

Dietary prevention of allergic diseases in infants and small children.

Part II: Evaluation of methods in allergy prevention studies and sensitization markers. Definitions and diagnostic criteria of allergic diseases*

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The role of primary prevention of allergic diseases has been a matter of debate for the last 40 years. In order to shed some light into this issue a group of experts of the Section of Pediatrics EAACI critically reviewed the existing literature on the subject. The design of observational and interventional studies was evaluated with relevance to the important factors influencing outcome of studies on allergy development/prevention. In this analysis the statements of evidence as defined by WHO were applied. Best evidence of recommendations are those fulfilling the criteria for statements category 1 and 2 and grade of recommendations A and B as proposed by WHO. This survey include target group for dietary prevention and methods and diagnostic criteria of atopic dermatitis, asthma and food allergy for prevention studies.

*An extensive review by an expert group set up by the Section on Pediatrics, European Academy of Allergology and Clinical Immunology.

Antonella Muraro¹, Sten Dreborg², Susanne Halken³, Arne Høst⁴, Bodo Niggemann⁵, Rob Aalberse⁶, Syed H. Arshad⁷, Andrea von Berg⁸, Kai-Håkon Carlsen⁹, Karel Duschén¹⁰, Philippe Eigenmann¹¹, David Hill¹², Catherine Jones¹³, Michael Mellon¹⁴, Göran Oldeus¹⁵, Arnold Oranje¹⁶, Cristina Pascual¹⁷, Susan Prescott¹⁸, Hugh Sampson¹⁹, Magnus Svartengren²⁰, Yvan Vandenplas²¹, Ulrich Wahn²¹, Jill A. Warner¹³, John O. Warner¹³, Magnus Wickman²² and Robert S. Zeiger¹⁴

¹Department of Pediatrics, University of Padua, Padua, Italy, ²ESPACI Past President, Lerum, Sweden, ³Department of Pediatrics, Sønderborg Hospital, Sønderborg, Denmark, ⁴Department of Pediatrics, Odense University Hospital, Odense, Denmark, ⁵Department of Pneumology and Immunology, University Children's Hospital Charité, Humboldt University, Berlin, Germany, ⁶Department of Allergy CLB, Amsterdam, The Netherlands, ⁷Clinical Allergy Research Unit, St Mary's Hospital, Newport, Isle of Wight, UK, ⁸Marien-Hospital, Abt. für Kinderheilkunde, Wesel, Germany, ⁹Voksentoppen National Centre of Asthma, Allergy and Chronic, Lung Diseases in Children, Oslo, Norway, ¹⁰Department of Paediatrics, University Hospital Linköping, Linköping, Sweden, ¹¹Allergologie/Pediatrie, University of Geneva, Geneva, Switzerland, ¹²Department of Allergy, Royal Children's Hospital, North Melbourne, Vic., Australia, ¹³Child Health, Level G (803) Centre Block, Southampton General Hospital, Southampton, UK, ¹⁴Kaiser Permanente San Diego, San Diego, CA, USA, ¹⁵Department of Paediatrics, County Hospital Ryhov, Jönköping, Sweden, ¹⁶Department of Dermatology and Venerology, University Hospital (Sophia) Rotterdam, Rotterdam, The Netherlands, ¹⁷Servicio de Alergia, Hospital Infantil Universitario La Paz, Madrid, Spain, ¹⁸Department of Paediatrics, University of Western Australia, Subiaco, WA,

Australia, ¹⁹Department of Pediatrics, Division of Allergy and Immunology, Mount Sinai School of Medicine, Mount Sinai, New York, NY, USA, ²⁰Department of Public Health Sciences, Division of Occupational Medicine, Karolinska Hospital, Stockholm, Sweden, ²¹A.Z.-Kinderen, Free University of Brussels, Brussels, Belgium, ²²Department of Environmental Health, Karolinska Hospital, Stockholm, Sweden

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Antonella Muraro, MD, PhD, Department of Pediatrics, University of Padua, Via Giustiniani 3, 35128 Padua, Italy
Tel.: +39 049 8213505-06, +39 049 8212538
Fax: +39 049 8213509
E-mail: muraro@pediatria.unipd.it

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Methods in allergy prevention studies

Design of observational and interventional studies

Epidemiologic studies can be carried out with different designs. A proper design is crucial for any conclusions drawn from the study. The study design of both non-interventional and interventional studies should be true prospective studies including well-defined inclusion criteria (unselected vs. selected high-risk infants), predefined outcome measures, investigations both at fixed intervals and in case of symptoms, well-defined diagnostic criteria, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation (Table 1). Additionally, interventional studies should include, double blinding, and a control for confounders as well as documentation of compliance and outcomes of dropouts. Most importantly, adequately concealed random allocation in clinical trials should be guaranteed (1–3).

Due to recall bias, selection bias, retrospective studies should not be used for evaluation of predictive/risk factors for development of allergic diseases. Likewise, cross-sectional studies are not suitable for the assessment of cause–effect relationships between exposure to allergens/adjuvant factors and development of allergic diseases (Table 2). Prospective cohort studies including non-selected infants may be useful for the generation of hypotheses for possible determinants of atopic sensitization as well as clinical

manifestations and chronicity of certain phenotypes of diseases. These studies may help to identify modifiable risk factors and their potential role for prevention.

Prospective intervention studies are necessary to document a possible cause–effect relationship and to demonstrate an effect of preventive measures. In order to evaluate the effect of primary preventive measures birth cohorts must be studied (Table 2).

It is important to be aware of potential differences and confounders including geographic area, ethnicity, season, hospital material, age, methods of recruitment (consecutive patients or self-selection?) and dropouts.

Before the initiation of a prospective longitudinal cohort study it is essential to do a power analysis on the basis of expected outcomes during the observation period. Population-based 1-year birth cohorts are preferable, both in case of selected and non-selected cohorts – in order to adjust for seasonal influences. Selected cohorts require precise definition of inclusion criteria (Table 1).

Best evidence for recommendations

The randomized controlled trial is traditionally the gold standard for judging the benefits of treatment/intervention mainly because it is conceptually easier to attribute any observed effect

Table 1. Important factors influencing outcome of studies on allergy development/prevention

Table 2. Assessment of cause–effect relationships between exposure to allergens/adjuvant factors and the development of allergic disease. Evaluation of different kinds of studies

Study	Utility
Retrospective	Not useful*
Cross-sectional	Not useful*
Prospective non-interventional	Generation of hypotheses
Prospective interventional	Proper confirmation

*May be useful for generation of hypothesis in some cases.

Table 3. Statements of evidence (4)

Ia	Evidence obtained from meta-analyses of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies (including retrospective and cross-sectional studies)
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Table 4. Grades of recommendations (4)

A.	Requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation (evidence levels Ia, Ib)
B.	Requires the availability of well-conducted controlled clinical studies without randomization (evidence levels IIa, IIb)
C.	Requires evidence obtained from well-designed descriptive studies, comparative studies, correlation studies and case studies (evidence level III)
D.	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (level IV)

to the treatment/intervention being compared. In contrast, in non-randomized observational studies, the outcomes may be caused by differences among people being given the two treatments/interventions. Such unrecognized confounding factors can always interfere with attempts to correct for identified differences between groups. Therefore a hierarchy of evidence, with randomized controlled studies at the top, controlled observational studies in the middle, and uncontrolled studies and opinions at the bottom have been proposed (1, 4). The World Health Organization (WHO) has followed these considerations in the recommendations regarding statements of evidence (Table 3) and grades of recommendations (Table 4). Thus, for practical purposes recommendations on allergy prevention should primarily be based on the results of randomized controlled studies on condition that the demands of high quality as described above are fulfilled. However, high-quality observational studies may extend evidence over a wider population and are likely to be dominant in the identification of risk factors/predictive factors and when randomized controlled studies are unethical or logistically impractical (1). An excellent example is the assessment of allergy preventive effect of breastfeeding. Randomization to breastfeeding or formula feeding is both unethical and impossible. Another example is the assessment of the effect of exposure to tobacco smoking, as it is impossible to randomize exposure to tobacco smoke. In spite of attempts to adjust for the influence of such factors in studies on allergy development/prevention, there will always be some uncertainty on the validity of the results. Furthermore, some possible confounding factors, e.g. tobacco smoking, breastfeeding and socio-economic status seem to be interrelated, making statistical adjustment difficult.

Definition of inclusion criteria, selected vs. non-selected cohorts

Allergic diseases are complex and multifactorial. The development and phenotypic expression of allergic diseases depends upon an interaction between genetic and environmental factors. At present, it is estimated that genetic factors account for around 50–70% of asthma and allergy (5). Although it is well documented that atopic heredity is associated with an increased risk for development of allergic diseases (6–8), it has also been demonstrated that many children who develop ‘atopic’ diseases during the first years of life come from families without an atopic heredity (6, 9).

Table 5. Different definitions of allergic heredity

- First-degree relative(s) with allergic disease
 - Definition of allergic disease?
 - Self-reported/physician diagnosed?
 - Confirmed by allergy test?
- Single
 - One parent or sibling?
 - One parent and/or one or more sibling(s)?
- Double
 - Both parents (biparental)
 - One parent and one sibling
- Allergic heredity combined with elevated cord blood IgE (cut-off value ?)

Varying definitions of high-risk infants have been used (Table 5), but according to a recent joint statement (10) high-risk infants are defined as infants with a well-defined increased risk of developing allergic disease; that is, infants with at least one first-degree relative (parent or sibling) with documented allergic disease. In some studies 'high-risk' has been defined as double parental heredity or single heredity (parent or sibling) combined with elevated cord blood immunoglobulin E (IgE).

Target population

Preventive measures may include both avoidance of allergen and adjuvant exposure and promotion of protective factors, pharmacologic agents, and immune modulation. Considering that environment and genetics differ in different parts of the world, preventive measures may differ between affluent and non-affluent groups. Some preventive measures may be beneficial for the general population and supplementary measures may be beneficial and recommendable only for high-risk individuals. Different preventive approaches may be needed for prevention of the different forms of allergic diseases and for atopy/IgE-mediated immunologic symptoms. Therefore, preventive measures may address the general population, children at risk for development of allergic disease (high-risk infants), children with early allergic symptoms or children with chronic disease. In fact it would be surprising if the same preventive measures would prevent diseases with different mechanisms.

Sensitization markers

Sensitization is often studied in epidemiologic trials investigating the natural course and effects of intervention in food/cow's milk and even inhalant allergy in infants. *Immunologically*, sensitization means any sign of influence of an antigen on the immune system, e.g., by inducing T-cell proliferation, or production of specific

IgG, IgA, IgE antibodies (IgE-Ab) or any other specific response.

Clinically, however, sensitization means induction of allergen-specific IgE response. It also means signs of 'non-IgE-mediated' allergy although markers for such sensitization are still not fully defined (11). Therefore, the definition of markers of sensitization used in this paper is the demonstration of the presence of IgE-Ab in, e.g., serum, cord blood, or other body fluid or by skin tests demonstrating the presence of allergen-specific IgE on skin mast cells.

Thus to demonstrate IgE sensitization there are mainly two methods available for epidemiologic studies in infants and young children, i.e.:

1. Determination of specific IgE-Ab in serum.
2. The skin prick test (SPT). Other skin test methods are painful (intradermal skin test) and less reliable (intradermal skin test and scratch test) (12).

For both IgE-Ab (13) and SPT, quality control techniques have been published (12, 14). Too often such methods are not used in epidemiologic studies in children, a fact that makes it difficult to compare figures on sensitization.

Other tests such as basophil histamine release, i.e. *in vitro* demonstration of IgE-Ab on basophils, is more complicated for routine investigation, but may be a helpful tool in certain cases (15).

There are some main problems, which must be considered:

1. The relevance, potency, composition and other properties of the allergenic material used.
2. The technique used for performance of the test: precision, variation between investigators/laboratory assistants/equipment, etc.
3. The influence of the technique on possible differences in the frequency of sensitization over time and between locations.
4. Definition of a cut-off for a positive test used.

The first point has, unfortunately, not been taken care of by all manufacturers.

It is complicated to demonstrate consistency over time of epitopes available on the solid phase of serum concentration of IgE (S-IgE) tests. *In vitro* IgE tests have been improved continuously (13). This is beneficial from a diagnostic point of view, but has limitations when it comes to comparison between trials performed at different times by different investigators. Even the use of the same brand does not assure comparable results over time. The simple solution is to save serum sample aliquots in the freezer (-20°C) and

test all samples at the same time after the trial. This procedure will ensure a precision in the order of 10–15%.

It is most important that information is given in detail on all possible properties of allergenic material for skin prick test (SPT), as the composition and potency of the material varies even within the same brand. The EAACI position paper on allergen standardization and skin tests (16) differs between units, which can be reproduced, and ‘manufacturers units’, i.e. units defined by manufacturers without published results on the repeatability. However, extracts with the potency given in µg of major allergen/ml produced by different manufacturers can only be compared provided the products are analyzed with the same method by the same laboratory.

Fresh food in combination with the prick–prick skin test method has been proposed (17), recommended (12, 18), and is often used. It is most important to clearly define the raw material to make it possible to repeat the procedure in other centers. Many studies have been performed without knowing the potency (19) making reproducibility difficult (20).

Only using S-IgE tests with well-documented properties will minimize variability.

Inherent problems exist for SPT reproducibility. Special precautions must be taken to document the precision of the SPT test. By giving the coefficient of variation (c.v.), i.e. by using duplicate tests with all materials in all patients, which can be difficult in infants and children, is it possible to evaluate the SPT technique. Similar technique between centers should be documented by repeated histamine tests in the same patients at the same time (14). The c.v. of the median wheal size and the 95% confidence interval of the median, should be calculated. No difference should be found by 95% confidence interval. Only then is there a possibility to compare results from one trial with those from another trial (14). There are a few such studies (21). If these points are not fully considered, there is no possibility to compare results from time to time or between centers (22, 23).

Sensitization means induction of IgE-Ab, but some investigators claim that they do not consider all IgE ‘clinically relevant’ and therefore do not consider low specific IgE-Ab levels positive. However, leading manufacturers spike with high levels of non-specific IgE (thousands of kU_A/l) in their laboratories to assure that the levels above the given cut-off for the test are not false-positive (13). However, in patients with multiple sensitizations, it might be that low levels of allergen-specific IgE are of low or no clinical importance.

But that has nothing to do with the question whether the patient has been sensitized or not, i.e. stimulated to produce specific IgE-Ab against the antigen or not.

Due to differences in cut-off values for sensitization used by different investigators (specific IgE-Ab class 1 or 2), it is difficult to compare results.

Conclusion

To compare sensitization between trials and over time, it is recommended to use *in vitro* IgE-Ab tests with documented cut-offs and declaration of the properties of the product. SPT techniques should adhere to well-defined recommendations. In clinical trials determination of specific IgE-Ab in serum is preferable to SPT. It is recommended:

- To use *in vitro* IgE-Ab tests on stored samples (frozen at –20°C) if possible, or
- To use SPT with a 3-mm wheal diameter with an extract with known composition and potency and standardized SPT technique.

Sensitization markers should be used to document possible IgE association of symptoms reported or diagnosed in the family and in study infants at fixed predetermined time-points and when symptoms appear.

Definitions and diagnostic criteria of allergic diseases

Eczema

In a recent position paper on a revised nomenclature for allergy the term ‘eczema’ (E) was proposed (11). According to this nomenclature E was divided into atopic and non-atopic E (Fig. 1). Almost invariable constant features of E are dry skin, pruritus, and relapses and remissions and a chronic course. The features are age related, and different diagnostic criteria seem appropriate above (24) and below 2 years of age (25–30).

For future studies we need standardized and validated criteria for the study of E to guarantee comparable results. Evaluation of severity of disease of E may be helpful using a validated scoring system, e.g. the SCORAD (31). The criteria for E by Williams et al. (26–28) are validated for epidemiologic and clinical studies.

For clinical studies the criteria by Williams et al. can be used in children older than 2 years (Table 6). In young children below 2 years the Sampson/Oranje criteria (Table 7) are advised

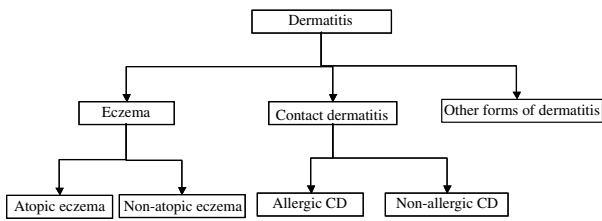


Fig. 1. Eczema in the new revised nomenclature.

Table 6. Diagnostic criteria for eczema (26–28)

<p>Must have</p> <ul style="list-style-type: none"> • An itchy skin condition (or report of scratching or rubbing in a child) <p>Plus three or more of the following</p> <ul style="list-style-type: none"> • History of flexural involvement (or the cheeks in children under 4 years) • History of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4 years) • General dry skin in the past year • Visible flexural eczema (or eczema affecting the cheeks or forehead and outer limbs in children under 4 years) • Onset in the first 2 years of life (not used in children under 4 years)

Table 7. Diagnostic criteria for eczema (<2 years) according to Sampson 1990, slightly modified by Oranje 1995

<p>Major features</p> <ul style="list-style-type: none"> • Evidence of pruritic dermatitis • Typical facial or extensor eczematous or lichenified or nummular dermatitis • Eczema-free skin of nose–mouth area and or diaper area • Family history of AEDS <p>Minor features</p> <ul style="list-style-type: none"> • Xerosis/ichthyosis/hyperlinear palms • Peri-auricular fissures • Chronic scalp scaling • Perifollicular accentuation
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At least two major and two minor criteria must be present.

and for epidemiologic studies the ‘three-item severity’ (TIS) score is useful (32).

Asthma

The diagnosis of bronchial asthma is a clinical diagnosis, based upon the occurrence of recurring episodes of bronchial obstruction. According to the most recent international definition, airways inflammation is an important part of asthma as is the variation in lung function, occurring either spontaneously or after bronchodilating drugs (33). When allergy is diagnosed and found to have influence upon asthma, allergic asthma is diagnosed. In schoolchildren approximately 60–90% of the asthmatic children are found to be allergic (34).

In epidemiologic studies it has been common to use positive answers to questions like: ‘Has

your child ever had asthma?’ as a diagnostic marker of asthma. Alternatively, asking for symptoms, and in particular of wheeze, has been used as a definition of asthma (35). However, such questionnaire-based criteria may cause an over-diagnosis of asthma. Optimally such symptoms should be witnessed by a physician or use of video should ensure correct labeling of respiratory sounds as wheeze or not (36, 37).

In schoolchildren the diagnosis of asthma may be verified by the objective registration of variation in lung function. Daily variation in peak expiratory flow (PEF) rate has been noted as a diagnostic marker of asthma, but it may not be optimal in diagnosing or monitoring childhood asthma (38). A generally accepted criteria for diagnosing asthma is an increase in forced expiratory volume in 1 second (FEV₁) ≥ 12% after inhalation of a suitable bronchodilator. In preschool children measurements of reversibility by simple means of lung function (tidal breathing, Rint) may be employed (39, 40).

It is recommended that the diagnosis of asthma in observational or interventional studies is based on a careful history and clinical examination. As a criterion for asthma, three episodes of bronchial obstruction can be employed. These episodes should preferably be verified by examination by a physician during at least one of the episodes. Further characterization can be made, at least in older children, by objective measurements of lung function, reversibility to inhaled β₂ agonist or by measuring either indirect or direct bronchial responsiveness, but not as a substitution of a clinically based diagnosis of asthma (Table 8).

Food allergy

According to a revised nomenclature for allergy (11) food hypersensitivity can be divided into food allergy and non-allergic food hypersensitivity, with the former subdivided into IgE- and non-IgE-mediated food allergy (Fig. 2). No symptoms are pathognomonic for food allergy and no single laboratory tests are diagnostic for food allergy. Therefore, the diagnosis has to be based on controlled elimination and challenge procedures. Allergy testing may be helpful in identifying relevant food allergens and the challenge procedure when a clear-cut case history is lacking.

The diagnostic work-up of suspected food allergy includes SPT (12), the measurement of food-specific IgE-Ab using serologic assays (41, 42), and more recently the atopy patch test (APT) (43–45). While immediate type clinical reactions to food can quite easily be identified by

Table 8. Levels of asthma diagnosis

- Questionnaire data
- Case history and clinical examination
- Variation in lung function, spontaneously or due to therapy

Supported by

Bronchial responsiveness

Direct

Inhaled metacholine

Inhaled histamine

Indirect

Exercise test

Cold air with or without simultaneous exercise

Hypotonic saline

Inhaled adenosine monophosphate

Inhaled mannitol

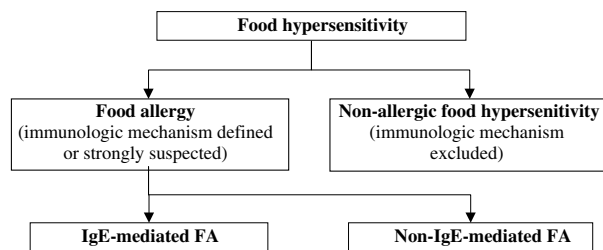
Inflammation markers?

Fig. 2. Food hypersensitivity.

history or measurement of specific IgE in combination with positive oral food challenges, late phase reactions still present diagnostic difficulties – particularly in polysensitized children with atopic dermatitis (46). The ‘gold standard’ of diagnosing food allergy is therefore still properly performed double-blind, placebo-controlled oral food challenges (DBPCFC)(41, 42, 47, 48).

Indication for food allergy evaluation. At suspected (persistent/relapsing) symptoms of food allergy from the skin, the gastrointestinal or the respiratory tract an evaluation for food allergy should be carried out, but only on the condition that other relevant differential diagnoses have been ruled out (Table 9).

Diagnostic elimination and challenge procedures.

Controlled elimination/challenge tests are mandatory for the diagnosis, which is based on:

- symptoms on a diet containing suspected foods,
- disappearance of symptoms on elimination diet,
- recurrence of identical symptoms after controlled challenge,
- exclusion of lactose intolerance and coincidental infection.

Table 9. Characteristics of food allergy

- Persistent or reproducible symptoms
- Symptoms related to food intake
- Allergic predisposition
- Often ≥ 2 different symptoms
- Often symptoms in ≥ 2 different organs

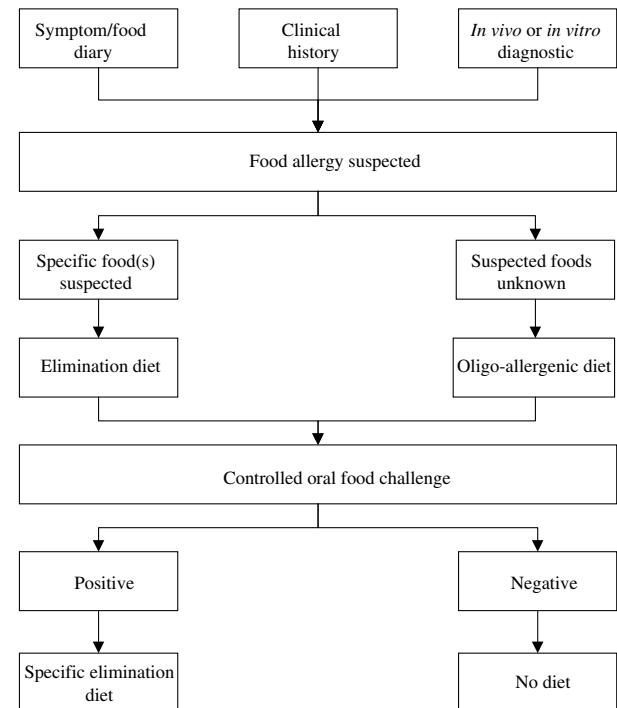


Fig. 3. Proposal for a standardized procedure when food allergy is suspected.

The purpose of the elimination diet is to reduce/eliminate symptoms in order to allow an evaluation of a food challenge.

Proposal for standardized procedure at suspicion of food allergy is shown in Fig. 3.

Baseline diet. At least 2 weeks before the oral challenges and during the challenge procedure, all infants should be fed with an appropriate elimination diet excluding the relevant food item(s). Oligoantigenic diet is sometimes needed. Young infants with suspicion of food allergy are treated in the same way receiving an elimination diet avoiding cow’s milk proteins, and in that case an extensively hydrolyzed formula or an amino acid based formula can be used as a substitute for cow’s milk.

Medication. Antihistamines should be completely withheld and stopped at least 72 hours prior to challenge. If topical glucocorticosteroids

are needed, they should be allowed up to twice daily at a concentration of 1% hydrocortisone or 0.01% β -methasone. The most important point is, to keep any medication stable during the entire challenge procedure. In case of ongoing medication false-negative reactions should be considered. No β_2 agonists for 8–12 hours prior to challenge. Long acting β_2 agonists should be withheld at least 36 hours before challenge. Leukotriene antagonists should be withheld at least 1 week before challenge.

Choice of allergens. Fresh foods should be preferred, e.g., fresh pasteurized cow's milk, hen's egg, soymilk or wheat.

Titration steps. Depending on the severity of reaction intervals and increments of dose may be changed. An example of titration of dose is as follows: every 20 min successive doses (0.1, 0.3, 1.0, 3.0, 10.0, 30.0 and 100.0 ml). Raw hen's egg should be given in a similar way except that the highest dose is omitted. In case of risk of *Salmonella* infection, heat-treated raw hen's egg should be used.

Highest administered dose. If no clear reaction is observed, the total amount of allergen should represent an average meal, e.g., one hen's egg, 100 ml cow's milk or soy milk or, 5 g of wheat protein (wheat-gliadin) equaling two to three slices of bread. Negative reactions should be documented by continued open challenge for 1 wk.

Open or blind challenges? In suspected clinical early type reactions, it may be justified to perform open challenges in a controlled manner in a specialist setting, especially in infancy. In older children DBPCFC should be preferred. Open challenges may also be used in case of objective observable anaphylactic reactions. In case of equivocal or subjective reactions DBPCFC should always be performed.

Relation of placebo and allergen. The relation of placebo to allergen should be at least be 1:2. Challenges with 'active food'/placebo are performed in a randomized order and planned free intervals of at least 1 day. Possible symptoms related to previous challenge should be gone before continuation of the challenge schedule.

Stopping the challenge. The provocation should be stopped if clear clinical symptoms are observed or the highest dose is reached. The

food challenges should be scored as positive by a trained pediatric allergy specialist if one or more of the following objective clinical reactions are noted: urticaria, angioedema, wheezing, vomiting, diarrhea, abdominal pain, shock or exacerbation of eczema. Minor symptoms (such as single vomiting) should be followed by the next titration dose.

Early and/or late clinical reactions. Early reactions are defined as clinical symptoms within 2 hours after administering the highest dose, late ones if symptoms occur after more than 2 hours.

Safety measures. Full emergency equipment with adrenaline, antihistamines, glucocorticosteroids, and β_2 -agonists should be at hand (49). The personnel should be regularly trained to cope with severe reactions.

Documentation. All results should be documented on a form and signed by the responsible physician (1) at 24 hours (2) at 48 hours and (3) after 1 week for a few patients with suspected late reactions.

Conclusion

Standardized oral food challenges should be used to show whether or not symptoms appearing in observational and interventional studies are elicited by the food under study.

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Appendix 1. Definitions

Full name	Definition
Atopy	A personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis or eczema/dermatitis
Allergic diseases	The clinical manifestation of allergy
Allergy	A hypersensitivity reaction initiated by immunologic mechanisms
Allergenicity	The ability to stimulate an IgE response and induce IgE-mediated reactions
Antigenicity	Ability to stimulate an immune response
Cow's milk allergy	An immunologically mediated hypersensitivity reaction to cow's milk, including IgE-mediated and/or non-IgE-mediated allergic reactions
Eczema	Replaces the provisional term 'AEDS' and most countries the older term 'atopic dermatitis (AD)'
Food allergy	An immunologically mediated hypersensitivity reaction to any food, including IgE-mediated and/or non-IgE-mediated allergic reactions
Partly hydrolyzed formula	A formula with moderately reduced allergenicity*
Extensively hydrolyzed formula	A formula with extensively reduced allergenicity*
Hypersensitivity	Objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects
Hypoallergenic	With reduced allergenicity† both IgE and non-IgE-mediated allergenicity
Hypoallergenic formula for treatment	A formula with low allergenicity tolerated with 95% confidence by 90% of CMA patients
IgE-mediated allergy	An allergy with proven IgE-mediated reaction
Non-IgE-mediated allergy	An allergy (immunologically mediated hypersensitivity reaction) without involvement of IgE. In food allergy probably T-cell-mediated
Sensitization, immunologic	Any immune response to a foreign antigen
Sensitization, IgE-mediated	An IgE response to foreign antigen (allergen), as measured by <i>in vitro</i> IgE determination or SPT
Sensitization, non-IgE-mediated allergy	A reactivity toward allergen as measured by cell stimulation or APT

*Commission of the European Communities. Commission directive 96/4 EC of 16 February 1996 amending directive 91/321/EEC on infant formulae and follow-on formulae. *Official Journal of the European Commission* 1996; 39: 12–16.

†Reduced allergenicity is defined as: content of immunoreactive protein of <1% of nitrogen containing substances.