POSITION PAPER

EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy

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Abbreviations

APT, atopy patch test; BAT, basophil activation test; CRD, component-resolved diagnosis; DBPCFC, double-blind, placebo-controlled food challenge; EAACI, European Academy of Allergy and Clinical Immunology; EoE, eosinophilic esophagitis; FA, food allergy; FPIES, food protein-induced enterocolitis syndrome; GERD, gastroesophageal reflux disease; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IgE, immunoglobulin E; IgG4, immunoglobulin G4; LR, likelihood ratio; LTP, lipid-transfer proteins; NIAID, National Institute of Allergy and Infectious Diseases; NPV, negative predictive value; NSAID, nonsteroidal anti-inflammatory drugs; OFC, oral food challenge; PPV, positive predictive value; RCTs, randomized controlled trials; sIgE, specific IgE; SLIT, sublingual immunotherapy; SPT, skin prick test; US, United States.

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Abstract

Food allergy can result in considerable morbidity, impact negatively on quality
of life, and prove costly in terms of medical care. These guidelines have been
prepared by the European Academy of Allergy and Clinical Immunology's
(EAACI) *Guidelines for Food Allergy and Anaphylaxis Group,* building on pre-
vious EAACI position papers on adverse reaction to foods and three recent
systematic reviews on the epidemiology, diagnosis, and management of food
allergy, and provide evidence-based recommendations for the diagnosis and
management of food allergy. While the primary audience is allergists, this doc-
ument is relevant for all other healthcare professionals, including primary care
physicians, and pediatric and adult specialists, dieticians, pharmacists and para-
medics. Our current understanding of the manifestations of food allergy, the
role of diagnostic tests, and the effective management of patients of all ages
with food allergy is presented. The acute management of non-life-threatening
reactions is covered in these guidelines, but for guidance on the emergency
management of anaphylaxis, readers are referred to the related EAACI Ana-
phylaxis Guidelines.

Food allergy has been defined as adverse reactions to food in
which 'immunologic mechanisms have been demonstrated' (1,
2); this term therefore encompasses both immunoglobulin E
(IgE)-mediated and non-IgE-mediated food allergies
(Tables 1 and 2). Food allergy can result in considerable
morbidity and in some instances results in life-threatening

Table 1 Key terms (85)

Allergen	Any substance stimulating the production of immunoglobulin IgE or a cellular immune response, usually a protein
Atopic eczema/dermatitis	Chronic inflammatory skin disease characterized by typical age-related lesions with pruritus and personal or family history of atopic disease
Cofactors	Patient-related external circumstances that are associated with more severe allergic reactions. They are known also as augmentation factors
Eosinophilic esophagitis	A chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation
Food	Any substance, whether processed, semi-processed, or raw, which is intended for human consumption, and includes drink, chewing gum, and any substance which has been used in the manufacture, preparation, or treatment of 'food' but does not include cosmetics or tobacco or substances used only as drugs (Codex Alimentarius)
Food allergy	An adverse reaction to food mediated by an immunologic mechanism, involving specific IgE (IgE-mediated), cell-mediated mechanisms (non-IgE-mediated) or both IgE- and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated)
Food desensitization	Induction of short-term tolerance that may disappear after withdrawal of the treatment
Oral tolerance	A state of local and systemic immune unresponsiveness induced by oral administration of innocuous antigens/allergens
Oligo-allergenic diet	An empirical elimination diet with minimal content of major food allergens for the given population
Oral tolerance induction	A state of local and systemic permanent immune unresponsiveness induced by following oral administration consumption of innocuous antigens such as food proteins, does not disappear after withdrawal of the antigens
Prebiotic	Nondigestible substances that provide a beneficial physiological effect for the host by selectively stimulating the favorable growth or activity of a limited number of indigenous bacteria
Probiotic	Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host
Sensitization	Presence of specific IgE to an allergen
Symbiotics	A mixture of probiotics and prebiotics

Table 2 Food-induced allergic disorders (classified based on the underlying immunopathology)

Immunopathology	Disorder	Clinical features	Typical age group	Prognosis
IgE mediated	Pollen food allergy syndrome	Pruritus, mild edema confined to oral cavity	Onset after pollen allergy established (adult > young child)	May be persistent and may vary by season
	Urticaria/angioedema	Triggered by ingestion or direct contact	Children > adults	Depends on food
	Rhinoconjunctivitis/asthma	Accompanies food-induced allergic reaction but rarely isolated symptoms May be triggered by the inhalation of aerosolized food protein	Infant/child > adult, except for occupational disease	Depends on food
	Gastrointestinal symptoms	Symptoms such as nausea, emesis, abdominal pain, and diarrhea triggered by food ingestion	Any age	Depends on food
	Anaphylaxis	Rapid progressive, multisystem reaction	Any age	Depends on food
	Food-dependent, exercise-induced anaphylaxis	Food triggers anaphylaxis only if ingestion is followed temporally by exercise	Onset in late childhood/adulthood	Presumed persistent
Mixed IgE and cell mediated	Atopic eczema/dermatitis	Associated with food in 30–40% of children with moderate/severe eczema	Infant > child > adult	Usually resolves
	Eosinophilic gastrointestinal disorders	Symptoms vary depending on the site of the intestinal tract involved and degree of eosinophilic inflammation	Any age	Likely persistent
Cell mediated	Dietary protein-induced proctitis/proctocolitis	Mucus-laden, bloody stools in infants	Infancy	Usually resolves
	Food protein-induced enterocolitis syndrome	Chronic exposure: emesis, diarrhea, poor growth, lethargy Re-exposure after restriction: emesis, diarrhea, hypotension a couple of hour after ingestion	Infancy	Usually resolves

Modified from Sicherer and Sampson (86) with permission.

anaphylaxis. These guidelines aim to provide evidence-based recommendations for the diagnosis and management of patients of any age with suspected or confirmed food allergy. Development of the guidelines has been based on three systematic reviews of the epidemiology, diagnosis, and management of food allergy (3–5) with weaker forms of evidence being used where there were insufficient data from more robust studies or where high-level evidence is practically or ethically unobtainable. These guidelines build on the previous EAACI position paper on adverse reaction to foods (6) and are complementary to the other current food allergy guidelines, including the United States (US) National Institute of Allergy and Infectious Diseases (NIAID) Guidelines (7). Distinctive features include a European focus and the placing of particular emphasis on the practical issues associated with diagnosis and long-term management of food allergy. Details on the production of these guidelines, the approaches used, and the involvement of experts and stakeholders are summarized in the Data S1 and Table S1 (Box 1).

Epidemiology

To estimate the incidence and prevalence, time trends, and potential risk and prognostic factors for food allergy in Europe, we conducted a systematic review of recent (i.e.,

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> **Box 1:** Key questions addressed in the supporting systematic reviews: diagnosis and management (3–5)
>
> - What is the epidemiology (i.e., frequency, risk factors, and outcomes) of food allergy in Europe and how does this vary by time, place, and person?
> - What is the diagnostic accuracy of tests aimed at supporting the clinical diagnosis of food allergy?
> - What is the effectiveness of pharmacological and nonpharmacological interventions for the management of acute, non-life-threatening food-allergic reactions?
> - What is the effectiveness of pharmacological and nonpharmacological interventions for the longer-term management of food allergy?

2000–2012) European studies (3). One hundred and nine articles were assessed for eligibility, and 75 (comprising 56 primary studies) were included in a narrative synthesis and 30 studies in a meta-analysis. Most of the studies were graded as at moderate risk of bias.

A summary of the key findings is presented in Table 3. The point prevalence of self-reported food allergy was approximately six times higher than the point prevalence of challenge-proven food allergy. The prevalence of food allergy

Table 3 Summary of the pooled prevalence of food allergy (FA) in Europe, by age and region: studies published January 1, 2000–September 30, 2012*

	Self-reported food allergy		Sensitization to at least one food allergen (point prevalence)		Symptoms + sensitization to at least one food allergen (point prevalence)		Convincing clinical history or positive food challenge† (point prevalence)	Positive open food challenge or DBPCFC† (point prevalence)
	Life time prevalence	Point prevalence	Positive specific IgE	Positive skin prick test	Symptoms + positive specific IgE	Symptoms + positive skin prick		
All	17.3 (17.0–17.6)	5.9 (5.7–6.1)	10.7 (9.4–10.8)	3.0 (2.7–3.3)	2.7 (1.7–3.7)	1.5 (1.3–1.7)	2.6 (2.1–3.1)	0.9 (0.8–1.1)
Age								
Children (0–17 years)	17.4 (16.9–18.0)	6.9 (6.6–7.2)	12.2 (11.4–13.1)	3.0 (2.7–3.3)	3.6 (2.8–4.4)	1.5 (1.3–1.7)	2.6 (2.1–3.1)	1.0 (0.8–1.2)
Adults (≥18 years)	17.2 (16.0–17.6)	5.1 (4.8–5.3)	4.1 (3.2–5.1)	–‡	2.2 (0.8–3.7)	–‡	–‡	0.9 (0.8–1.0)
Region§								
Western Europe	23.8 (22.9–24.7)	3.3 (3.1–3.5)	11.7 (9.8–13.6)	1.8 (1.5–2.1)	2.6 (1.3–3.8)	1.4 (1.1–1.7)	–‡	3.1 (2.6–3.7)
Eastern Europe	41.6 (39.5–43.7)	3.3 (1.2–5.4)	–‡	–‡	–‡	–‡	–‡	–‡
Southern Europe¶	8.6 (8.2–9.0)	3.5 (2.5–4.5)	–‡	4.2 (2.2–6.3)	–‡	1.8 (1.3–2.3)	–‡	0.2 (0.1–0.3)
Northern Europe	30.3 (28.7–31.9)	14.5 (13.9–15.2)	9.8 (9.0–10.5)	5.4 (4.6–6.1)	3.0 (2.1–3.9)	1.6 (0.9–2.3)	2.6 (2.1–3.1)	1.1 (0.9–1.3)
Europe**	19.2 (18.6–19.8)	5.0 (4.6–5.5)	–‡	–‡	–‡	–‡	–‡	–‡

DBPCFC, double-blind, placebo-controlled food challenge.

Figures are percentages (95% CI).

*The pooled prevalence of FA was based on random-effects meta-analysis for 30 clinically and methodologically comparable studies.

†Where a study reported estimates for both open food challenges and DBPCFC, the DBPCFC estimates were always used; otherwise open food challenges estimates were used if DBPCFC was not carried out in the study.

‡No study undertaken for this group for this particular outcome.

§European regions were classified based on the United Nations classification (http://unstats.un.org/unsd/methods/m49/m49regin.htm#europe, accessed on December 28, 2012).

¶We further added studies from Turkey into southern Europe.

**For studies that included several European countries and gave overall estimate for all the countries and in which it was not possible to calculate the frequency for each country studied.

was generally higher in children than in adults. While the prevalence of primary food allergy appeared to be stable over time, the prevalence of secondary food allergy caused by cross-reactions of food allergens with inhalant allergens appears to be increasing. There were no consistent risk or prognostic factors for the development or resolution of food allergy. However, sex, age, country of residence, familial atopic history, and the presence of other allergic diseases may play an important role in its etiology.

Few studies employed double-blind, placebo-controlled food challenge (DBPCFC) in a population-based sample; further studies are therefore required to establish the actual prevalence of objectively confirmed food allergy in the general population. Further studies are also needed to investigate the long-term prognosis of food allergy.

Diagnosis

Patient's clinical history and examination

The clinical presentation of food allergy involves a large spectrum of symptoms ranging from skin (urticaria, angioedema, atopic eczema/dermatitis), gastrointestinal (i.e., vomiting, colic, abdominal pain, diarrhea, constipation),

respiratory (rhinorrhea, sneezing, cough, dyspnea) to circulatory (cardiovascular collapse; see Table 2). Attention should be paid to the fact that reactions can be triggered by food ingestion, inhalation, and skin contact. A careful dietary history is fundamental to the diagnosis of food allergy (see Data S2). It can establish the likelihood of the diagnosis, suggest whether an IgE or non-IgE mechanism is involved, and identify the potential food triggers. A small amount of literature indicates that the predictive value of the clinical history for immediate symptoms, either alone or in combination with skin prick tests (SPT) or serum-specific IgE (sIgE) blood tests, ranges from 50% to 100% (8–10). The clinical evaluation should include a thorough examination of nutritional status and growth, especially in children, as well as associated atopic diseases such as atopic eczema/dermatitis, allergic rhinitis, and asthma.

See *Recommendations Box 2A,B*.

Diagnostic tests for food allergy

In vivo SPT and sIgE for food allergens are the first-line tests to assess IgE sensitization. However, like the patient history, these tests cannot always accurately diagnose food allergy. Elimination diet for diagnostic purposes and oral food

Box 2: EAACI recommendation on the diagnosis of food allergy			
Recommendations	Evidence level	Grade	Key references
(A) Patient's clinical history			
Detailed clinical history is essential for the diagnosis of food allergy	IV	D	Expert opinion
When taking a clinical history eliciting allergens, timing and chronicity, symptoms, severity and signs, reproducibility, known risk (co)factors, family history, coexisting medical problems including other allergic diseases should be addressed	V	D	Expert opinion
The use of structured questions on symptoms, foods, and other background information is recommended	V	D	Expert opinion
(B) Determination of sensitization to food			
Where available, standardized tests and procedures should be used	IV	D	Expert opinion
IgE sensitization does not always predict clinically relevant food allergy, so specific allergy testing should be directed by case history	IV	C	(4)
Either SPT or sIgE can be the test of choice for sensitization depending on local availability and absolute and relative contraindications to SPT	IV	C	(4)
Evidence of IgE sensitization to common food and appropriate aeroallergens can support a diagnosis of food allergy in conjunction with clinical history and/or food challenge	I–III*	A–C	(4)
In the presence of a suggestive history, a negative SPT or sIgE needs to be interpreted with caution particularly as these are expected in non-IgE-mediated food allergy	IV	C	(4)
Where SPT and sIgE tests are inconclusive, component-resolved diagnostic test (if available) may provide additional diagnostic information	I–IV*	A–C*	(4, 22–24)
If clinical history with SPT and/or sIgE results is not *highly predictive* (see figure 1), an OFC is required	IV	D	Expert opinion
Determination of total IgE is particularly useful in patients with severe eczema; a very high total IgE level suggests that positive sIgE results should be interpreted with care as they may represent asymptomatic sensitization	IV	D	Expert opinion
(C) Elimination diets for diagnostic purposes			
Determining which foods to be avoided should be based on the allergy-focused diet history, clinical history, and allergy testing (SPTs and/or sIgE)	V	D	Expert opinion

Box 2: (Continued)

Recommendations	Evidence level	Grade	Key references
For each individually avoided food, the results of the diagnostic elimination diet should be carefully monitored and evaluated over 2–4 weeks of avoidance	V	D	Expert opinion
Where the elimination diet leads to a significant relief of symptoms, it should be continued until the provocation test is performed	V	D	Expert opinion
Where the elimination diet does not lead to a significant relief of symptoms, food allergy to the eliminated foods is highly unlikely	V	D	Expert opinion
(D) Oral food challenge (OFC)			
The OFC (particularly the double-blind placebo-controlled food challenge) is the gold standard investigation for the objective diagnosis of IgE- and non-IgE-mediated food allergy	IV	D	Expert opinion
OFCs should be used to demonstrate allergy or tolerance and in so doing facilitate safe dietary expansion or appropriate allergen avoidance	IV	D	Expert opinion
The DBPCFC should be performed when symptoms are subjective, with delayed or atypical symptoms, where patients and/or caregivers are anxious, and considered in all research settings	IV	D	(18, 20)
A negative DBPCFC should end with an open or cumulative ingestion of the food based on a normal age-appropriate portion to confirm oral tolerance	IV	D	Expert opinion
OFC must be performed in a specialist setting with emergency support immediately available; where there is a moderate-to-high risk of a severe reaction, intensive care support must be immediately available	IV	D	Expert opinion
(E) Diagnosis of EoE			
Every patient with EoE should be referred to an allergist/immunologist for workup	IV	D	(41)
EoE is diagnosed by an upper endoscopy with 2–4 biopsies from both the proximal and distal esophageal biopsies (43). Biopsies should be performed when the patient has been treated for at least 6 weeks with double-dose proton-pump inhibitors to rule out esophageal eosinophilia caused by gastroesophageal reflux disease and to exclude proton-pump inhibitor-responsive esophageal eosinophilia	IV	D	(41, 42)
The clinical utility of measuring serum food sIgE and SPT results to generate a successful elimination diet needs further investigation. Future studies should clearly document a clinical and histologic benefit from dietary interventions guided by results from serum IgE levels, skin prick testing, or atopy patch testing	IV	D	(41)
(F) Unconventional tests, including specific IgG testing			
There are no unconventional tests which can be recommended as an alternative or complementary diagnostic tool in the workup of suspected food allergy, and their use should be discouraged	III	C	(48)

DBPCFC, double-blind, placebo-controlled food challenge; SPT, skin prick test; OFC, oral food challenge; EoE, eosinophilic esophagitis; sIgE, specific IgE.

*For consistency with the EAACI Guidelines on Anaphylaxis, level III-1 to level III-3 for establishing diagnostic test accuracy are summarised as level III in this document.

challenges are still required for both IgE- and non-IgE-mediated food allergy in order to define the clinical relevance of the initial investigations. For some clinical manifestations such as food-induced enteropathies, endoscopy and biopsy are often required to establish the diagnosis. The diagnostic workup of food allergy is summarized in Fig. 1.

Specific IgE: in vitro and skin tests
The determination of sensitization to suspected food allergens includes the assessment of co- and cross-sensitization to related food or aeroallergens. To avoid identifying food allergens where sensitization is seen without clinical relevance, only food and aeroallergens related to the clinical presentation, age, geographic location, and ethnic dietary habits of the patient should be investigated.

Specific IgE and SPT are scientifically valid tests although not all are standardized. Currently, single recombinant protein solutions for SPT are not approved in the EU. However, in some countries, purified natural date profilin and Pru p 3 are available for SPT. Determination of total IgE levels can be helpful in the interpretation of results as very high IgE levels can be associated with multiple positive SPTs or sIgE results that are not clinically relevant.

Skin prick test can be undertaken in patients of any age although reactivity may be lower in infants and possibly the elderly (11). The choice of tests should be guided by the
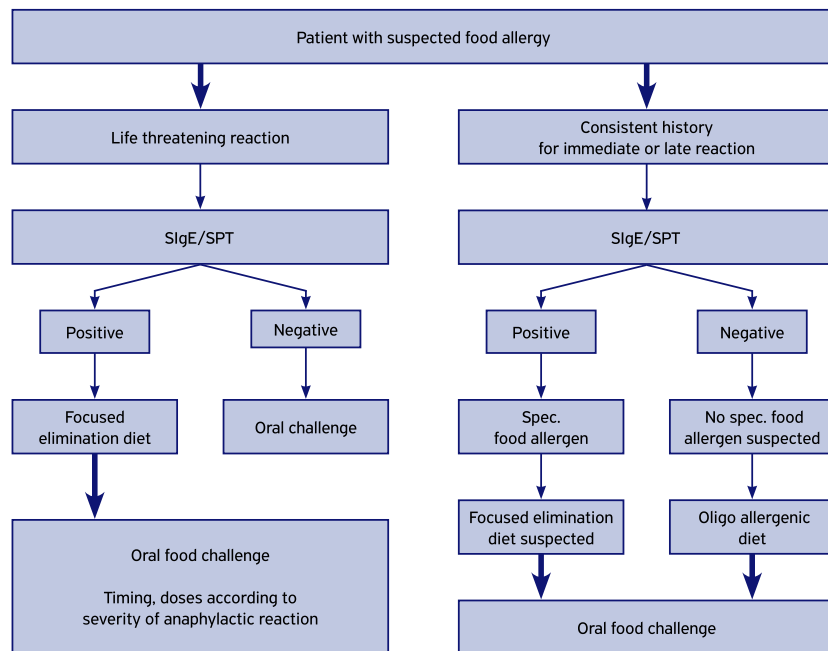
Figure 1 Algorithm for the diagnosis of food allergy.

detailed clinical history. The use of good-quality food allergen extracts, characterized by the demonstration of clinical efficacy and the presence of relevant allergens, is strongly recommended when available. Due to a possible under-representation of minor allergens or instability of the allergenic proteins, false-negative reactions can occur. Whenever these types of extracts are not available and/or minor or instable allergens are relevant for the sensitization (i.e., most fruits and vegetables), fresh foods should be used. Only trained healthcare professionals, able to interpret results and manage possible adverse reactions, should perform SPTs. These tests are performed on the forearm or upper back. Negative (saline 0.9%) and positive (histamine 10 mg/ml) controls are required and the maximum wheal diameter is reported with an arbitrary positive cut-off diameter ≥3 mm after 15 min (12, 13). There are numerous variables to be considered when performing and interpreting SPT including lancet type, recording of wheal diameter, timing, age, sex, and site of testing (12, 14). In addition, it should be considered that European parameters may differ from North American ones. For food allergy, intradermal skin testing is not recommended because of its low specificity, high potential for irritant reactions, and risk for systemic reactions, except in particular situations, for example alpha-gal allergy (15).

In our systematic review, we found reasonable sensitivity (70–100%), although less for most plant food allergies, but moderate specificity (40–70%) both for sIgE and for SPT using the DBPCFC as a reference test (4). Sensitivity and specificity of serum IgE testing and SPT varied depending on the food being tested and due to the heterogeneity of studies with respect to inclusion criteria for patients, their geographic background, and their age and ethnicity, as well as recruitment processes. High-quality performance of these tests is observed for allergens such as peanut, egg, milk,

hazelnut, fish, and shrimp, but less so for soy and wheat (4). For other plant-derived (carrot, celery, kiwi, lupine, maize, and melon) or animal-derived foods (chicken and pork), only single studies were included in the recent systematic analysis.

Specific IgE and SPT tests are good to confirm or rule out the involvement of IgE in (self-)reported food hypersensitivity. Interpretation is improved when presenting features and the magnitude of results are taken into account (see Data S2). However, they are often unable to differentiate between clinically relevant allergy and tolerance and oral challenges are therefore required.

Atopy patch test
Due to the lack of standardized test substances and the lack of studies showing advantages of atopy patch test (APT) over SPT or sIgE, APTs are not recommended for routine diagnosis of food allergy (16, 17).

See *Recommendations Box* 2*B*.

Elimination diet
An elimination diet for diagnostic purposes consists of the avoidance of the food(s) suspected of triggering allergic reactions based on the clinical history, allergy-focused diet history, and adjunct allergy testing such as SPT and sIgE. The duration of the avoidance should be no longer than necessary to achieve a significant relief of symptoms, usually 2–4 weeks for IgE-mediated symptoms and longer for non-IgE ones [e.g., up to 6 weeks for eosinophilic esophagitis (EoE)]. The diet should be thoroughly monitored and results evaluated to establish or refute the diagnosis to prevent unnecessary food restrictions. If the effect of the avoidance is limited, the diet needs to be carefully re-evaluated in case potential food allergens have been overlooked. Cofactors may also be impli-

cated. For cow's milk allergy, extensively hydrolyzed formula may not be effective in achieving remission, and an amino acid-based formula may be required. When a properly performed elimination diet does not ameliorate the symptoms, food allergy to the eliminated foods is highly unlikely. The avoidance phase should be followed by a planned reintroduction of the eliminated food(s). Where there is no risk of a severe reaction, reintroduction may occur at home. A reported clinical reaction should be confirmed by oral food challenge (OFC) under medical supervision.

See *Recommendations Box* 2C.

Oral food challenges

Oral food challenges are usually required to confirm the diagnosis of food allergy, to monitor food allergy, or to prove oral tolerance to a given food (Table 3). There are guidelines, including one from the EAACI (18, 19) and a recent PRACTALL consensus (20), that describe procedures of OFCs in detail. These recommendations deal with the many variables involved in designing a patient-specific challenge (Table 5). These include patient selection, safety criteria, type and quantity of the food allergen to be administered, timings between doses, outcome criteria, observation periods, and recipes to be used. Some of the key recommendations are summarized in Table 4.

Oral food challenges can be performed in an open or blinded manner. Blinded challenges can be single- or double-blinded. In many cases, an open OFC with an objective unequivocal reaction is sufficient for the diagnosis of food allergy. The DBPCFC is considered the gold standard diagnostic test for the diagnosis of food allergy. However, a negative open challenge of a regular age-appropriate serving or the negative outcome of the administration of a cumulative dose of the previous challenge on another day (21) is required for confirm-

ing the result of a negative DBPCFC (Fig. 2). Double-blind, placebo-controlled food challenge is time-consuming and resource-intensive to undertake. A negative OFC may be useful as a first step in ruling out food allergy. In patients with atopic eczema subjective or suspected psychological symptoms, the DBPCFC is superior to an OFC. The food should be blinded for taste, smell, texture, and appearance (consistency, color, and shape). The placebo and the active food should be sensory indistinguishable from each other.

In order to avoid severe reactions, patients receive the food in titrated doses often with half-logarithmic dose increments, at set intervals. For many foods such as cow's milk, hen's egg, peanut, or tree nuts, dose ranges from 3 mg to 3 g of food protein seem sufficient in clinical practice (see Data S2).

Food allergy challenges are usually stopped if objective clinical reactions are observed or the last dose is consumed without clinical symptoms. Immediate reactions usually appear within 2 h after the last food intake, atopic eczema may worsen several hours or days following an oral challenge. Urticaria and angioedema are the most common objective signs, and gastrointestinal, respiratory or cardiovascular system involvement is also common.

To optimize safety, vital signs should be closely monitored during OFC and equipment and appropriately trained staff should be in place to deal with allergic reactions – including anaphylaxis.

For patients with non-IgE-mediated reactions, challenges tailored on the individual modalities of reactions should be designed.
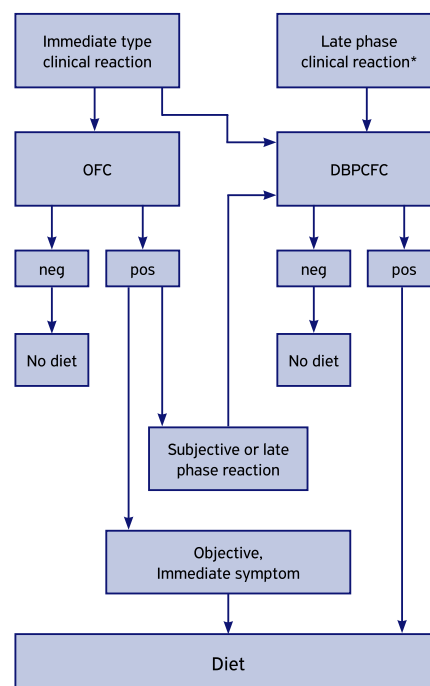
See *Recommendations Box* 2D.

Table 4 Indications for oral challenge tests

Indication	Rationale
Demonstrate allergy	Uncertain diagnostic outcome despite the use of detailed clinical history and IgE sensitization testing
	Suspected food-allergic reaction for which the cause is uncertain despite allergy testing (e.g., composite meal eaten)
	Determine threshold dose of causative allergen
Demonstrate tolerance	When allergy tests suggest tolerance but food has never been eaten and patients and/or parents too cautious to introduce at home
	Nonclinically relevant cross-reactivity suspected, for example a patient with a low positive IgE result to hazelnut but high positive birch pollen sensitization
	When the diet is restricted due to a suspicion that one or more foods are resulting in delayed allergic symptoms (e.g., eczema)
	Allergy suspected to have been outgrown
Monitor therapy for food allergy	To monitor response to immunomodulatory treatment in research setting

Figure 2 Algorithm for oral food challenge. *Atopic dermatitis, gastrointestinal symptoms.

Table 5 Variables associated with oral food challenges

Variable	
Design	May be open (cumulative or incremental) or blinded (single- or double-blinded). Design selected according to the indication and purpose for which the challenge is being performed
Form of challenge food	The challenge food should closely replicate the usual edible form of the food or form of the food implicated in allergic reaction
	Food processing can significantly influence allergenicity of the food (e.g., baked *vs* raw egg)
	For oral food challenges performed to diagnose the pollen food syndrome, fresh fruit and vegetables should be used, as the responsible proteins are commonly heat labile
Choice of food matrix	Strictly avoid use of allergenic ingredients for individual patient
	Minimize the number of ingredients used
	Provide adequate allergen protein in a manageable portion size
	For placebo foods, sensory qualities should closely replicate those of active challenge food
Doses	
Number of doses	In most cases, half-logarithmic dose increments are indicated. If a negative outcome is anticipated, and there are no safety concerns, a single cumulative dose is appropriate
Initial dose	In clinical settings, 3 mg of food protein seems adequate for most common food allergens such as cow's milk, hen's egg, peanuts, and tree nuts. Lower doses are used for threshold studies in research setting or for patients at high risk of a severe reaction
Top dose	Equivalent to an 'age-appropriate' portion, 3 g of food protein seems adequate for the most common food allergens such as cow's milk, hen's egg, peanuts, and tree nuts
Time intervals between doses	15–30 min, but may be adjusted to the patient's history
Total challenge duration	Usually completed within 8 h (immediate symptoms) and 1–4 weeks (delayed symptoms)

Promising novel diagnostic approaches

In molecular or component-resolved diagnostic tests (CRD), sIgE antibodies are measured against individual allergenic molecules from foods with the potential to improve the specificity of serum IgE testing and the specificity for selected food. This can be performed either in single test formats or in a microarray, testing a range of purified allergens simultaneously. For peanut allergy, determination of sIgE for the major allergen, Ara h 2, showed sensitivity of 100% and specificity of 70–80% in two recent studies (22, 23). The determination of omega-5-gliadin proved to be of high diagnostic relevance in exercise-induced food allergy to wheat in a number of recent case reports and cohort studies (24) as well as the determination of rGly m 4 for allergy to soy milk in birch-sensitized patients (25). For certain fruits (i.e., apple, peach, kiwi, and melon), vegetables (i.e., carrot and celery), tree nuts and peanut, soy, fish, and shrimp, CRD are also available and provide better insight into sensitization patterns (23). The technique of CRD is promising and broadly studied, and some important clinical results are summarized in Data S2. Evidence from well-designed randomized controlled studies on the diagnostic test accuracy of CRD is still required to properly assess its diagnostic value (see Box 2B).

Basophil activation tests (BATs) have been applied in the diagnosis of cow's milk, egg, and peanut allergy (22, 26, 27) as well as in the diagnosis of pollen food syndromes in small clinical studies (28, 29). Basophil activation test has shown higher specificity and negative predictive value than SPT and sIgE, without losing sensitivity or positive predictive value. However, BAT requires a specialized laboratory setting and large clinical studies on its diagnostic performance are lacking. Thus, the use of this promising test is still limited to research purposes on food allergy.

Another promising research area is the determination of IgE antibodies against overlapping synthetic linear peptides of food allergens, as it has been performed for milk (30–32), peanut (33, 34), egg (35), and shrimp (36, 37).

See *Recommendations Box 2B*.

Diagnostic workup of gastrointestinal non-IgE-mediated symptoms

Infants in the first year of life may present with gastrointestinal food-related clinical manifestations such food protein-induced enterocolitis syndrome (FPIES), proctocolitis, and enteropathy (38). Usually, patients have negative food sIgE testing (see Table 2). The diagnosis is based on symptoms, clinical history, elimination diet for up to 3 weeks, and specifically designed OFCs (39). Endoscopy with biopsies might be helpful in confirming bowel inflammation. Currently, there is scarce evidence that APT is helpful in diagnosing food allergy in such types of food allergy (40).

Eosinophilic esophagitis is defined as a chronic, immune-/antigen-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. All age groups can be affected and the current estimated prevalence is around one in 24 000 adults (41). Adult patients mostly present with dysphagia, less frequently with retrosternal pain and food bolus impaction, whereas the symptom presentation in children is much more variable and includes failure to thrive, vomiting, regurgitation, thoracic and abdominal pain. Eosinophilic esophagitis is diagnosed by an upper endoscopy and biopsies (42). Biopsies should be performed when the patient has been treated for at least 6 weeks with double the standard dose proton-pump inhibitors to rule out esophageal eosinophilia caused by gastroesophageal reflux disease (GERD) and to exclude proton-pump inhibitor-responsive

esophageal eosinophilia. Other disorders associated with esophageal eosinophilia such as Crohn's disease, celiac disease, achalasia, or eosinophilic gastroenteritis should be ruled out. Approximately 15–43% EoE patients are diagnosed with food allergies and sensitization rate to aeroallergens is up to 80% (43). A close collaboration between gastroenterologists and allergists is essential to optimize management of patients with EoE (41).

See *Recommendations Box* 2E.

Unconventional tests including specific IgG testing

A number of expensive diagnostic alternative approaches are sometimes promoted to physicians and often used by complementary and alternative medicine practitioners in cases of suspected food allergy. Examples are bioresonance, kinesiology, iridology, hair analysis, cytotoxic test, and IgG and IgG4 determination. These tests are not currently validated and cannot be recommended in diagnosing food allergy (43–47). For example, IgG measurements cannot be correlated with any clinical symptoms or disease. Food-specific IgG4 levels indicate that the atopic individual has been repeatedly exposed to high doses of food components, which are recognized as foreign proteins by the immune system. Therefore, EAACI gave a clear recommendation not to use these tests (48).

See *Recommendations Box* 2F.

Barriers and facilitators to implementation of recommendations and gaps and research needs for food allergy diagnosis are summarized in Tables S2 and S3, respectively.

Management of food allergy

The clinical management of food allergy includes short-term interventions to manage acute reactions and long-term strategies to minimize the risk of further reactions. The latter aim is primarily achieved through dietary modification, education, and behavioral approaches to avoid allergens and pharmacological and nonpharmacological management strategies for further reactions. There is growing interest in the effectiveness of potential immunomodulatory treatment approaches, including sublingual and oral immunotherapy to induce tolerance (49).

Management of acute reactions

Most foods contain proteins which may be allergenic and cause food allergy and, in some cases, anaphylaxis. Recently, severe reactions have been attributed to carbohydrate [e.g., alpha-gal (15)]. Assessment of the risk of severe reactions is crucial in successfully managing patients with food allergy. The risks vary in different patient subgroups; for example, patients with previous anaphylaxis or severe asthma have a higher risk than other patients; known cofactors include non-steroidal anti-inflammatory drugs (NSAID), exercise, infections, and mastocytosis. For detailed guidance on the emergency management of anaphylaxis, readers are referred to the EAACI Anaphylaxis Guideline Chapter (50).

In our systematic review, we found weak evidence to support the benefits of H1 antihistamines for children and adults with acute non-life-threatening symptoms from food allergy in three randomized trials and two nonrandomized comparisons (5). Importantly, there is no evidence for efficacy of antihistamines in the treatment of more severe symptoms. The prophylactic administration of antihistamines can mask early symptoms of anaphylaxis and lead to delayed treatment of dangerous reactions with adrenaline (epinephrine).

See *Recommendations Box* 3A.

Long-term management strategies

Elimination diet and dietary interventions

Dietary avoidance is the key intervention in the management of food allergy resulting in complete or almost complete resolution of symptoms. Little research has been published about dietary eliminations due to the difficultly to perform randomized controlled trials (RCTs) in subjects for ethical issues. The findings from the few studies available (51–54) are mixed, and all had a high risk of potential bias. The lack of evidence does not mean that elimination diets are not effective, just that any recommendations made about elimination diets may need to rely on expert opinion and experience rather than a high-quality research base.

Dietary restrictions should eliminate the culprit food allergen(s) and be tailored to the individual's specific allergic and nutritional needs. This will cover a wide spectrum of issues such as the nutritional needs of food-allergic infants who are currently being introduced to solid foods, which are very different, form the nutritional needs of adults with primary or secondary fruit and vegetable allergies. Extensive and long-term avoidance should be carefully monitored as it can result in nutritional compromises and impair the quality of life. Ideally, the patient should receive proper counseling by a dietician with specific competence in food allergy. This is particularly important in infants and children. In addition, it is crucial to take into account that individual tolerance levels to the allergenic food may differ and change overtime, especially in children, and may affect the stringency of avoidance advice. In breast-fed infants suffering symptoms due to maternal intake of food allergens, the mother should eliminate the foods in question and following a dietetic review, receive a calcium supplement following a dietetic review if cow's milk, cow's milk substitutes, and derivatives are eliminated.

Education is the key pillar of an effective long-term elimination diet. Patients, their families, close relatives, and caregivers should be aware of risk situations and should be instructed in reading labels and how to avoid the relevant food allergens both in and outside the home (e.g., at restaurants). They should know that European Union (EU) directives ask for the declaration of allergenic ingredients in foods and be informed about precautionary labeled foods. They should also be provided with information on possible substitute products for most food allergens.

Patients should be re-evaluated at regular intervals to assess whether they have developed tolerance to avoid inappropriate or unnecessarily lengthy dietary elimination. This is discussed below.

Box 3: EAACI recommendation on the management of food allergy

Recommendations	Evidence level	Grade	Key references
(A) Acute management			
The patient at risk of severe reactions should be properly and timely identified	IV	D	Expert opinion
Antihistamines and mast cell stabilizers			
There is evidence to support the benefits of antihistamines for children and adults with acute non-life-threatening symptoms from food allergy	III	C	(5)
The prophylactic application of antihistamines is not recommended	V	D	Expert opinion
Mast cell stabilizers are not recommended for the prophylactic treatment of food allergy	III	C	(5)
(B) Long-term management strategies			
(B1) Elimination diet			
A sufficient elimination diet should be based on a formal allergy diagnosis identifying the food allergen(s) responsible of the patient's symptoms/reactions. The indications should be re-evaluated at appropriate intervals	IV	D	(51, 52, 54)
Appropriate dietary avoidance is the key treatment in the management of food allergy	IV	D	Expert opinion
Patients with food allergy who are on long-term elimination diets should have access to appropriate dietetic counseling, ideally by a dietitian with competencies in food allergy, and regular monitoring of growth (in children)	IV	D	Expert opinion
Extensively hydrolyzed cow's milk formulas with documented hypoallergenicity can be recommended as first choice for the treatment of cow's milk allergy, especially in infants and young children. Amino acid formulas can also be recommended especially for the subgroup of patients with more severe symptoms	I	A	(55, 57, 59, 84)
Soy formulas should not be recommended before 6 months of age and at any age in the presence of gastrointestinal symptoms. From 6 to 12 months, it can be considered on a case-by-case basis	I	B	(5)
Currently, probiotic supplements cannot be recommended for the management of food allergy	I	D	(5, 69)
(B2) Education and risk assessment			
Patients and caregivers need to be informed about the foods that should be avoided and practical advice given on avoidance measures, how to recognize a further reaction and the self-management of these reactions	V	D	Expert opinion
The diagnosis of food allergy should, with permission, be communicated to all relevant caregivers	V	D	Expert opinion
Patients/carers should be encouraged to join an appropriate patient support organization	V	D	Expert opinion
All patients with food allergy require a management plan with appropriate education for the patient, caregiver including school	V	D	Expert opinion
Education should cover allergen avoidance, symptom recognition, and indication for specific treatment and administration of specific mediation	V	D	Expert opinion
Absolute indications with adrenaline autoinjector include previous anaphylaxis to any food, food allergy associated with persistent or severe asthma, and exercise-induced food-dependent anaphylaxis	IV	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
Relative indications for adrenaline autoinjector with food allergy include (i) food allergies that are likely to be persistent; (ii) mild-to-moderate allergic reaction to peanut and/or tree nut; (iii) mild-to-moderate reaction to very small amounts of food; and (iv) specific high-risk groups, e.g., adolescents, young adult males, poor access to medical care	IV–V*	C–D*	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
Adrenaline should be immediately administered for cardiovascular symptoms and/or respiratory symptoms such as altered voice, stridor, or bronchospasm that are thought to be induced by food allergy	IV	C	Refer to the Anaphylaxis Guidelines Chapter
Short-acting beta agonists should be included in the management plan for all patients with coexisting asthma and should be administered for bronchospasm after adrenaline has been administered	V	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
Patient held glucocorticosteroids may be given with reactions to possibly prevent late-phase respiratory symptoms (self-administered if traveling far from medical care, otherwise in emergency center)	V	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter

Box 3: Continued

Recommendations	Evidence level	Grade	Key references
Any patient who has received adrenaline should be reviewed in an emergency department	IV	D	Expert opinion, refer to the Anaphylaxis Guidelines Chapter
(B3) Specific immunotherapy			
Food allergen-specific immunotherapy for primary food allergy is a promising immunomodulatory treatment approach (I), but it is associated with risk of adverse reactions, including anaphylaxis (I); it is therefore not currently recommended for routine clinical use	III	C	(5)
For patients with respiratory or other allergy symptoms to inhalant allergens that may also cause cross-reactive food allergy, specific immunotherapy is only recommended for the treatment of the respiratory symptoms, not for cross-reactive food allergy	IV	D	Expert opinion
(B4) Anti-IgE			
The use of anti-IgE alone or in combination with specific immunotherapy is currently not recommended for the treatment of food allergy although it represents a promising treatment modality	IV	D	(5)
(B5) Challenges at regular intervals to assess achievements of tolerance			
Oral food challenge should be performed at regularly at intervals, as appropriate for the specific food and patient's history, in order to assess achievement of tolerance	V	D	Expert opinion
Specific IgE testing (*in vitro* and skin prick test) has limited value in guiding adequately the timing of oral food challenges for the development of tolerance	V	D	Expert opinion
(B6) Cofactors			
In food allergy reactions, the potential augmenting role of cofactors (e.g., exercise, NSAID, omeprazole, alcohol intake) should be assessed in a structured history	III–IV**	D	Expert opinion
In allergic reactions occurring after exercise, NSAID or alcohol intake, an underlying allergy to foods consumed in the previous hours should be assessed (especially gliadin sensitization or lipid-transfer proteins in southern Europe)	IV	D	(24, 72, 73)

NSAID, nonsteroidal anti-inflammatory drugs.
*Range of levels of evidence and grades are due to range of indications.
**Range of levels of evidence and grades are due to range of different cofactors.

Cow's milk substitutes

In children with cow's milk allergy, several substitutes are available. In infants and young children, these products are especially necessary to ensure a diet that is adequate for growth and development. In infants younger than 6 months, such formulas have to fulfill the general requirements for full nutrition until the introduction of complementary foods. In addition, these substitutes may also be required in older children to ensure a satisfactory caloric intake. There is some moderate-level evidence about some alternatives to cow's milk. However, most of the research is of low quality and there are a relatively small number of studies about each type of alternative formula. There is some evidence to suggest that extensively hydrolyzed formula, amino acid-based formula, and soy-based formula may all be useful long-term management strategies. Extensively hydrolyzed cow's milk formulas are the first choice as an alternative to cow's milk. However, amino acid-based formulas are the only completely nonallergenic formula and they can be effective in patients not responding to extensively hydrolyzed formulas and in subgroups of children. These include infants with severe growth faltering (55–57), those with cow's milk protein allergy with severe symptoms and non-IgE-mediated syndromes such as food protein-induced enterocolitis and enteropathies, eosinophilic gastroenteropathies. Soy formulas may be useful provided that nutritional evaluation regarding the phytate and phyto-oestrogens content is considered, and they cannot be recommended before 6 months of age. Rice hydrolyzed formulas have been recently introduced to the market in some European countries, and further research is needed to compare these formulas with extensively hydrolyzed formula and soy formulas. The substitutes for cow's milk should fulfill the criteria for documented hypoallergenicity and for nutritional adequacy (58, 59). To achieve these requirements, the formula should be investigated in consecutive patients with both IgE- and non-IgE-mediated cow's milk protein allergy (60). Some extensively hydrolyzed formulas have been investigated and fulfill these criteria (56, 61–63). In addition, attention should be paid to taste and price as reimbursement policies for these types of formulas differ across the EU.

Based on several reports, partially hydrolyzed cow's milk-based formulas are not regarded as safe for patients with

cow's milk allergy (64, 65). There is less evidence regarding other mammalian milk. Goat milk and sheep's milk are very similar to the proteins in cow's milk and therefore should not be recommended for patients with cow's milk allergy (66). Camel, donkey, or mare's milk has been shown to be less cross-reactive than goat's milk, although evidence for recommendations is lacking as well as for chicken-based formula (67) or meat-based formula (68). In summary, it is recommended that the choice of an appropriate cow's milk substitute should be assessed carefully balancing the following factors: age, type of food allergy (IgE/non-IgE), coexistence of gastrointestinal symptoms, history of life-threatening reactions, and nutritional requirements as well as cost-effectiveness.

Probiotics and prebiotics

Probiotics have been investigated as another option for the management of patients with food allergy, particularly cow's milk allergy, either added to formulas or given as a supplement. Evidence that probiotic supplements have preventative or therapeutic activity for food allergy is lacking (5), and further research is needed to make recommendations in this area (69).

See *Recommendations Box 3B1*.

Pharmacological treatment

Studies on the prophylaxis of food allergy with mast cell stabilizers have led to different clinical results (5). Four randomized trials and two nonrandomized comparisons found that mast cell stabilizers reduced symptoms of food allergy, but three randomized trials found no benefits. Overall, the evidence is not sufficient to recommend mast cell stabilizers for the prophylactic treatment of food allergy.

Education and risk assessment

Education and training are a fundamental part of managing food allergies and should be combined with a risk assessment of those patients at risk of severe reactions (70). A personalized management plan, including an emergency plan, should be issued as part of the overall educational package offered to patients (family and caregivers; see also Anaphylaxis Guidelines). The plan should be personalized to take into account the many variables that may influence the identification and treatment of allergic reactions: age of the patient, literacy of patient and family, type and range of food allergy, concomitant disease, geographic location, and access to medical support. Training should cover patient-specific avoidance strategies at home and in the wider environment, interpretation of warning signals, when and how to treat reactions including use of self-injectable adrenaline if appropriate (6). All professionals, including family doctors, school nurses, dieticians, school teachers, and nursery staff, should be trained. There is some evidence that a multidisciplinary clinical approach (5) and the provision of educational printed and online materials for food allergy (71) improve knowledge, correct use of adrenaline autoinjectors, and reduce reactions (see Anaphylaxis Guidelines).

See *Recommendations Box 3B2*.

Cofactors

Several augmentation factors are known to increase the severity of some food-allergic reactions. Sometimes these factors are even obligatory to elicit symptoms of food allergy. Among the best characterized factors are physical exercise and NSAID, and others include alcohol, fever, and acute infection. One example is wheat-dependent exercise-induced anaphylaxis due to omega-5-gliadin sensitization (24); other allergens such as lipid-transfer proteins (LTP) seem to be relevant in certain geographic areas (72, 73). Potential cofactors should be assessed in any case of food allergy.

See *Recommendations Box 3B6*.

Immunomodulation

Specific immunotherapy of food allergy

For the treatment of food allergy, specific immunotherapy with food allergens using the subcutaneous, oral, or sublingual route has been assessed (5). Most controlled studies have been performed with peanuts, hazelnut, hen's egg, or cow's milk. For pollen-associated food allergy, immunotherapy has been performed with subcutaneous or sublingual pollen allergens and the oral or sublingual food allergen.

Two low-quality controlled cross-over studies suggest that subcutaneous immunotherapy with food allergens is effective. For pollen-associated food allergy, three very low-quality RCTs (74, 75) and two nonrandomized studies showed conflicting efficacy for the injection treatment with pollen allergen.

Four randomized trials found that sublingual immunotherapy (SLIT) with food allergens was associated with improved tolerance and reduced symptoms for those with peanut, hazelnut, and peach allergies (76, 77). One trial with birch pollen allergen found no benefit in subjects with apple allergy (78).

For oral immunotherapy, two systematic reviews, eight randomized trials, and three nonrandomized comparisons found that oral immunotherapy with food allergens was associated with improved tolerance and reduced symptoms for children and adults with various food allergies (5). However, around 90% of participants have side-effects although these were usually not severe. Oral immunotherapy was more efficacious for desensitization to cow's milk than SLIT but was accompanied by more systemic side-effects in one study (79). One randomized trial found no benefit (80). The two systematic reviews found mixed evidence and suggested that oral immunotherapy should not currently be recommended as routine treatment (81, 82). In light of its potential benefit, it should be performed only in highly specialized centers, with expert staff and adequate equipment, and in accordance with clinical protocols approved by local ethics committees.

The evidence from these studies supports the need for further exploration of immunotherapy with food allergens (5), although especially in subcutaneous and oral immunotherapy the treatment seems to be associated with significant adverse effects. In regard to pollen-associated food allergy, there is conflicting evidence on efficacy of subcutaneous and SLIT with pollen allergens; these therapeutic interventions should only be used for the pollen allergy symptoms.

See *Recommendations Box 3B3*.

Anti-IgE treatment

Omalizumab is a humanized monoclonal anti-IgE antibody, which is licensed for the treatment of allergic asthma. The impact of omalizumab and another anti-IgE antibody (TNX-901) on food allergy has been investigated (5). Increased thresholds of tolerance to food allergens were found in a sub-group of participants. Studies suggest that the clinical benefits of omalizumab are achieved after just a few doses of omalizumab. Moreover, it has been demonstrated that more rapid up-dosing and higher doses of milk protein could be administered when omalizumab was used as an adjunct therapy (83).

See *Recommendations Box* 3*B4*.

Challenges at regular intervals to assess development of tolerance

As tolerance can be acquired spontaneously for some food allergens, particularly in children, or can develop with pollen sensitization. There is therefore a need to regularly re-evaluate patients to prevent inappropriate or unnecessarily lengthy dietary eliminations that may impair the quality of life, affect normal growth, and incur unnecessary healthcare costs. Repeated IgE testing can be helpful to determine whether sensitization is decreasing (common in egg and milk allergy) and helpful to identify associated allergies [e.g., peanut, associated with tree nut, sesame (14)].

Currently, OFCs are the only tests that can predict with adequate certainty the achievement of tolerance although it has been shown that low food allergen sIgE levels at diagnosis and a decrease over time both correlate with clinical tolerance. It is therefore recommended that OFC should be performed at regular intervals in order to avoid unnecessary dietary restrictions. The eliciting food may influence this process as, for example, in cow's milk and hen's egg allergy the majority of children will become tolerant within a few years, while most patients with peanut or tree nut allergy remain allergic throughout their life. In cow's milk or hen's egg allergy, intervals for re-evaluation might be every 6–12 months, while for peanut and tree nut allergy OFC every 2 years in the absence of an accidental reaction would be more appropriate.

See *Recommendations Box* 3*B5*.

Management of EoE

Symptomatic EoE patients should be treated not only for quality of life reasons but also to reduce the risk for the occurrence of the potentially dangerous food bolus impactions. Untreated eosinophil-predominant inflammation leads to esophageal remodeling with narrowing of the esophageal caliper and a loss of function. Treatment modalities include drugs, diets, and esophageal dilation. Swallowed topical corticosteroids (budesonide or fluticasone) and diets have shown to reduce symptoms and eosinophilic infiltration. The following diet types are available: amino acid-based formula diet (necessitates often feeding tube), targeted elimination diet (according to allergy workup), and empiric elimination diet. Esophageal dilation of strictures can increase esophageal diameter and improve symptoms; however, it does not influence the underlying inflammation. The long-term treatment strategies are not yet defined. Close collaboration between allergists/immunologists and gastroenterologists is advised (41).

See *Recommendations Box* 3*B6*.

Barriers and facilitators to implementation of recommendations, gaps, and research needs for the management of food allergy are summarized in Tables S4 and S5, respectively.

Conclusions and future perspectives

Food allergy appears to be an increasing burden, which needs to be properly addressed in a structured diagnostic and management approach. The overall body of evidence indicates that patients' clinical history, through the use of structured questions on symptoms, food, and background information, should guide the allergy testing as IgE sensitization does not always equate with clinically relevant food allergy. Skin prick test and sIgE (and probably CRD) offer high sensitivity in relation to a range of allergens implicated in IgE-mediated food allergy. Direct comparisons among the tests are difficult given the limited body of evidence in which these tests have been compared in the same population. There is greater variation in the specificity of these tests, because they indicate sensitization that may not be of clinical relevance, with sIgE tending to have a higher rate of false-positive results. There is limited evidence for the value of APT in diagnosis. The comparability of the local population and the relative availability, safety, and costs of the tests will influence local protocols for diagnostic evaluation.

An elimination diet based on an allergy-focused clinical history and allergy testing should be followed until a significant relief of symptoms is achieved. Careful consideration should be given to the nutritional completeness of patients' diet. Given the limitation of other tests, OFC (ideally DBPCFC) is still the gold standard in IgE- and non-IgE-mediated food allergy in order to establish a firm diagnosis, to determine threshold reactivity, to assess tolerance and the response to immunomodulation. Facilities for OFC are lacking and reimbursement policies vary across national European countries. Efforts should be provided to adequate diagnostic facilities and capabilities to all food-allergic patients in Europe.

The optimal management of food allergy consists of a multidisciplinary and multifaceted approach, which encompasses the treatment of acute episodes of the disease, identification of patients at risk of severe reactions, and long-term management strategies in order to minimize recurrences of reactions and improve quality of life.

Although there are several management strategies available, evidence of effectiveness is very limited in this context. The data on pharmacologic treatment are limited with only H1 antihistamines considered to alleviating acute symptoms but only non-life-threatening ones. Dietary avoidance of properly identified culprit food(s) is the cornerstone of management. There is some evidence to recommend extensively hydrolyzed formulas with documented hypoallergenicity or amino acids formulas as alternatives to cow's milk formula. However, few extensively hydrolyzed formulas have been investigated for hypoallergenicity in properly designed studies, particularly in children with newly documented cow's milk protein allergy. There is currently no evidence for

recommending probiotics and prebiotics with the aim to induce tolerance, although there might be new findings in this field in the near future. Patients at risk of anaphylaxis should have access to self-injectable adrenaline for treating future severe reactions. Facilitated access to allergy consultations, counseling by dietitians with competencies in food allergy, psychological interventions as well as coordination among the several healthcare professionals dealing with the various clinical manifestations of the disease should all be ideally put in place for the effective treatment of these patients.

More proactive treatment for food allergy is urgently needed to address the associated health risk and social burden. Findings suggest that immunotherapy for food allergy through several routes (subcutaneous, sublingual, oral, epicutaneous) may help to increase tolerance with accidental exposure although the expected improvement may be small. Oral immunotherapy may be useful for IgE-mediated food allergy but is associated with a significant risk of local and systemic reactions. Overall, specific immunotherapy is not yet suitable for use in routine clinical care and should be performed in specialized clinical settings under supervision by an allergist with expertise in the field. As a long-term strategy, further research is required into whether immunotherapy could be offered in daily clinical practice.

Education is a key feature in the management of food allergy and should be heavily promoted to patients, families, and caregivers as well as to healthcare professionals. Developing and validating educational tools will further the establishment of vertical and horizontal networks between Centres of Excellence, allergy specialists, and primary care practitioners. Implementation at the community level should be in partnership with the patient organizations (see Community Guidelines Chapter). Adequate reimbursement from national healthcare systems and insurance bodies for diagnostic procedures and the management strategies, including education, should be available.

Expert panel

Acknowledgments

Author contributions

Conflict of interest

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Assigning levels of evidence and recommendations according to new grading system.

Table S2. Food allergy diagnosis: barriers and facilitators to implementation of recommendations.

Table S3. Diagnosis of food allergy: gaps and research needs in the diagnosis of food allergy.

Table S4. Management of food allergy: barriers and facilitators to implementation of recommendations.

Table S5. Gaps and research needs for the management of food allergy.

Data S1. Methodology used for the production of these guidelines.

Data S2. Tools to support implementation of diagnosis of food allergy.

References

1. Sackeyfio A, Senthinathan A, Kandaswamy P, Barry PW, Shaw B, Baker M; Guideline Development Group. Diagnosis and assessment of food allergy in children and young people: summary of NICE guidance. *BMJ* 2011;**342**:d747.

2. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**:832–836.

3. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. *Allergy* 2014;**69**:62–75.

4. Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K et al. The diagnosis of food allergy: a systematic review and meta-analysis. *Allergy* 2014;**69**:76–86.

5. de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K et al. Acute and long-term management of food allergy: systematic review. *Allergy* 2014;**69**:159–167.

6. Bruijnzeel-Koomen C, Ortolani C, Aas K, Bindslev-Jensen C, Bjorksten B, Moneret-Vautrin D et al. Adverse reactions to food. European Academy of Allergology and Clinical Immunology Subcommittee. *Allergy* 1995;**50**:623–635.

7. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;**126**(Suppl 6): S1–S58.

8. 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.

9. Breuer K, Heratizadeh A, Wulf A, Baumann U, Constien A, Tetau D et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004;**34**:817–824.

10. Sampson HA. Food allergy–accurately identifying clinical reactivity. *Allergy* 2005;**60**(Suppl 79):19–24.

11. Heinzerling LM, Burbach GJ, Edenharter G, Bachert C, Bindslev-Jensen C, Bonini S et al. GA(2)LEN skin test study I: GA(2)LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy* 2009;**64**:1498–1506.

12. EAACI. Position Paper: allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;**48**(Suppl 14):48–82.

13. Konstantinou GN, Bousquet PJ, Zuberbier T, Papadopoulos NG. The longest wheal diameter is the optimal measurement for the evaluation of skin prick tests. *Int Arch Allergy Immunol* 2010;**151**:343–345.

14. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG et al. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy* 2012;**67**:18–24.

15. Commins SP, Platts-Mills TA. Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1,3-galactose (alpha-gal). *Curr Allergy Asthma Rep* 2013;**13**:72–77.

16. Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA2LEN position paper: present status of the atopy patch test. *Allergy* 2006;**61**:1377–1384.

17. Mehl A, Rolinck-Werninghaus C, Staden U, Verstege A, Wahn U, Beyer K et al. The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006;**118**:923–929.

18. Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J et al. Standardization of food challenges in patients with immediate reactions to foods–position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004;**59**:690–697.

19. Werfel T, Ballmer-Weber B, Eigenmann PA, Niggemann B, Rance F, Turjanmaa K et al. Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. *Allergy* 2007;**62**:723–728.

20. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clin-

ical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;**130**:1260–1274.

21. Niggemann B, Lange L, Finger A, Ziegert M, Muller V, Beyer K. Accurate oral food challenge requires a cumulative dose on a subsequent day. *J Allergy Clin Immunol* 2012;**130**:261–263.

22. Glaumann S, Nopp A, Johansson SG, Rudengren M, Borres MP, Nilsson C. Basophil allergen threshold sensitivity, CD-sens, IgE-sensitization and DBPCFC in peanut-sensitized children. *Allergy* 2012;**67**:242–247.

23. Eller E, Bindslev-Jensen C. Clinical value of component-resolved diagnostics in peanut-allergic patients. *Allergy* 2013;**68**:190–194.

24. Morita E, Matsuo H, Chinuki Y, Takahashi H, Dahlstrom J, Tanaka A. Food-dependent exercise-induced anaphylaxis -importance of omega-5 gliadin and HMW-glutenin as causative antigens for wheat-dependent exercise-induced anaphylaxis. *Allergol Int* 2009;**58**:493–498.

25. Berneder M, Bublin M, Hoffmann-Sommergruber K, Hawranek T, Lang R. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. *Int Arch Allergy Immunol* 2013;**161**:229–233.

26. Sato S, Tachimoto H, Shukuya A, Kurosaka N, Yanagida N, Utsunomiya T et al. Basophil activation marker CD203c is useful in the diagnosis of hen's egg and cow's milk allergies in children. *Int Arch Allergy Immunol* 2010;**152**(Suppl 1):54–61.

27. Rubio A, Vivinus-Nebot M, Bourrier T, Saggio B, Albertini M, Bernard A. Benefit of the basophil activation test in deciding when to reintroduce cow's milk in allergic children. *Allergy* 2011;**66**:92–100.

28. Erdmann SM, Heussen N, Moll-Slodowy S, Merk HF, Sachs B. CD63 expression on basophils as a tool for the diagnosis of pollen-associated food allergy: sensitivity and specificity. *Clin Exp Allergy* 2003;**33**:607–614.

29. Ebo DG, Hagendorens MM, Bridts CH, Schuerwegh AJ, De Clerck LS, Stevens WJ. Flow cytometric analysis of in vitro activated basophils, specific IgE and skin tests in the diagnosis of pollen-associated food allergy. *Cytometry B Clin Cytom* 2005;**64**:28–33.

30. Jarvinen KM, Chatchatee P, Bardina L, Beyer K, Sampson HA. IgE and IgG binding epitopes on alpha-lactalbumin and beta-lactoglobulin in cow's milk allergy. *Int Arch Allergy Immunol* 2001;**126**:111–118.

31. Jarvinen KM, Beyer K, Vila L, Chatchatee P, Busse PJ, Sampson HA. B-cell epitopes as a screening instrument for persistent cow's milk allergy. *J Allergy Clin Immunol* 2002;**110**:293–297.

32. Cerecedo I, Zamora J, Shreffler WG, Lin J, Bardina L, Dieguez MC et al. Mapping of the IgE and IgG4 sequential epitopes of milk allergens with a peptide microarray-based immunoassay. *J Allergy Clin Immunol* 2008;**122**:589–594.

33. Beyer K, Ellman-Grunther L, Jarvinen KM, Wood RA, Hourihane J, Sampson HA. Measurement of peptide-specific IgE as an additional tool in identifying patients with clinical reactivity to peanuts. *J Allergy Clin Immunol* 2003;**112**:202–207.

34. Lin J, Bruni FM, Fu Z, Maloney J, Bardina L, Boner AL et al. A bioinformatics approach to identify patients with symptomatic peanut allergy using peptide microarray immunoassay. *J Allergy Clin Immunol* 2012;**129**:1321–1328.

35. Jarvinen KM, Beyer K, Vila L, Bardina L, Mishoe M, Sampson HA. Specificity of IgE antibodies to sequential epitopes of hen's egg ovomucoid as a marker for persistence of egg allergy. *Allergy* 2007;**62**:758–765.

36. Ayuso R, Sanchez-Garcia S, Lin J, Fu Z, Ibanez MD, Carrillo T et al. Greater epitope recognition of shrimp allergens by children than by adults suggests that shrimp sensitization decreases with age. *J Allergy Clin Immunol* 2010;**125**:1286–1293.

37. Ayuso R, Sanchez-Garcia S, Pascal M, Lin J, Grishina G, Fu Z et al. Is epitope recognition of shrimp allergens useful to predict clinical reactivity? *Clin Exp Allergy* 2012;**42**:293–304.

38. Leonard SA, Nowak-Wegrzyn A. Manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome. *Pediatr Ann* 2013;**42**:135–140.

39. Metcalfe DD, Sampson HA, Simon RA, editors. *Food Allergy*, 4th edn, Chapter 16. Malden, MA, USA: Blackwell Publishing, 2008.

40. Fogg MI, Brown-Whitehorn TA, Pawlowski NA, Spergel JM. Atopy patch test for the diagnosis of food protein-induced enterocolitis syndrome. *Pediatr Allergy Immunol* 2006;**17**:351–355.

41. Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;**67**:477–490.

42. Dellon ES, Gonsalves N, Hirano I, Furuta GT, Liacouras CA, Katzka DA. ACG clinical guideline: evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013;**108**:679–692.

43. Benson TE, Arkins JA. Cytotoxic testing for food allergy: evaluation of reproducibility and correlation. *J Allergy Clin Immunol* 1976;**58**:471–476.

44. Ernst E. Iridology: a systematic review. *Forsch Komplementarmed* 1999;**6**:7–9.

45. Garrow JS. Kinesiology and food allergy. *BMJ* 1988;**296**:1573–1574.

46. Niggemann B, Gruber C. Unproven diagnostic procedures in IgE-mediated allergic diseases. *Allergy* 2004;**59**:806–808.

47. Sethi TJ, Lessof MH, Kemeny DM, Lambourn E, Tobin S, Bradley A. How reliable are commercial allergy tests? *Lancet* 1987;**1**:92–94.

48. Stapel SO, Asero R, Ballmer-Weber BK, Knol EF, Strobel S, Vieths S et al. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. *Allergy* 2008;**63**:793–796.

49. Lack G. Clinical practice. Food allergy. *N Engl J Med* 2008;**359**:1252–1260.

50. Shreffler WG, Beyer K, Chu TH, Burks AW, Sampson HA. Microarray immunoassay: association of clinical history, in vitro IgE function, and heterogeneity of allergenic peanut epitopes. *J Allergy Clin Immunol* 2004;**113**:776–782.

51. Agata H, Kondo N, Fukutomi O, Shinoda S, Orii T. Effect of elimination diets on food-specific IgE antibodies and lymphocyte proliferative responses to food antigens in atopic dermatitis patients exhibiting sensitivity to food allergens. *J Allergy Clin Immunol* 1993;**91**:668–679.

52. Alonso A, Seoane MA, Iraneta SG, Scavini LM, Rodriguez SM. A citrus fruit-exclusion diet in sensitive patients and its influence on specific antibodies. *J Investig Allergol Clin Immunol* 1994;**4**:146–148.

53. Lever R, MacDonald C, Waugh P, Aitchison T. Randomised controlled trial of advice on an egg exclusion diet in young children with atopic eczema and sensitivity to eggs. *Pediatr Allergy Immunol* 1998;**9**:13–19.

54. Chen JL, Bahna SL. Spice allergy. *Ann Allergy Asthma Immunol* 2011;**107**:191–199.

55. Hill DJ, Murch SH, Rafferty K, Wallis P, Green CJ. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. *Clin Exp Allergy* 2007;**37**:808–822.

56. Niggemann B, von Berg A, Bollrath C, Berdel D, Schauer U, Rieger C et al. Safety and efficacy of a new extensively hydrolyzed formula for infants with cow's milk protein allergy. *Pediatr Allergy Immunol* 2008;**19**:348–354.

57. Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr* 2012;**55**:221–229.

58. EEC – European Communities Commission amending Directive 91/321/EEC 19. 1996.

59. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R et al. Dietary prevention of allergic diseases in infants and small children. Part III: critical review of published peer-reviewed observational and interventional studies and final recommenda-

tions. *Pediatr Allergy Immunol* 2004;**15**:291–307.

60. Muraro A, Dreborg S, Halken S, Host A, Niggemann B, Aalberse R et al. Dietary prevention of allergic diseases in infants and small children. Part I: immunologic background and criteria for hypoallergenicity. *Pediatr Allergy Immunol* 2004;**15**:103–111.

61. Halken S, Host A, Hansen LG, Osterballe O. Safety of a new, ultrafiltrated whey hydrolysate formula in children with cow milk allergy: a clinical investigation. *Pediatr Allergy Immunol* 1993;**4**:53–59.

62. Host A. Cow's milk protein allergy and intolerance in infancy. Some clinical, epidemiological and immunological aspects. *Pediatr Allergy Immunol* 1994;**5**(Suppl 5):1–36.

63. Giampietro PG, Kjellman NI, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. *Pediatr Allergy Immunol* 2001;**12**:83–86.

64. Ragno V, Giampietro PG, Bruno G, Businco L. Allergenicity of milk protein hydrolysate formulae in children with cow's milk allergy. *Eur J Pediatr* 1993;**152**:760–762.

65. Ellis MH, Short JA, Heiner DC. Anaphylaxis after ingestion of a recently introduced hydrolyzed whey protein formula. *J Pediatr* 1991;**118**:74–77.

66. Vita D, Passalacqua G, Di Pasquale G, Caminiti L, Crisafulli G, Rulli I et al. Ass's milk in children with atopic dermatitis and cow's milk allergy: crossover comparison with goat's milk. *Pediatr Allergy Immunol* 2007;**18**:594–598.

67. Jirapinyo P, Densupsoontorn N, Wongarn R, Thamonsiri N. Comparisons of a chicken-based formula with soy-based formula in infants with cow milk allergy. *Asia Pac J Clin Nutr* 2007;**16**:711–715.

68. Galli E, Chini L, Paone F, Moschese V, Knafelz D, Panel P et al. [Clinical comparison of different replacement milk formulas in children with allergies to cow's milk proteins. 24-month follow-up study]. *Minerva Pediatr* 1996;**48**:71–77.

69. Hol J, van Leer EH, Elink Schuurman BE, de Ruiter LF, Samsom JN, Hop W et al. The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. *J Allergy Clin Immunol* 2008;**121**:1448–1454.

70. Muraro A, Roberts G, Worm M, Bilò M, Brockow K, Fernández-Rivas M et al. Anaphylaxis: guideline from the European Academy of Allergology and Clinical Immunology. *Allergy* 2014;**69**:1026–1045.

71. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A et al. Going from evidence to recommendations. [Erratum appears in BMJ. 2008 Jun 21;336(7658): doi:10.1136/bmj.a402] *BMJ* 2008;**336**:1049–1051.

72. Cardona V, Luengo O, Garriga T, Labrador-Horrillo M, Sala-Cunill A, Izquierdo A et al. Co-factor-enhanced food allergy. *Allergy* 2012;**67**:1316–1318.

73. Romano A, Scala E, Rumi G, Gaeta F, Caruso C, Alonzi C et al. Lipid transfer proteins: the most frequent sensitizer in Italian subjects with food-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2012;**42**:1643–1653.

74. Miller JB. A double-blind study of food extract injection therapy: a preliminary report. *Ann Allergy* 1977;**38**:185–191.

75. King WP, Rubin WA, Fadal RG, Ward WA, Trevino RJ, Pierce WB et al. Provocation-neutralization: a two-part study. Part I. The intracutaneous provocative food test: a multi-center comparison study. *Otolaryngol Head Neck Surg* 1988;**99**:263–271.

76. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, Diaz de Durana MD, Garcia BE, Gonzalez-Mancebo E et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy* 2009;**64**:876–883.

77. Garcia BE, Gonzalez-Mancebo E, Barber D, Martin S, Tabar AI, Diaz de Durana AM et al. Sublingual immunotherapy in peach allergy: monitoring molecular sensitizations and reactivity to apple fruit and Platanus pollen. *J Investig Allergol Clin Immunol* 2010;**20**:514–520.

78. Kinaciyan T, Jahn-Schmid B, Radakovics A, Zwolfer B, Schreiber C, Francis JN et al. Successful sublingual immunotherapy with birch pollen has limited effects on concomitant food allergy to apple and the immune response to the Bet v 1 homolog Mal d 1. *J Allergy Clin Immunol* 2007;**119**:937–943.

79. Keet CA, Wood RA, Matsui EC. Limitations of reliance on specific IgE for epidemiologic surveillance of food allergy. *J Allergy Clin Immunol* 2012;**130**:1207–1209.

80. Fisher HR, du Toit G, Lack G. Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?: a meta-analysis of published RCTs. *Arch Dis Child* 2011;**96**:259–264.

81. Chafen JJ, Newberry SJ, Riedl MA, Bravata DM, Maglione M, Suttorp MJ et al. Diagnosing and managing common food allergies: a systematic review. *JAMA* 2010;**303**:1848–1856.

82. Calvani M, Giorgio V, Miceli Sopo S. Specific oral tolerance induction for food. A systematic review. *Eur Ann Allergy Clin Immunol* 2010;**42**:11–19.

83. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011;**127**:1622–1624.

84. Niggemann B, Binder C, Dupont C, Hadji S, Arvola T, Isolauri E. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. *Pediatr Allergy Immunol* 2001;**12**:78–82.

85. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. *Qual Saf Health Care* 2003;**12**:18–23.

86. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010;**125**(2 Suppl 2):S116–S125.