is known that up to a third do not manage to introduce the food for various reasons.[25] From a questionnaire sent by the Task Force to patients who underwent a food challenge test, it is known that 37% wished they had been followed up more effectively after the challenge test. From these data it may be concluded that follow-up after a challenge test may be improved and that good follow-up probably leads to better long-term results.

Although there are no studies on the optimal form of follow-up for patients after a challenge test, the Task Force offers advice based on expert opinion and consensus. Following a negative challenge test it is advised to (re) introduce foods with the help of an introduction schedule for home use. Such introduction schedules include an explanation on how a patient can introduce the food over the course of a few days so that ultimately he or she feels confident eating a normal portion. In the event the patient experiences symptoms attributable to ingesting the food being introduced, contact with an allergist, dietitian or an experienced allergy nurse should be sought to discuss if the introduction should be continued with or without an adjustment of the schedule, or stopped. It is also advised to contact the patient a few months after the introduction to ask if the food is now being eaten regularly. If consumption of the food has been stopped, the reason for this may be ascertained and assistance offered to solve the problem.[26]

Patients in whom the food allergy has been confirmed should be instructed how to read labels, how to deal with advisory labelling (i.e. 'may contain') and be prescribed an epinephrine auto-injector where appropriate. Such a prescription should be accompanied by written and repeated oral instructions on how to treat a reaction in the event of accidental ingestion. Especially if the allergenic food cannot be easily avoided and/or if the food is part of the staple diet, such as wheat or milk, it is advised to refer the patient to an experienced dietitian. The dietitian can instruct the patient on the correct interpretation of food labels, find alternative ingredients for recipes and prescribe supplements if the diet lacks essential nutrients. The dietician may also support the patient and family members in dealing with the food allergy.

INSTRUCTION AND PRACTICAL ADVICE

In the last chapter of the guideline some practical advice is given on topics for which no evidence exists. This advice is based on expert opinion and consensus of the members of the Task Force.

The Task Force deems it important that one supervisor is appointed to be responsible for the decision to continue or terminate the challenge test and determine and administer the treatment in the event of a reaction. This supervisor should be an experienced paediatrician specialised in allergies for challenges that are performed in children and an experienced allergist or dermatologist for challenges performed in adults. During the challenge test the patient should always be monitored by healthcare providers who are trained to recognise allergic symptoms and are capable of starting treatment and supporting advanced treatment of a severe anaphylactic reaction.

The full text of the guideline provides information on how to instruct the patient, and how long the patient should be observed depending on if the patient reacted and the severity of the reaction.

DISCLOSURES

This guideline is funded by Stichting Kwaliteitsgelden Medisch Specialisten (SKMS).

The authors declare to have no conflicts of interest in relationship to this manuscript.

REFERENCES

1. Goossens NJ, Flokstra-de Blok BM, Meulen GN van der, et al. Health-related quality of life in food-allergic adults from eight European countries. Ann Allergy Asthma Immunol. 2014;113:63-8.
2. Smits-Wintjens VE, Zwart P, Brand PLP. Veronderstelde koemelkei-witovergevoeligheid bij excessief huilende zuigelingen: gewenste en ongewenste effecten van een eliminatiedieet. Ned Tijdschr Geneeskd. 2000;144:2285-7.
3. Perkin MR, Logan K, Tseng A, Raji B, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. N Engl J Med. 2016;374:1733-43.
4. Soares-Weiser K, Takwoingi Y, Panesar SS, et al. The diagnosis of food allergy: a systematic review and meta-analysis. Allergy. 2014;69:76-86.
5. Klemans RJ, Broekman HC, Knol EF, et al. Ara h 2 is the best predictor for peanut allergy in adults. J Allergy Clin Immunol Pract. 2013;1:632-8 e1.
6. Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, et al. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. J Allergy Clin Immunol. 2013;132:393-9.

7. Beyer K, Grabenhenrich L, Hartl M, et al. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. Allergy. 2015;70:90-8.
8. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130:1260-74.
9. Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI Food allergy and anaphylaxis guidelines diagnosis and management of food allergy. Allergy. 2014;69:1008-25.
10. Vlieg-Boerstra BJ, van der Heide S, Bijleveld CM, Kukler J, Duiverman EJ, Dubois AE. Placebo reactions in double-blind, placebo-controlled food challenges in children. Allergy. 2007;62:905-12.
11. Venter C, Pereira B, Voigt K, et al. Comparison of open and double-blind placebo-controlled food challenges in diagnosis of food hypersensitivity amongst children. J Hum Nutr Diet. 2007;20:565-79.
12. Vlieg-Boerstra BJ, Tissen I, Sprikkelman AB. Diagnostiek van koemelkallergie op het CB aanzienlijk verbeterd door dubbelblinde provocatietest. Nederlands Tijdschrift voor Allergologie. [submitted].
13. Summers CW, Pumphrey RS, Woods CN, McDowell G, Pemberton PW, Arkwright PD. Factors predicting anaphylaxis to peanuts and tree nuts in patients referred to a specialist center. J Allergy Clin Immunol. 2008;121:632-8.c632.
14. Van Erp FC, Knulst AC, Kentie PA, Pasmans SG, van der Ent CK, Meijer Y. Can we predict severe reactions during peanut challenges in children? Pediatr Allergy Immunol. 2013;24:596-602.
15. Pumphrey RSH, Sturm G. Risk factors for fatal anaphylaxis. In: Moneret-Vautrin DA (ed). Advances in anaphylaxis management. London: Future Medicine. 2014:32-48.
16. Boeve MM, Rottier BL, Mandema JM, Rings EH, Kieboom JK, Dubois AE. Anafylaxie door pinda en notenallergie bij 2 kinderen: aanbevelingen voor beleid. Ned Tijdschr Geneeskd. 2007;151:602-6.
17. http://www.nvdv.nl/wp-content/uploads/2014/08/Richtlijn-voedselprovocatie-29-09-2015.pdf
18. Vlieg-Boerstra BJ, Bijleveld MA, Heide S van der, et al. Development and validation of challenge materials for double-blind, placebo-controlled food challenges in children. J Allergy Clin Immunol. 2004;113:341-6.
19. Vlieg-Boerstra BJ, Herpertz I, Pasker L, et al. Validation of novel recipes for double-blind, placebo-controlled food challenges in children and adults. Allergy. 2011;66:948-54.
20. Ronteltap A, van Schaik J, Wensing M, Rynja FJ, Knulst AC, de Vries JH. Sensory testing of recipes masking peanut or hazelnut for double-blind placebo controlled food challenges. Allergy. 1004;59:457-60.
21. Blom WM, Vlieg-Boerstra BJ, Kruizinga AG, van der Heide S, Houben GF, Dubois AE. Threshold dose distributions for 5 major allergenic foods in children. J Allergy Clin Immunol. 2013;131:172-9.
22. Eller E, Hansen TK, Bindslev-Jensen C. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. Ann Allergy Asthma Immunol. 2012;108:332-6.
23. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, et al. How much is too much? Threshold dose distributions for 5 food allergens. J Allergy Clin Immunol. 2015;135:964-71.
24. Van Erp FC, Knulst AC, Meijer Y, Gabriele C, van der Ent CK. Standardized food challenges are subject to variability in interpretation of clinical symptoms. Clin Transl Allergy. 2014;4:43.
25. Van der Valk JP, van Wijk RG, Vergouwe Y, de Jong NW. Failure of introduction of food allergens after negative oral food challenge tests in children. Eur J Pediatr. 2015;174:1093-9.
26. Vlieg-Boerstra J, Dubois AEJ, van der Heide S, et al. Ready-to-use introduction schedules for first exposure to allergenic foods in children at home. Allergy. 2008:63:903-9.