

Standardization of oral challenge tests in suspected food allergies

Guidelines of the Deutsche Gesellschaft für Allergologie und klinische Immunologie (DGAKI), of the Ärztenverband Deutscher Allergologen (ÄDA) and of the Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA)

B. Niggemann¹, K. Beyer², S. Erdmann³, T. Fuchs⁴, J. Kleine-Tebbe⁵, U. Lepp⁶, M. Raithel⁷, I. Reese⁸, J. Saloga⁹, C. Schäfer¹⁰, Z. Szépfalusy¹¹, S. Vieths¹², T. Zuberbier¹³, T. Werfel¹⁴ and M. Worm¹³

¹Pädiatrische Allergologie und Pneumologie, Hedwig-von-Rittberg-Zentrum, DRK-Kliniken Westend, Berlin, ²Allergie-Centrum-Charité, Klinik für Pädiatrie mit Schwerpunkt Pneumologie und Immunologie, Charité – Universitätsmedizin Berlin, ³Praxis für Dermatologie, Bergisch-Gladbach, ⁴Abteilung Dermatologie und Venerologie, Universitätsmedizin Göttingen, ⁵Allergie- und Asthma-Zentrum Westend, Berlin, ⁶Herz-Lungen-Praxis, Stade, ⁷Gastroenterologie, Pneumologie und Endokrinologie, Medizinische Klinik 1, Universität Erlangen, ⁸Ernährungstherapie, München, ⁹Hautklinik und Poliklinik, Universitätsmedizin der Johannes-Gutenberg-Universität, Mainz, ¹⁰Ernährungstherapie, Hamburg, ¹¹Universitätsklinik für Kinder- und Jugendheilkunde, Medizinische Universität Wien, Österreich, ¹²Abteilung Allergologie, Paul-Ehlich-Institut, Langen, ¹³Allergie-Centrum-Charité, Klinik für Dermatologie, Venerologie und Allergologie, Charité – Universitätsmedizin Berlin, ¹⁴Klinik und Poliklinik für Dermatologie und Venerologie, Medizinische Hochschule Hannover

Introduction

Food is frequently suspected to cause manifold symptoms. The proof of causality, however, is frequently very difficult. The previous Guidelines of the DGAKI, ÄDA and GPA [33] has been updated and revised. The new version is designed to contribute to the standardization of the diagnosis of immunoglobulin E (IgE)-mediated reactions to food. It also includes non-IgE-mediated immunologic reactions such as, e.g., lymphocyte-mediated reactions [55]. Other food-induced reactions, like for instance enzyme defects or non-allergic hypersensitivity (e.g., reactions to food additives and natural food components like flavoring substances) are not included [43, 60].

Diagnosis of food allergy

In the diagnosis of food allergies no single verifying parameter exists [32, 44]. A multistep procedure that takes into account individual factors is advisable. The diagnostic work-up for food allergy does not differ considerably from the diagnostic work-up for other allergic diseases (Table 1) [6, 9].

The diagnosis of food allergies is always based on numerous verifying parameters that are only meaningful as a whole.

Patient history is still the first and most important piece of the puzzle of diagnosis when a food allergy is suspected [7]. Patient history can help to establish a connection between clinical symptoms and the ingestion of certain foods and differentiate IgE-mediated reactions from non-allergic hypersensitivity [47]. If, for example, a patient reports that typical immediate-type symptoms repeatedly occurred within minutes after the ingestion of peanuts (e.g., lip edema, generalized urticaria) and a specific IgE against peanut is detected, oral challenge testing is not abso-

Table 1. Options for diagnosis of food allergies.

1. Patient history By physician or nutritionist
2. Diet and symptom diary
3. In-vitro investigation Specific IgE (plus total IgE) Specific questions: Allergen-induced mediator release (histamine, cysteinyl leukotriene, eosinophil cationic protein (ECP), urine methyl histamine) Allergen-induced lymphocyte stimulation
4. In-vivo examination Skin testing (skin prick test, atopy patch test) Diagnostic elimination diets (specific elimination/oligoallergenic diet) Controlled oral challenges (open or double-blind)

lutely necessary [59]. On the other hand, if a patient (e.g., with atopic dermatitis) suspects that the eczema worsens due to certain foods, challenge testing – if possible in the form of a double-blind, placebo-controlled oral food challenge (DBPCFC) [56] – is strongly recommended. Earlier evaluations of late-type reactions after oral challenge show that patient history does not have a high diagnostic specificity in these cases [8, 36].

Patient history is very important in immediate-type allergies; in delayed allergic reactions it is of less significance.

A food and symptom diary, kept for about 2–4 weeks, can provide insight into the food eaten by the patient and his/her environment and thus allows clinicians to relate symptoms to certain foods. In cases of hidden food components that do not have to be indicated on a label, e.g., commercially produced but unpacked food (restaurants, bakeries, butchers), the diary method is only of limited value.

Food and symptom diaries can add to the patient history when a food allergy with delayed reactions is suspected.

A current guideline of the GAKI in cooperation with four other societies exists [22] on in-vitro diagnosis of food allergies, in particular on the determination of specific IgE for routine clinical practice. Particularly in food, the informational value strongly depends on the allergen [13, 45, 49]. So-called decision points, that predict the probability of a positive oral challenge test, can only rarely supersede oral challenges. In approximately 10% of all positive oral challenges in infants with atopic dermatitis, neither was a skin prick test positive, nor could specific IgE be detected in the serum [34]. Skin prick

testing can be an alternative to the determination of specific IgE in the serum; skin prick tests should be carried out with native food rather than with extracts [19, 54]. But also a positive skin prick test alone cannot predict a positive oral provocation with absolute certainty.

The determination of specific IgE or skin prick testing can corroborate allergy diagnosis when a food allergy is suspected. The determination of IgG, on the other hand, is not at all useful for diagnosis.

Another diagnostic instrument to test for food allergies is the atopy patch test (APT; a patch test using native food). In several studies in infants, a high diagnostic sensitivity and specificity with regard to orally provoked eczematous reactions was demonstrated [35, 45, 53]. It is necessary that an APT be carried out by well-trained staff, as irritant reactions are frequent in children with atopic dermatitis. For adults no data on APT for suspected food allergies exist. Due to the fact that the APT is very time-consuming, that no standardized test substances are available, that an extremely experienced investigator is necessary, and finally that it only rarely supersedes oral challenge testing, this test cannot be generally recommended for routine practice [26].

The atopy patch test with food is a valuable diagnostic test; however, due its manifold drawbacks it is not suitable for everyday diagnostic practice.

Abbreviations

AAF	Amino acid formula nutrition
ACE	Angiotensin converting enzyme
ÄDA	Ärzteverband Deutscher Allergologen
APT	Atopy patch test
ASS	Acetyl salicylic acid
DBPCFC	Double-blind placebo-controlled food challenge
DGAKI	Deutsche Gesellschaft für Allergologie und klinische Immunologie
ECP	Eosinophil cationic protein
EHF	Extensively hydrolyzed formula
FEV ₁	Forced expiratory volume in the first second
GPA	Gesellschaft für Pädiatrische Allergologie und Umweltmedizin
IgE	Immunoglobulin E
OAS	Oral allergy syndrome
SCORAD	Score of atopic dermatitis

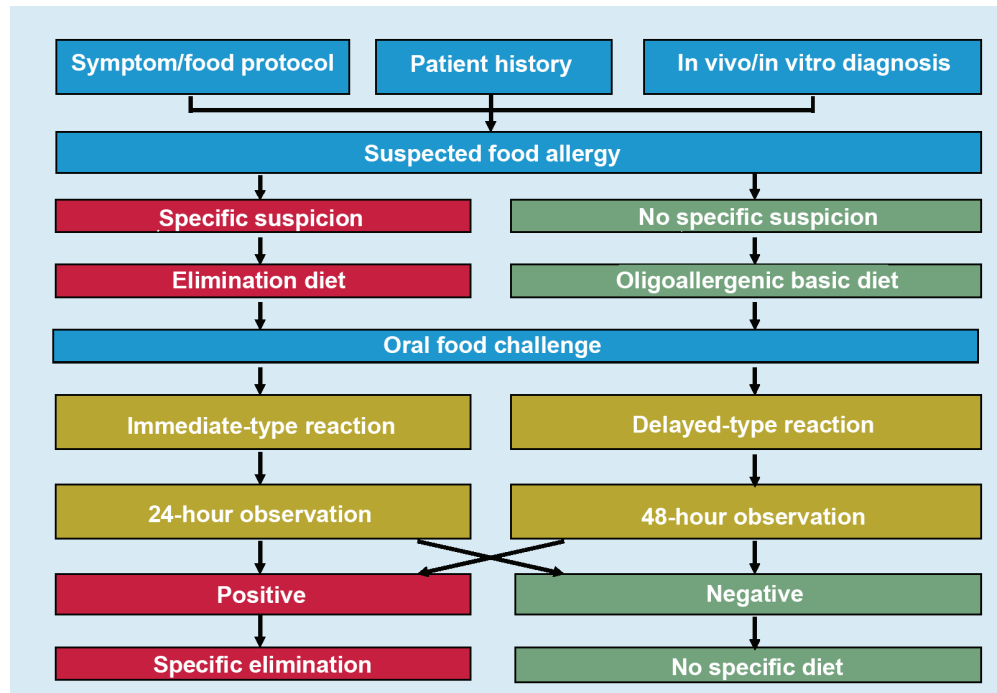


Figure 1. Flow chart for diagnostic work-up when a food allergy is suspected.

The “gold standard” for food allergy diagnosis is still the double-blind, placebo-controlled oral food challenge (DBPCFC) [2, 3, 7, 27]. This procedure allows clinicians to confirm the clinical relevance of existing sensitizations or supposedly observed symptoms – independently of subjective factors. The realization of oral challenge testing under the current conditions of diagnosis-related groups (DRG; i.e., inpatient reimbursement of costs according to diagnosis and not according to bed occupancy) is perhaps only possible to a limited extent. For the procedures of oral challenge testing in the context of pollen-associated food allergies please refer to the guidelines by Henzgen et al. [20].

The “gold standard” for food allergy diagnosis is the double-blind, placebo-controlled oral food challenge (DBPCFC).

In patients with anaphylactic reactions that are clearly attributable to certain foods, usually no challenge testing is carried out [4, 25]. It could, however, be useful to roughly determine the allergen amount necessary to trigger a reaction or to investigate the impact of augmentation factors. Current investigation shows that the determination of recombinant single allergens allows a better evaluation of the risk of severe reactions (e.g.,

Ara h 2 for peanut or Cor a 9 for hazelnut). Likewise, pollen-associated food allergies in terms of oral allergy syndrome (OAS) [39] can mostly be diagnosed based on the clinical features and the corresponding patterns of sensitization and usually do not necessitate oral challenge. On the other hand, if they cause delayed or chronic symptoms (eczema exacerbation or occurrence of gastrointestinal symptoms), oral challenging is useful.

Life-threatening, clearly attributable anaphylactic reactions are usually a contraindication for oral challenge testing.

Table 2. Example of an oligoallergenic basic diet after infancy*.

Wheat: rice
Meat: lamb, turkey
Vegetables: cauliflower, broccoli, cucumber
Fat: Refined plant oil, mild-free margarine
Beverages: mineral water, black tea
Spices: salt, sugar

*The composition of the diet should be based on the individual diagnostic work-up and the patient's needs.

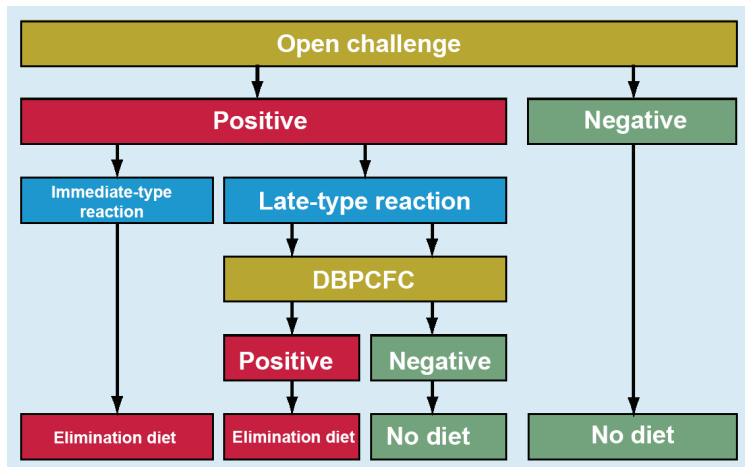


Figure 2. Differential indication for open vs. double-blind challenge.

Table 3. Example for the sequence of foods for challenging or re-introduction after oligoallergenic basic diet*.

1. Cow's milk (if necessary, soy milk)
2. Hen's egg
3. Pure wheat products
4. Further types of vegetables (e.g., parsnip, pumpkin) and potatoes
5. Further types of fruits (e.g., apple, pear, banana)
6. Further sorts of wheat (e.g., oats) and if necessary soy flour
7. Further types of meat (e.g., beef)
8. Miscellaneous: spices, herbs, celery, tree nuts, peanuts

*Must be adjusted for each patient.

Procedure when a food allergy is suspected

When a food allergy is suspected mainly due to a corresponding patient history, in-vivo (e.g., skin tests) and/or in-vitro examinations (e.g., specific serum IgE) should follow (Figure 1) [30, 31]. When the relationship is unclear or when the symptoms are delayed, a food and symptom diary can support diagnosis as long as no life-threatening reactions occur. If the patient experienced life-threatening reactions, hospitalization is required for further diagnostic work-up.

If the symptoms cannot be attributed to the intake of certain foods (e.g., in cases of severe atopic dermatitis with multiple sensitization), an oligoallergenic basic diet should be kept. In babies, it consists of an extensive-

ly hydrolyzed cow's milk formula or an amino acid formula, and in older babies it should be supplemented with 1 – 2 tolerated foods from every food group (example in Table 2). In advance, the tolerability of the used foods should be confirmed by adequate diagnostic work-up (medical history; IgE; skin prick test, if necessary and possible).

In older infants and adults an oligoallergenic diet is mostly not necessary, but if it is used, it also consists of individually tolerated foods that only rarely cause allergic reactions. Orientation can be provided by basic nutritional requirements, patient history, specific IgE antibodies, and skin prick testing. Extremely strict diets should be avoided because when kept for a longer period of time they can lead to qualitative and quantitative malnutrition.

If the clinical picture (e.g., the eczema) does not improve under an oligoallergenic diet, a food allergy is unlikely to be the reason for the symptoms. In this case, challenge tests are usually not necessary, and dietary restrictions are not required. If symptom improvement is observed, oral challenge tests need to follow.

If a specific food is suspected, an elimination diet is carried out (usually for at least 7 days); the foods in question (e.g., milk, eggs) are completely avoided. This elimination diet can be started at home. Subsequently, oral challenge tests are carried out by a health-care professional with allergy training. The best method is a DBPCFC.

Open oral challenges are of significance if their results are negative (Figure 2). On the other hand, open challenge tests are limited by psychological factors, lack of objectivization, and when late-type reactions are to be expected. Prior to extensive dietary measures, particularly when it comes to cow's milk-free nutrition in babies and infants as well as in atopic dermatitis, oral challenges should always be carried out as double-blind and placebo-controlled tests.

If the oral challenge test is positive, the food in question is eliminated from the diet and its nutrients are replaced. If the test result is negative and if a false negative reaction can be excluded, specific dietary restrictions are not necessary. Reasons for false positive reactions can for instance be subjective reactions to food. False negative reactions can

Table 4. Examples for an adequate procedure for oral challenging.

1. Strictly avoid suspected foods for 5 – 7 days (elimination diet) or 7 – 14 days (oligoallergenic diet) before and during challenge testing (counseling by nutritionist recommended)
2. Discontinue systemic glucocorticoids and antihistamines at least 72 hours in advance
3. Reduce topic therapies (e.g., glucocorticoids) and phototherapies to a minimum and maintain this
4. In cases of anaphylaxis in patient history, avoidance of beta-blockers and angiotensin converting enzyme (ACE) inhibitors
5. Make sure that blinding is guaranteed (e.g., by a nutritionist)
6. Use native or lyophilized foods
7. Offer food in liquid medium, if possible
8. Ratio of placebo : active episodes (at least) 1 : 2
9. Always administer the same volumes of active and placebo
10. Foods should be ingested in fasted condition or after only a small snack
11. Increase dose every (15 –) 30 (– 60) minutes (until maximum dose is reached or clinical reaction occurs)
12. The total dose should approximately correspond to an age-adjusted serving (e.g., 1 egg, 150 ml of milk)
13. The observation period should be 24 hours when early-type reactions are to be expected and at least 48 hours when late-type reactions are possible (i.e., always in case of atopic dermatitis)
14. In cases of atopic dermatitis, it might be necessary to carry out the challenge with the same food for several days
15. Challenges should only be carried out by individuals trained in allergic emergency treatment; emergency set must always be ready
16. Make sure that the clinical evaluation (monitoring) is always made by the same person (e.g., SCORAD, FEV ₁)

occur due to the absence of “everyday conditions”.

The sequence of challenging foods is based on

- allergologic findings,
- individual food patterns and
- nutritional requirements.

This is valid for the sequence of oral challenge tests (preferably DBPCFC) after an elimination diet as well as for the following sequence: 1. oligoallergenic diet; 2. challenge with certain important foods (also as DBPCFC); 3. re-introduction of further foods. Possible guidelines for the sequence of challenge and re-introduction of foods after the oligoallergenic diet are listed in Table 3 but should be based on the individual clinical picture of each patient.

Practical information about the DBPCFC procedure

Oral challenge tests should be standardized as far as possible in order to avoid pitfalls [1, 29]. In the following section we

would like to address some aspects of the procedure. Oral challenges should be carried out in a symptom-poor interval. If a stable situation cannot be reached by avoidance alone, for example in cases of atopic dermatitis, the local therapy needs to be intensified before the start of the challenge testing and continued consistently. The most important point that has to be considered when a DBPCFC is carried out (particularly in atopic dermatitis) is that all concomitant therapies (including diet) and circumstances should be changed as little as possible. Only a continuously stable situation can be a basis for the correct evaluation of the clinical reaction. If external steroids are unavoidable, the once-daily administration of a weak steroid (Class 1 or 2) is possible. Clinically relevant reactions are not prevented by this, but the natural variations of the eczema can be balanced. Systemic antihistamines should be discontinued at least 72 hours before the initiation of challenge testing. Systemic therapies, light therapy, and specific immunotherapy during the dose-increase period need to be excluded (4 weeks).

Oral challenge testing should be carried out in a symptom-poor, stable phase of the disease or when no symptoms are present at all.

Food that is to be tested in a double-blind and placebo-controlled way should be administered in liquid form (e.g., as an extensively hydrolyzed protein formulation, as an amino acid formula, or mixed with locust bean gum/rice). With this form of testing, foods that are either liquid (e.g., fresh pasteurized cow's milk or soy milk) or can be dissolved as a powder in liquid (e.g., wheat protein or lyophilized food) can be tested. Solid foods can be mixed (e.g., in puréed form) into a purée or, if this is not possible, have to be tested openly. Also, in food that has a strong taste of its own, open challenging can usually not be avoided.

It has to be taken into account that in the context of pollen-associated food allergies the allergenic activity of challenge meals can diminish quickly, and thus the meal has to be eaten as soon as possible after preparation. This applies particularly to challenge meals with freshly prepared fruits and vegetables.

The administration of foods in capsules has not proven to be successful because

Table 5. Suggestion for a titrated DBPCFC.

Basic solution (liquid medium) = for example 100 ml EHF or AAF**Placebo = 100% basic solution****Active = 1 + 1 mixture of basic solution plus allergen in basic solution**

0.1 ml	+	0.1 ml	=	0.2 ml	For example in syringe
1.0 ml	+	1.0 ml	=	2.0 ml	
3.0 ml	+	3.0 ml	=	6.0 ml	
10.0 ml	+	10.0 ml	=	20.0 ml	For example in bottle, mug, cup
30.0 ml	+	30.0 ml	=	60.0 ml	
100.0 ml	+	100.0 ml	=	200.0 ml	

Because in highly sensitized patients severe symptoms and even lethal reactions can occur [10, 51], oral challenges have to be carried out in the form of titration, particularly if early reactions need to be expected. In Table 5 we present a proposal based on cow's milk as an example. In challenges with, e.g., hen's egg, the highest step of titration (100 ml; corresponding to 200 ml total solution) is omitted or replaced by the basic solution in order

Table 6. Volumes and absolute amounts of protein in titrated oral challenge.

	Level of titration	1	2	3	4	5	6	7	Total
Milk	Volume milk (ml)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Volume BS (ml)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Total volume (ml)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.003	0.01	0.033	0.1	0.33	1.0	3.3	4.8
Hen's egg	Volume egg (ml)	0.04	0.11	0.38	1.14	3.8	11.4	39.0	54.9
	Volume BS (ml)	0.16	0.49	1.62	4.86	16.2	48.6	162.0	233.9
	Total volume (ml)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.005	0.014	0.05	0.14	0.46	1.4	4.6	6.2
Wheat	Volume wheat (ml)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Volume BS (ml)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Total volume (ml)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.003	0.008	0.028	0.083	0.28	0.83	2.8	4.0
Soy	Volume egg (ml)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Volume BS (ml)	0.1	0.3	1.0	3.0	10.0	30.0	100.0	144.4
	Total volume (ml)	0.2	0.6	2.0	6.0	20.0	60.0	200.0	288.8
	Protein (g)	0.004	0.011	0.04	0.11	0.36	1.1	3.6	5.2

*BS = basic solution.

Table 7. Suggestion for a titrated DBPCFC.

Level of titration	Peanut (g)	Protein (g)
1	0.012	0.003
2	0.04	0.01
3	0.12	0.03
4	0.4	0.1
5	1.2	0.3
6	3	0.75
7	8	2.0

- only small amounts of the food can be filled in the capsules,
- oral symptoms as a possible first clinical sign do not occur with capsules and
- this method of testing is not suitable for infants.

At least if severe reactions (airway and/or circulatory symptoms) are possible, oral challenges should be carried out while an intravenous access is present. Table 4 presents the most important practical information for the DBPCFC procedure.

to warrant a constant maximum amount. The dosages for frequent foods are listed in Table 6, for peanut they are listed in Table 7.

A practical problem is the masking (blinding) of foods in terms of taste, color, and consistency. In infants, the use of an extensively hydrolyzed protein preparation or an amino acid formula is advantageous because the remaining allergenicity is insignificant and the bitter taste disguises many (but not all) other tastes. A disadvantage is the – understandably – poor acceptance by children and adults. For these age groups, a milk protein-free mixture on the basis of rice and locust bean gum can be used alternatively. Recipes for the blinding of food allergens for DBPCFC are published in Werfel and Reese [57]. It needs to be taken into account that the technique of blinding can influence the allergenic properties of a food (e.g., by a very high fat content or by resulting insoluble compounds) so that false negative results might occur.

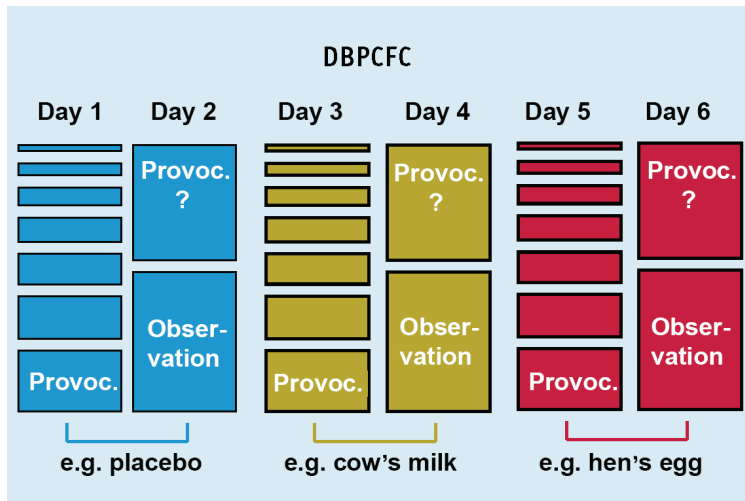


Figure 3. Procedure of titrated oral challenge presented in blocks. If challenge is positive on Day 1 and no medication was administered, the next part can be started the next day.

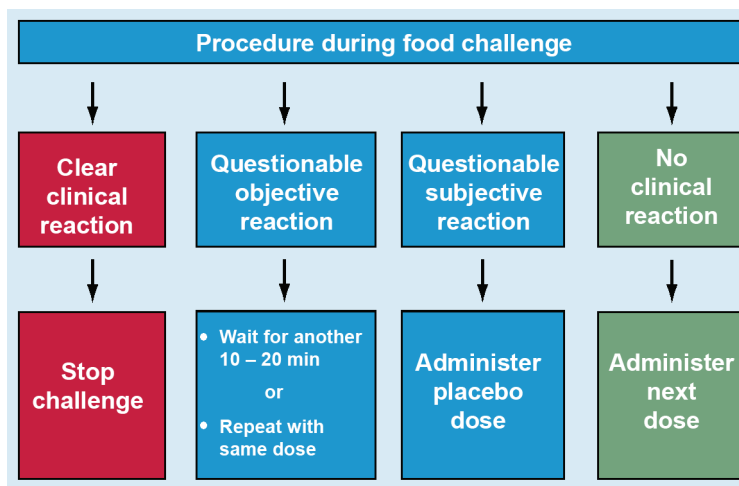


Figure 4. Practical procedures during oral challenge testing.

The test of the challenge mixture can be improved either by sweetening with, for example, pear syrup or by adding a flavoring substance, which additionally reduces the food's own taste. The foods added to the challenge need to be checked for tolerability. Finally, cooling of the food can reduce its typical taste further. The color of the administered test solution can be changed or adjusted by carrot or currant juice or cocoa (if possible from an allergologic point of view). If it is not possible to mask the color, the food has to be given in a disguising way (e.g., using a syringe covered with aluminum foil, non-transparent bottle or the like). To

adjust the consistency, either wheat protein, corn or rice gruel can be used, depending on the patient's tolerability.

When oral challenge testing is carried out in breastfed babies, the mother should also adhere to a corresponding elimination diet (e.g., milk- and/or egg-free) during the test period, as in rare cases allergens eaten by the mother can cause symptoms in the child [47] that could falsify the test results.

The ratio of placebo challenge : allergen challenge should ideally be 1 : 1 (at least). Due to practical reasons (e.g., shorter time, compliance of the families), frequently a ratio of 1 : 2 is also possible. For instance, placebo, egg, and milk can be given in a randomized sequence as a first block (Figure 3). As the titrated challenge on Day 1 can rapidly induce oral tolerance, the cumulative total dose should be administered again on Day 2 if the result of the first day was negative.

In daily practice, a placebo challenge : allergen challenge ratio of 1 : 1 or 1 : 2 should be aimed for.

In the rare case of a delayed clinical reaction occurring at the patient's home after an open oral test had initially been negative, this challenge has to be repeated under double-blind, placebo-controlled conditions [11]. Furthermore, in patients with atopic dermatitis and a negative challenge test, the same food has to be given repeatedly under observation of the clinical symptoms for several days and using higher doses in order to avoid false negative challenge test results. Augmentation factors that possibly played a role in the reported reaction can also cause a negative test result under standardized conditions.

The clinical evaluation is carried out by a physician who should not be changed for at least one block. An early-type reaction is defined as a clinical reaction occurring within the first 2 hours after application of the food in question; later reactions are called late-type reactions. A provocation should be evaluated as positive if the symptoms fulfil one or more of the following criteria [28]:

- objective (visible and measurable),
- severe or reproducible,
- persisting.

In atopic eczema, aggravation can be objectified using a severity score and an ag-

Table 8. Procedure after blinding.

Active	Placebo	Procedure
+	–	Elimination diet
+	+	Repeat test
–	–	No diet
–	+	No diet

gravation of at least 10 – 15 points on the Scoring Atopic Dermatitis (SCORAD) scale should be reached. Figure 4 illustrates how to proceed in cases of unclear reactions. Table 8 shows the procedures after “de-blinding”. For ethical reasons, the challenge is not carried out until the maximum level of symptoms is reached, but only until symptoms occur that allow for a clear classification as positive or negative.

A major aspect of oral challenge testing is the documentation of the test results on an adequate documentation form that has to consider the type of food, the amount administered, and all clinical reactions. The physician evaluating the clinical reaction should write down a clear yes or no every 24 hours. The total evaluation of the challenges is carried out at the end of testing. Subjective symptoms have to be re-challenged. The code of the sequence of allergen or placebo challenge should be “de-blinded” after a block of 3 phases of (24 or) 48 hours each. The results are discussed with the patients or their parents after each block. On this occasion a second block can be scheduled. Fortunately, most patients do not suffer from more than 1 – 3 clinically relevant food allergies [14, 36, 40].

The clinical evaluation of a challenge test is carried out by the same person and should result in an unambiguous statement (yes or no).

A positive challenge test is the proof of a food intolerance and has to be interpreted with regard to a specific sensitization or the clinical symptoms. When only gastrointestinal symptoms are present, the following differential diagnoses should be considered: lactose malabsorption or intolerance when challenge with cow’s milk was positive; fructose malabsorption when challenge with fruits was positive; celiac disease when challenge with cereal products was positive.

A positive reaction to placebo impedes the correct interpretation of a positive chal-

Challenge protocol for augmentation factors

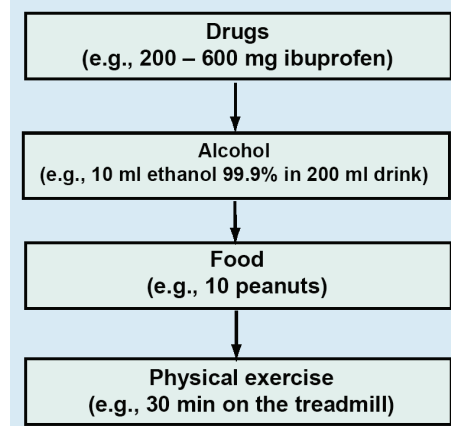


Figure 5. Exemplary diagram for food challenge under augmentation factors. The conditions for challenging must be adjusted to each patient as well as to their age and activities.

lenge with the test substance [4] if the placebo mixture was really tested for tolerability before: in this case, the previous tests have to be repeated, and placebo challenges have to be carried out more intensively. If the test result is negative, it has to be taken into account that augmentation factors could play a role: physical stress, hormonal and mental factors, intercurrent infections, drug use or alcohol. In addition, it is also possible that only the combination of several foods or of food and drugs (e.g., acetylsalicylic acid (ASS)) or additives causes the symptoms.

In patients with exercise-induced allergic reactions to food, an age-adapted physical exercise (e.g., on the treadmill) has to be carried out about 45 – 60 minutes after oral challenging [24]. An example for challenge testing with consideration of augmentation factors is presented in Figure 5.

If sufficient experience is present and if the indication allows for it, oral challenge testing can also be carried out on an outpatient basis. Indications for an inpatient diagnostic work-up are listed in Table 9. When carried out on an outpatient basis, oral challenge tests can be performed to stepwise re-introduce individual foods after a corresponding elimination or oligoallergenic basic diet. This can, for example, be carried out in the sequence presented in Table 3. Every 4 – 7 days a food is re-introduced and then kept in the diet. In this case, many challenges can only be carried out as open, non-placebo-

Table 9. Indications for hospitalization for oral challenge testing.

– Threatening reactions in patient history (if not clearly attributable to a certain food)
– Unclear reactions in patient history (e.g., unclear diagnosis) and to basic food
– Reported symptoms outside outpatient observation period
– In babies and infants: Marked sensitization without previous contact to the food in question

controlled tests. If uncertainties arise from outpatient testing or patient history, the patient should be hospitalized for DBPCFC.

Special caution is necessary after longer phases of allergen avoidance (i.e., long interval between last administration of the food and re-challenge) [18]. Late-type reactions to foods can occur in isolation or be linked to previous immediate-type reactions [48, 50]. The evaluation of challenge tests in children suggests that approximately 25% of all clinical reactions occur only after 2 hours or later [36].

Patients who are sensitized against birch pollen can respond with isolated eczema aggravation to oral challenge with cross-reactive food allergens [8, 41]. This suggests that the issue of oral inducibility of atopic dermatitis has so far been underestimated.

Monitoring of the challenge tests

Due to the above described difficulties in evaluating an oral food challenge purely on a clinical basis, all subjective and objective symptoms should be recorded. According to the individual patient history it is recommended to

- control heart rate and blood pressure, if the patient experienced anaphylaxis;
- monitor the challenge tests by controlling the peak flow (better: with an extensive examination of lung function) in patients who possibly react with obstructive airway symptoms;
- use rhinomanometry in patients with rhinitic symptoms;
- examine mouth and pharynx in patients with oral allergy syndrome;
- use standardized severity scores for evaluation of the course (e.g., Scoring Atopic Dermatitis (SCORAD) index) in patients with atopic dermatitis [16].

In oral food challenge testing all collectable subjective and objective symptom data should be assessed.

For scientific purposes, it is possible to objectify clinical reactions by measuring cell-specific inflammation mediators from biologic liquids. This concerns the determination of the eosinophil count in the peripheral blood as well as the measurement of the serum concentration of eosinophil cationic protein (ECP) [31, 52], the measurement of 1-methyl histamine in the urine and the serum tryptase concentration [5] or an increase of the basophil activation before and after challenging [58]. However, the determination of these parameters is not routinely necessary as it does not provide individual predictability.

The determination of ex-vivo parameters for the monitoring of food challenges is not necessary in daily practice.

Conclusions

Even with sophisticated procedures like a well standardized oral challenge test it is not always possible to find out the exact trigger(s) of a food allergy. This is due to the still insufficient possibilities to evaluate the symptoms objectively (particularly in late-type reactions) as well as the fact that several factors (various allergens, physical or mental stress, etc.) can interact to cause the allergic reaction.

In some patients, the effort when carrying out a DBPCFC is relatively high (even hospitalization for several weeks might be necessary), but in many cases it is absolutely justified and even inevitable in order to avoid food causing clinical reactions, but also to keep the patients from unsecured or even useless diets that (modified from Przybilla)

- impair patients without achieving any benefit,
- can lead to significant deficiencies,
- discharge therapists from any responsibility and
- inhibit useful therapies.

In many cases, the effort undertaken for food challenges is justified and necessary to make a clear diagnosis or to avoid unsecured diets.

Several case reports have been published on the topic of considerable side effects due to strict unbalanced diets [12, 15, 17]. In children, dietary recommendations, even if they are based on solid challenge testing, are only valid for 12 – 18 months because many early-childhood allergies have a good prognosis. After this period, re-examination of the specific IgE and periodical oral challenge tests are necessary to re-evaluate the current clinical situation until tolerance is reached. For adults, longer intervals may be more useful. This is also true for foods with a worse prognosis, like tree nuts or peanuts. Dietary recommendations made by a physician can only be realized with the help of a nutritionist with allergy training. This topic is also addressed in the guidelines on therapeutic options in IgE-mediated food allergy [23].

Long-term diets should only be realized after extensive counseling by a nutritionist with allergy training.

Finally, all patients with a proven severe food allergy should be provided with an emergency set, adequately trained, and registered in the anaphylaxis registry.

Procedure of guideline development

Update of earlier guidelines; expert group; update of AWMF-Nr. 061/010; next revision planned in July 2015; ICD-10 numbers affected: T 78.0, T 78.1, T 78.4, L 20.9.

References

- [1] *AG Nahrungsmittelallergie der GPA*. Orale Nahrungsmittelprovokationen bei Verdacht auf eine Nahrungsmittelallergie im Säuglings- und Kindesalter. www.gpaev.de/typo/Arbeitsgruppen.111.o.html.
- [2] Anderson JA. Milestones marking the knowledge of adverse reactions to food in the decade of the 1980s. *Ann. Allergy*. 1994; 72: 143-154.
- [3] Asero R, Fernandez-Rivas M, Knulst AC, Brujinzeel-Koomen CAFM. Double-blind, placebo-controlled food challenge in adults in everyday clinical practice: A reappraisal of their limitations and real indications. *Curr Opin Allergy Clin Immunol*. 2009; 9: 379-385.
- [4] Bahna SL. Blind food challenge testing with wide-open eyes. *Ann Allergy*. 1994; 72: 235-238. [PubMed](#)
- [5] Beyer K, Niggemann B, Schulze S, Wahn U. Serum tryptase and urinary 1-methylhistamine as parameters for monitoring oral food challenges in children. *Int Arch Allergy Immunol*. 1994; 104: 348-351. [doi:10.1159/000236690 PubMed](#)
- [6] Bindselev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, Knulst AC, Moneret-Vautrin DA, Nekam K, Niggemann B, Osterballe M, Ortolani C, Ring J, Schnopp C, Werfel T; European Academy of Allergy and Clinical Immunology. Standardization of food challenges in patients with immediate reactions to foods – position paper from the European Academy of Allergy and Clinical Immunology. *Allergy*. 2004; 59: 690-697. [doi:10.1111/j.1398-9995.2004.00466.x PubMed](#)
- [7] Bock SA, Sampson HA, Atkins FM, Zeiger RS, Lehrer S, Sachs M, Bush RK, Metcalfe DD. Double-blind, placebo-controlled food challenge (DBPCFC) as an office procedure: A manual. *J Allergy Clin Immunol*. 1988; 82: 986-997. [doi:10.1016/0091-6749\(88\)90135-2 PubMed](#)
- [8] Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D, Kapp A, Werfel T. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy*. 2004; 34: 817-824. [doi:10.1111/j.1365-2222.2004.1953.x PubMed](#)
- [9] Brujinzeel-Koomen C, Ortolani C, Aas K, Bindselev-Jensen C, Björkstén B, Moneret-Vautrin D, Wüthrich B. Adverse reactions to food – position paper. *Allergy*. 1995; 50: 623-635.
- [10] Caffarelli C, Petroccione T. False-negative food challenges in children with suspected food allergy. *Lancet*. 2001; 358: 1871-1872. [doi:10.1016/S0140-6736\(01\)06897-0 PubMed](#)
- [11] Canadian Paediatric Society. Fatal anaphylactic reactions to food in children. *Can Med Assoc*. 1994; 150: 337-339.
- [12] Carvalho NF, Kenney RD, Carrington PH, Hall DE. Severe nutritional deficiencies in toddlers resulting from health food milk alternatives. *Pediatrics*. 2001; 107: e46-e52. [PubMed doi:10.1542/peds.107.4.e46](#)
- [13] Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, Niggemann B. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy*. 2005; 35: 268-273.
- [14] Crespo JF, Pascual C, Burks AW, Helm RM, Esteban MM, Beyer K, Niggemann B. Frequency of food allergy in a pediatric population from Spain. *Pediatr Allergy Immunol*. 1995; 6: 39-43. [doi:10.1111/j.1399-3038.1995.tb00256.x PubMed](#)
- [15] Davidovits M, Levy Y, Avramovitz T, Eisenstein B. Calcium-deficiency rickets in a four-year-old boy with milk allergy. *J Pediatr*. 1993; 122: 249-251. [doi:10.1016/S0022-3476\(06\)80124-1 PubMed](#)
- [16] European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: The SCORAD index. *Dermatology*. 1993; 186: 23-31. [PubMed](#)
- [17] Grüttner R. Mangelzustände bei Fehlernährung durch alternative Kost im Säuglings- und Kleinkindesalter. *Dtsch Arztebl*. 1992; 89: B462-B466.
- [18] Flinterman AE, Knulst AC, Meijer Y, Brujinzeel-Koomen CAFM, Pasmans SGMA. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy*. 2006; 61: 370-374.

- [19] Henzgen M, Balmer-Weber BK, Erdmann S, Fuchs T, Kleine-Tebbe J, Lepp U, Niggemann B, Raithel M, Reese I, Saloga J, Vieluf I, Vieths S, Zuberbier T, Werfel T. Hauttestungen mit Nahrungsmittelallergenen. *Allergo J.* 2008; 17: 401-406.
- [20] Henzgen M, Vieths S, Reese I, Erdmann S, Fuchs T, Jäger L, Kleine-Tebbe J, Lepp U, Niggemann B, Saloga J, Vieluf I, Zuberbier T, Werfel T. Nahrungsmittelallergien durch immunologische Kreuzreaktionen. *Allergo J.* 2005; 14: 48-59.
- [21] Kato Y, Watanabae H, Matsuda T. Ovomucoid rendered in soluble by heating with wheat gluten but not with milk casein. *Biosci Biotechnol Biochem.* 2000; 64: 198-201.
- [22] Kleine-Tebbe J, Ballmer-Weber B, Beyer K, Erdmann S, Fuchs T, Henzgen M, Huttegger I, Jappe U, Jäger L, Lepp U, Niggemann B, Raithel M, Reese I, Saloga J, Szepfalusi Z, Vieths S, Worm M, Zuberbier T, Werfel T. In-vitro-Diagnostik und molekulare Grundlagen von IgE-vermittelten Nahrungsmittelallergien. *Allergo J.* 2009; 18: 132-146.
- [23] Lepp U, Ballmer-Weber B, Beyer K, Erdmann S, Fuchs T, Henzgen M, Heratizadeh A, Huttegger I, Jappe U, Kleine-Tebbe J, Niggemann B, Raithel M, Reese I, Saloga J, Schäfer C, Szepfalusi Z, Vieths S, Werfel T, Zuberbier T, Worm M. Therapiemöglichkeiten bei der IgE-vermittelten Nahrungsmittelallergie. *Allergo J.* 2010; 19: 187-195.
- [24] Loibl M, Schwarz S, Ring J, Halle M, Brockow K. Definition of an exercise intensity threshold in a challenge test to diagnose food-dependent exercise-induced anaphylaxis. *Allergy.* 2009; 64: 1560-1561.
- [25] May CD. Are confusion and controversy about food hypersensitivity really necessary? *J Allergy Clin Immunol.* 1985; 75: 329-333. [doi:10.1016/0091-6749\(85\)90067-3](https://doi.org/10.1016/0091-6749(85)90067-3) PubMed
- [26] Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K, Niggemann B. The Atopy Patch Test in the diagnostic work-up of suspected food related symptoms in children. *J Allergy Clin Immunol.* 2006; 118: 923-929.
- [27] Metcalfe DD, Sampson HA. Workshop on experimental methodology for clinical studies of adverse reactions to foods and food additives. *J Allergy Clin Immunol.* 1990; 86: 421-422.
- [28] Niggemann B. When is an oral food challenge positive? *Allergy.* 2010; 65: 2-6. [doi:10.1111/j.1398-9995.2009.02170.x](https://doi.org/10.1111/j.1398-9995.2009.02170.x) PubMed
- [29] Niggemann B, Beyer K. Pitfalls in double-blind, placebo-controlled oral food challenges. *Allergy.* 2007; 62: 729-732. [doi:10.1111/j.1398-9995.2007.01396.x](https://doi.org/10.1111/j.1398-9995.2007.01396.x) PubMed
- [30] Niggemann B, Beyer K, Pohl C, Wahn U. Diagnostisches Vorgehen beim Verdacht auf Nahrungsmittelallergie im Kindesalter. *Monatsschr Kinderheilkd.* 1996; 144: 65-73.
- [31] Niggemann B, Beyer K, Wahn U. The role of eosinophils and their granule protein ECP in monitoring oral food challenge tests in children with food sensitive atopic dermatitis. *J Allergy Clin Immunol.* 1994; 94: 963-971. [doi:10.1016/0091-6749\(94\)90114-7](https://doi.org/10.1016/0091-6749(94)90114-7)
- [32] Niggemann B, Ehnert B, Wahn U. Diagnostik der Nahrungsmittelallergie im Kindesalter – was ist gesichert? *Allergologie.* 1991; 14: 208-213.
- [33] Niggemann B, Erdmann S, Fuchs T, Henzgen M, Jäger L, Kleine-Tebbe J, Lepp U, Raithel M, Reese I, Saloga J, Vieluf I, Vieths S, Zuberbier T, Werfel T. Standardisierung von oralen Provokationstests bei Nahrungsmittelallergien. *Allergo J.* 2006; 15: 262-270.
- [34] Niggemann B, Reibel S, Roehr CC, Felger D, Ziegert M, Sommerfeld C, Wahn U. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol.* 2001; 108: 1053-1058.
- [35] Niggemann B, Reibel S, Wahn U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy.* 2000; 55: 281-285. [doi:10.1034/j.1398-9995.2000.00464.x](https://doi.org/10.1034/j.1398-9995.2000.00464.x) PubMed
- [36] Niggemann B, Sielaff B, Beyer K, Binder C, Wahn U. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy.* 1999; 29: 91-96. [doi:10.1046/j.1365-2222.1999.00454.x](https://doi.org/10.1046/j.1365-2222.1999.00454.x) PubMed
- [37] Niggemann B, Wahn U, Sampson HA, Niggemann B. Proposals for standardization of oral food challenge tests in infants and children. *Pediatr Allergy Immunol.* 1994; 5: 11-13. [doi:10.1111/j.1399-3038.1994.tb00212.x](https://doi.org/10.1111/j.1399-3038.1994.tb00212.x) PubMed
- [38] Nöhle N, Schwanitz HJ. Zusammengesetzte Lebensmittel: Ein Problem für die Allergenidentifikation. *Allergologie.* 1997; 20: 270-273.
- [39] Pfau A, Stolz W, Landthaler M, Przybilla B. Neue Aspekte zur Nahrungsmittelallergie. *Dtsch Med Wschr.* 1996; 121: 346-350.
- [40] Rancé F, Kanny G, Dutau G, Moneret-Vautrin DA. Food hypersensitivity in children: Clinical aspects and distribution of allergens. *Pediatr Allergy Immunol.* 1999; 10: 33-38. [doi:10.1034/j.1399-3038.1999.101008.x](https://doi.org/10.1034/j.1399-3038.1999.101008.x) PubMed
- [41] Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen related food trigger atopic dermatitis with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol.* 1999; 104: 466-472.
- [42] Reekers K, Wulf A, Constien A, Tetau D, Kapp A, Werfel T. Birch pollen-related food as a provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. *Allergy.* 2004; 59: 988-994. [doi:10.1111/j.1398-9995.2004.00493.x](https://doi.org/10.1111/j.1398-9995.2004.00493.x) PubMed
- [43] Reese I, Zuberbier T, Bunselmeyer B, Erdmann S, Henzgen M, Fuchs T, Jäger L, Kleine-Tebbe J, Lepp U, Niggemann B, Raithel M, Saloga J, Vieths S, Werfel T. Diagnostisches Vorgehen bei Verdacht auf eine pseudoallergische Reaktion durch Nahrungsmittelinhaltsstoffe. *Allergo J.* 2008; 17: 540-549.
- [44] Ring J, Vieluf D, Hamm M, Behr-Völtz B. Einführung in die Problematik der Nahrungsmittel-Allergie und anderer nahrungsmittelbedingter Unverträglichkeitsreaktionen. *Allergo J.* 1995; 4: 384-388.
- [45] Roehr C, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch test together with level of specific IgE reduces the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol.* 2001; 107: 548-553. [PubMed doi:10.1067/mai.2001.112849](https://doi.org/10.1067/mai.2001.112849)

- [46] Sampson HA. IgE-mediated food intolerance. *J Allergy Clin Immunol*. 1988; *81*: 495-504.
- [47] Sampson HA. The role of food allergy and mediator release in atopic dermatitis. *J Allergy Clin Immunol*. 1988; *81*: 635-645. doi:10.1016/0091-6749(88)91033-0 PubMed
- [48] Sampson HA, Albergo R. Comparison of results of skin tests, RAST, and double-blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol*. 1984; *74*: 26-33. doi:10.1016/0091-6749(84)90083-6 PubMed
- [49] Sampson HA, Ho DG. Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol*. 1997; *100*: 444-451.
- [50] Sampson HA, McCaskill CC. Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients. *J Pediatr*. 1985; *107*: 669-675. doi:10.1016/S0022-3476(85)80390-5 PubMed
- [51] Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med*. 1992; *327*: 380-384. doi:10.1056/NEJM199208063270603 PubMed
- [52] Suomalainen H, Soppi E, Isolauri E. Evidence for eosinophil activation in cow's milk allergy. *Pediatr Allergy Immunol*. 1994; *5*: 27-31. doi:10.1111/j.1399-3038.1994.tb00215.x PubMed
- [53] Vanto T, Juntunen-Backman K, Kalimo K, Klemola T, Koivikko A, Koskinen P, Syvänen P, Valovirta E, Varjonen E. The patch test, skin prick test, and serum milk-specific IgE as diagnostic tools in cow's milk allergy in infants. *Allergy*. 1999; *54*: 837-842. doi:10.1034/j.1398-9995.1999.00134.x PubMed
- [54] Verstege A, Mehl A, Rolinck-Werninghaus C, Staden U, Nocon M, Beyer K, Niggemann B. The predictive value of the skin prick test weal size for the outcome of oral food challenges. *Clin Exp Allergy*. 2005; *35*: 1220-1226. doi:10.1111/j.1365-2222.2005.2324.x PubMed
- [55] Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol*. 2004; *4*: 379-385.
- [56] Werfel T, Erdmann S, Fuchs T, Henzgen M, Kleine-Tebbe J, Lepp U, Niggemann B, Raithe M, Reese I, Saloga J, Vieths S, Worm M, Zuberbier T. Vorgehen bei vermuteter Nahrungsmittelallergie bei atopischer Dermatitis. *Allergo J*. 2008; *17*: 476-483.
- [57] Werfel T, Reese I. Diätetik in der Allergologie. Diätvorschläge, Positionspapiere und Leitlinien zur Nahrungsmittelallergie und anderen Unverträglichkeiten. 3. Auflage. München – Orlando: Dustri; 2010.
- [58] Worm M, Hompes S, Fiedler EM, Illner AK, Zuberbier T, Vieths S. Impact of native, heat-processed and encapsulated hazelnuts on the allergic response in hazelnut-allergic patients. *Clin Exp Allergy*. 2009; *39*: 159-166. doi:10.1111/j.1365-2222.2008.03143.x PubMed
- [59] Wüthrich B. Zur Nahrungsmittelallergie: Begriffsbestimmung, Diagnostik, Epidemiologie, Klinik. *Schweiz Med Wochenschr*. 1996; *126*: 770-776. PubMed
- [60] Zuberbier T, Pfrommer C, Specht K, Vieths S, Bastl-Bormann R, Worm M, Henz BM. Aromatic components of food as novel eliciting factors of pseudoallergic reactions in chronic urticaria. *J Allergy Clin Immunol*. 2002; *109*: 343-348. PubMed

Prof. Dr. med. B. Niggemann
 Pädiatrische Allergologie und Pneumologie
 Hedwig-von-Rittberg-Zentrum
 DRK-Kliniken Westend
 Spandauer Damm 130
 D-14050 Berlin
 e-mail: b.niggemann@drk-kliniken-berlin.de