Guidelines on the management of IgE-mediated food allergies

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Allergy – food – diagnostic – therapy – prevention

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Preamble

The present guideline updates and summarizes S1- and S2-guidelines published by the German Association of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF) which have been published on various aspects of food allergy [1, 2, 3, 4, 5, 6, 7].

It fulfills the methodological requirements set out by the AWMF on the development of guidelines for diagnosis and treatment and represent S2k-guidelines according to the AWMF three-level concept. DELBI criteria were taken into account [9].

The strength of recommendation for the individual recommendations is expressed in the guidelines using standardized formulations (**Tab. 1**) [10].

The guideline is based on the current European Academy of Allergy and Clinical Immunology (EAACI) S3-guideline on the diagnosis and treatment of food allergy [11], as well as on systematic EAACI reviews [12, 13] from 2014, for which systematic literature searches of PubMed, meta-analyses, clinical studies, and other scientific investigations were undertaken. Consensus on the present guideline was achieved independently from the European guidelines by an interdisciplinary panel of German-speaking experts who were nominated by the participating societies.

1. Epidemiology and the most common food allergy triggers

How are food allergies differentiated on the basis of their sensitization pathway?
How common are food allergies?
What are the risk factors for food allergy?
What is the prognosis of a food allergy?
What are the most common food allergies?

1.1. Classification

Immunoglobulin E (IgE)-mediated food allergies are divided into primary and secondary food allergies, which can vary in terms of their course.

- Primary food allergies primarily occur as a result (most likely) of gastrointestinal sensitization to predominantly stable food allergens (glycoproteins).
- A secondary food allergy develops after primary sensitization to airborne allergens (e. g., pollen allergens) with subsequent reactions (due to cross-reactivity) to structurally related often labile allergens in (plant) foods.

1.2. Prevalence of food allergies

The prevalence of food allergies varies from region to region and has risen in some countries in recent years. Thus, the prevalence of peanut and tree nut allergy increased three-fold in the US over the last decade. A food allergy results in a reduction in the quality of life of affected individuals and can follow a lethal course in rare cases [15]. In order to assess the:

- incidence,
- prevalence,
- current developments,
- potential risks and
- prognostic factors ...

of food allergy in Europe, studies aimed at answering these questions and published in the period between 2000 and 2012 were evaluated in a meta-analysis [16]. The point prevalence of self-reported food allergy was approximately six times higher compared with food allergy tested using oral food challenge. The prevalence of primary food allergy was higher in children compared with adults. On the other hand the increased prevalence of secondary food allergies due to cross reactions with inhalation allergens can also be attributed to an increased awareness and improved diagnosis in recent years.

Only a few studies on the epidemiology of food allergies in Germany are available. A study from 2004 revealed a prevalence of food allergy of 3.7 % in adults [17] and 4.2 % in children [18], as verified

Abbreviations

AAAAI	American Academy of Allergy, Asthma & Immunology
AGATE	Working Group on Anaphylaxis Training and Education (Arbeitsgemeinschaft Anaphylaxie – Training und Edukation)
ASS	Acetylsalicyl acid
BAT	Basophil activation test
OD	Occupational disease
CCD	Cross-reactive carbohydrate determinants
CSACI	Canadian Society of Allergy and Clinical Immunology
DBPCFC	Double-blind placebo-controlled food challenge
DGES	Study on the health of adults in Germany
EAACI	European Academy of Allergology and Clinical Immunology
EGID	Eosinophilic gastrointestinal disorders
FPIES	Food protein-induced enterocolitis syndrome
HMW	High molecular weight
IgE	Immunoglobulin E
IgG	Immunoglobulin G
GER	Gastroesophageal reflux
CI	Confidence interval
CU	Contact urticaria
FIR	Food Information Regulation
LoQ	Limit of quantation
LTP	Lipid transfer protein
RCW	Reduced capacity to work
NPV	Negative predictive value
NSAID	Non-steroidal anti-inflammatory drugs
nsLTP	Non-specific lipid transfer protein
OAS	Oral allergy syndrome
OIT	Oral immunotherapy
PCD	Protein contact dermatitis
PPI	Proton pump inhibitor
PPV	Positive predictive value
PR-10	Pathogenesis-related protein family 10
SCIT	Subcutaneous immunotherapy
SIT	Specific immunotherapy
SLIT	Sublingual immunotherapy
WDEIA	Wheat-dependent, exercise-induced anaphylaxis

Tab. 1: Strengths of recommendation

Strength of recommendation	Syntax
Strong recommendation	Shall
Recommendation	Should
Open recommendation	Can

by double-blind, placebo-controlled oral food challenge. A recent study on adult health in Germany (DGES) conducted between 2008 and 2012 revealed a lifetime prevalence of food allergy of 6.4 % in women, 2.9 % in men and as 4.7 % for the entire adult cohort (95 % confidence interval, 4.1–5.4) [19].
Prevalence of food allergy in Germany:
- Suspected: ~20 %
- Confirmed by oral food challenge (2004):
- Children: 4.2 %
- Adults: 3.7 %

1.3. Risk Factors

At present, there are no consistent risk or prognostic factors for the development or outcome of food allergy. However, the following factors influence the prevalence of food allergy:
- sex and age
- Place of residence/geographic location
- Family history of atopy
- Concomitant allergic diseases

From a geographical perspective, the highest prevalence of food allergy in children compared with adults was in North-West Europe. A lower prevalence of self-reported and confirmed food allergy was found in Southern Europe. The authors of the meta-analysis recommend that data on the prevalence of food allergy should be interpreted with caution due to the heterogeneity of the studies and/or methodological or diagnostic differences within one, and between (different) geographical regions of Europe.

The prevalence of food allergy is challenging to determine for a variety of reasons:
- presence of augmentation factors (factors that promote the onset of food allergy symptoms)
- lack of reproducibility of convincingly described symptoms
- presence of hidden foodstuffs and of novel foods
- insufficient knowledge of threshold values
- inadequate consideration of individual sensitization profiles
- natural tolerance development and new onset of allergies at different ages in life

1.4. Prognosis

Data on the course of food allergies show that milk protein allergy in early childhood has a good prognosis for the spontaneous tolerance development, while peanut and tree nut allergies tend to persist into adulthood. Further studies are required in the future to define the long-term prognosis of food allergy.

1.5. Primary triggers of food allergies according to age

The most frequent triggers of food allergy in children and adolescents include: milk and hen's egg, soy, wheat, peanut and tree nuts. In adults pollen-associated food allergy is more prevalent and mostly induced by apple and other pome and stone fruits, including shell fruits (see also **Tab. 6**), vegetables (celery, carrots), and shellfish. The profile of food allergens that trigger severe allergic reactions is shown in **Fig. 1**.

Core statements

Food allergy prevalence is age-dependent. A study on food allergy prevalence in Germany shows a prevalence of 4.2% in children and 3.7% in adults.	strong consensus
IgE-mediated food allergies are differentiated into primary (predominantly in early childhood) and secondary (predominantly pollen-related) allergies, which follow courses of varying severity.	consensus
Food allergies can significantly reduce the quality of life and may be lethal in rare cases.	consensus

Worm, Jappe

2. Food allergy prevention

Which measures are capable of influencing/reducing the occurrence of a food allergy?

The goal of primary prevention is to reduce the risk of allergic sensitization and allergic disease. To achieve this, causal or predisposing factors are either altered or an individual's tolerance raised. In terms of the prevention of allergic diseases, a small number of recommendations apply exclusively to high-risk individuals whose father, mother, and/or

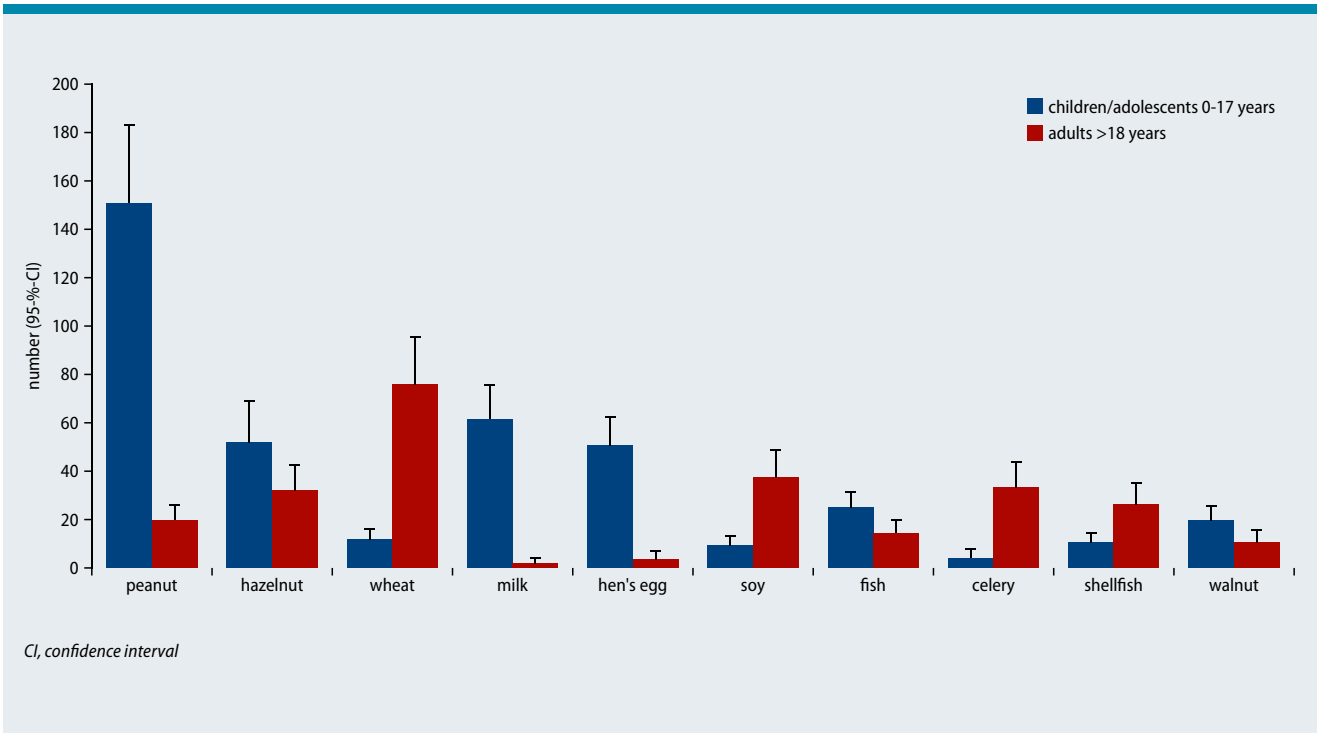

Fig. 1: Food allergens as triggers in different age groups [20] (n=665, children and adolescents aged 0–17 years, adults from 18 years). Cases from the anaphylaxis register (1 January 2006 to 31 March 2013)

siblings are already affected by allergic disease. Most recommendations are also appropriate for non-high-risk individuals.

The German evidence- and consensus-based S3-guideline on allergy prevention in Germany from 2004 was updated in 2009 [21] and 2014 [22]. The recommendations cover following guideline areas:

a) breastfeeding
b) mother and child nutrition,
c) exposure to inhalation allergens or indoor and outdoor air pollutants, including tobacco smoke,
d) keeping animals,
e) vaccinations and
f) mode of delivery in childbirth.

The following individual recommendations (level of recommendation: A–C) related to these areas are:

- Full breastfeeding for the first 4 months (A)
- Hydrolyzed formulas to be used in cases where high-risk infants up to the age of 4 months are not, or only insufficiently, breastfed (A)
- No dietary restrictions in mothers (during pregnancy/breastfeeding) (A) and infants (B) as a means of primary prevention
- No delay in the introduction of solid foods (A)
- Fish to be consumed by mother and child (B)
- Avoidance of overweight/obesity (A)
- No specific measures to reduce house dust mite allergens as a means of primary prevention (B)
- No restrictions on the keeping of domestic pets in at-risk children, no acquisition of cats in at-risk children (B)
- Avoidance of indoor conditions supporting to the development of mold (high humidity, insufficient ventilation), and minimization of exposure to indoor air pollutants (B)
- Minimization of exposure to motor vehicle emissions (B)
- Avoidance of active and passive exposure to tobacco smoke—as early on as during pregnancy (A)
- Vaccination according to STIKO recommendations for all children, irrespective of allergy risk (A)
- infants delivered by caesarean section have an increased risk of allergy (B)
- In addition, the following statements were adopted:
  - There is evidence that the consumption of fruit and vegetables (a so-called Mediterranean diet), ω-3-fatty acids (FA) (or a good ω-3:ω-6 ratio), and milk fat has a preventive effect on atopic diseases.
  - Probiotics have only been shown to have a preventive effect on atopic dermatitis. Due to the he-

terogeneity of bacterial strains used and study designs applied, it is not possible to make recommendations on specific preparations, modes of administration, or duration and time of use.
- As yet, prebiotics have only been shown to have a preventive effect on atopic dermatitis. Due to the small number and heterogeneity of studies, no recommendations can be made.
- Associations described between the use of antibiotics, paracetamol, or acetaminophen and atopic disease cannot be reliably interpreted and no causal link has been found between the use of these pharmaceutical drugs and the development of atopic disease(s).
- There is evidence that adverse psychosocial factors (e. g., stressful life events) during pregnancy and childhood can contribute to the onset of atopic disease.

In addition to the S3-guideline, there is evidence that the use of antacids can promote the risk of sensitization and increase the severity of food allergy [23].

Section in its entirety	strong consensus

Beyer, Reese

3. Symptoms and the differential diagnosis of food allergy

3.1. Clinical symptoms

What are the most common symptoms of a food allergy?

A variety of symptoms may be elicited by an IgE-mediated food allergy depending on [24, 25]:
- Use (site of exposure) of a food protein
- Underlying disease
- Frequency of exposure
- Dose

Most symptoms are not observed exclusively in food allergy and can be caused by other diseases.

Although the immune system is most commonly exposed to food proteins via oral/gastrointestinal routes, exposure can also take place via the following routes:
- Percutaneous (via the skin, e. g., contact urticaria)
- Inhalation (via the respiratory tract, e.g., baker's asthma, see Sect. 7 below)
- Parenteral (via the vascular system, e. g., contamination of injection solutions with food proteins).

The exposure route is relevant in terms of clinical symptoms. A variety of symptoms – often in combination – can be observed depending on the organ system affected (modified according to [26]) (**Tab. 2, Tab. 3**).

Tab. 2: Food allergy symptoms

Target organ	Symptoms
Systemic, circulatory	Anaphylaxis
	Hypotension, shock
	Tachycardia (in rare cases, bradycardia in anaphylaxis)
	Drowsiness, dizziness
	Syncope
Skin	Erythema (transient, flush)
	Eczema (exacerbation)
	Urticaria
	Itching
	Angioedema
	Rash
Eyes	Itching
	(conjunctival injections)
	Lacrimation
	Periorbital edema
Upper respiratory tract	Nasal congestion
	Itching
	runny nose (rhinorrhea)
	Laryngeal edema, stridor
	Hoarseness
	Dry cough
Lower respiratory tract	Cough
	Chest tightness
	Difficulty in breathing, respiratory distress (dyspnea)
	Wheezing
	Cyanosis
Oropharyngeal	Swelling of the lips, tongue, and/or gums (angioedema)
	Oral and/or pharyngeal itching (pruritus)
	Swelling of the tongue
Gastrointestinal tract	Nausea
	Vomiting
	Colic-like abdominal pain
	Gastroesophageal reflux (GER)
	Diarrhea

Core statements/recommendations	
Symptoms of IgE-mediated food allergies are diverse and affect a variety of organ systems (most notably skin and mucosa, less often the gastrointestinal tract, respiratory tract, and cardiovascular system).	strong consensus
In order to diagnose food allergy, a clear and reproducible association between symptoms and the intake of a defined food and an improvement in symptoms upon avoidance in conjunction with IgE sensitization needs to be present.	strong consensus
In the case of intermittent tolerance to foods, augmentation factor-dependent allergies such as food-related exercise-induced anaphylaxis need to be taken into consideration.	consensus

Tab. 3: Symptoms in delayed reactions or chronic exposure

Nausea
Vomiting
Abdominal pain
Gastroesophageal reflux (GER), dysphagia, and food bolus impaction
Loss of appetite and refusal to eat
Diarrhea, malassimilation
Hematochezia (blood in stools)
Failure to thrive and weight loss

Classen, Lange, Rabe, Koletzko

3.2. Manifestations and differential diagnoses

Which other diseases can cause the symptoms of a food allergy?

What are the clinical manifestations of a food allergy?

Foods can cause a variety of diseases. These are based on differing pathophysiological mechanisms and can involve different, sometimes multiple, organ systems (see also Sect. 7, **Tab. 17**).

Tab. 4 provides an overview of food allergy manifestations and differential diagnoses.

Non-allergic mechanisms: Food additives and natural flavorings can also potentially activate mast cells and imitate clinical symptoms of an IgE-mediated food allergy: for example, G-protein-coupled receptor activation, changes in eicosanoid metabolism, and increased mediator production/expression have been postulated. Isolated cases of non-allergic food intolerance reactions triggered by natural flavorings, sulfur compounds, benzoic acid compounds, histamine-containing foods, and glutamate have been described. Augmentation factors may be necessary to elicit a reaction, thus these should be considered where oral challenge is negative.

It is unlikely that salicylate-containing foods are of any relevance in acetylsalicylic acid (ASA) intolerance, since salicylic acid is not commonly found in foods [28]; however, this has not been sufficiently researched.

Core statements	
In the case of suspected food allergy, it is important to consider in the differential diagnosis chronic inflammatory diseases, carbohydrate malabsorption and functional or somatoform disorders.	strong consensus
Depending on patient symptoms and age, other diseases need to be taken into consideration in the differential diagnosis of suspected food allergy.	strong consensus
A (pediatric) gastroenterologist should be involved in the diagnostic work-up in the case of suspected non-IgE-mediated gastrointestinal intolerance reactions.	consensus

Classen, Lange, Rabe, Koletzko

4. Food allergy diagnosis

How can one reliably diagnose a food allergy?

Approach in suspected food allergy: In suspected IgE-mediated food allergy, diagnosis is based on a number of components (**Fig. 2**):

- Patient history (including diet and symptom protocols where appropriate) (4.1.)

Tab. 4: Manifestations and differential diagnoses of food allergy (modified from [25])

Immunopathology	Disease	Clinical characteristics	Typical age group	Prognosis
IgE-mediated	Acute urticaria/ angioedema	Elicited by ingestion or direct skin contact	Children > Adults	Depending on the triggering food
	Rhinoconjunctivitis/ bronchial asthma	Accompanies food protein-induced allergic reactions, on rare occasions airway symptoms (exception: inhalation exposure to aerosolized food protein, often occupational)	Infant > adult, with the exception of occupational diseases	Depending on the triggering food
	Anaphylaxis	Rapidly progressive multisystem reaction	All ages	Depending on the triggering food and underlying disease
	Delayed food-induced anaphylaxis to mammalian meat [27]	Anaphylaxis 3–6 s following ingestion; triggered by antibodies to galactose-α-1,3-galactose	Adults > Children	Unclear
	Food- and risk factor-induced anaphylaxis	Food only triggers anaphylaxis in the presence of augmentation factors such as exertion, as well as alcohol or acetylsalicylic acid (ASA) before or after food intake	Onset in late childhood/ adulthood	Probably permanent
	Secondary allergic cross-reactions (predominantly pollen-associated food allergies)	Oropharyngeal irritation; mild edema restricted to the oral cavity More rarely, perioral or generalized urticaria Airway symptoms (cough); In rare cases, systemic reactions (including anaphylaxis) in some pollen-associated allergies	Onset following pollen-allergy manifestation (adult > young child)	May persist; may vary seasonally
	Gastrointestinal allergic immediate-type reactions	Rapid-onset nausea following ingestion, followed by abdominal colic and diarrhea later	All ages	Depending on the triggering food
Mixed IgE- and cell-mediated	Atopic eczema/ dermatitis	Associated with food in 30 %–40 % of children with moderate/severe eczema	Infants > children > adults	In general, tolerance development
	Eosinophil-associated gastrointestinal disorders (EGID)	Symptoms vary: depending on the affected segment of the gastrointestinal tract and the degree of eosinophilic inflammation	All ages	Likely to be persistent
Cell-mediated	Food protein-induced proctitis/proctocolitis Food protein-induced enterocolitis syndrome (FPIES)	Mucous, bloody stools in infants Acute exposure: severe manifestations ranging from vomiting, (bloody) diarrhea, and exsiccosis to shock Chronic exposure Vomiting, diarrhea, failure to thrive, lethargy Re-exposure following avoidance: vomiting, diarrhea, hypotension 1–3 h following ingestion	Infants Infants – young children	In general, tolerance development In general, tolerance evelopment
	Food protein-induced enteropathy	Diarrhea, vomiting, failure to thrive, edema; no colitis	Infants – Young children > Adults	In general, tolerance development
	Celiac disease	Multiple manifestations, mono-, oligo-, and polysymptomatic, triggered by gluten in the case of genetic predisposition	All ages	Persistent (necessitating strict, lifelong gluten avoidance)
Non-allergic (non-immunological intolerance)	Carbohydrate malassimilation/malabsoption (lactose, fructose, sorbitol, in rare cases: sucrose, glucose-galactose)	(Osmotic) diarrhea, meteorism, abdominal pain 1–4 h following intake, possibly also obstipation	Lactase deficiency typically from school age, otherwise all ages Fructose malabsorption/ sorbitol: all ages, very rarely: congenital lactase deficiency, glucose-galactose intolerance, sucrose-isomaltase malabsorption	generally persistent (lactose, glucose-galactose); fructose, sorbitol

- Sensitization test (colloquially known as an „allergy test")
- IgE determination (Sect. 4.2) and/or
- Skin prick test (Sect. 4.3)
- Determining clinical relevance (interpretation)
- Plausibility based on clinical information (in the patient history)
- Where appropriate, diagnostic elimination diet and
- Oral challenge testing (Sect. 4.4)

Test sequence and test reagents are selected on the basis of:

a) Patient history
b) Patient age
c) Testing methods available (discussed in subsections)

Diagnostic tests identify sensitization. This is achieved by:

- Directly determining allergen-specific IgE to food extracts/allergens in serum (Sect. 4.2), or by
- positive skin testing (skin prick test) (Sect. 4.3) with food (extracts) as indirect evidence of functional (i.e., capable of cross-linking) allergen-specific IgE on skin mast cells.

The qualitative results (positive vs. negative) of IgE tests and skin prick tests allow the following interpretation:

- A negative result excludes sensitization.
- A positive result indicates sensitization which, however, is only clinically relevant in the presence of corresponding symptoms.

A single test (IgE test or skin test) may be sufficient to verify a sensitization to food. It is common for a number of tests to be used to detect sensitization (**Fig. 2**). Results are not always consistent; in such cases, a positive result is more likely to be correct than a (false) negative result. Consistent results (concordant positive or negative) increase diagnostic accuracy, particularly if mostly different food reagents (native preparation, extracts, single allergens) are used in skin or IgE tests.

Test interpretation: The patient history is of central importance in the interpretation of sensitization tests: A food allergy can only be diagnosed or excluded in the case of clear concordance between clinical patient information and test results (skin prick test/IgE determination). In the case of absent or insufficient concordance (e. g., due to unclear or inadequate patient history), clinical relevance should be investigated using oral challenge (**Fig. 2**; Sect. 4.4).

The term „allergy test" (for skin or IgE tests) is in this context ambiguous and represents the greatest cause of misinterpretation of diagnostic results: A positive result, e. g., to food (i. e., sensitization) can only be successfully interpreted when the clinical reaction is known.

Approximately half of the atopic sensitizations detectable in a population are genuinely associated with symptoms and thus of clinical relevance. Thus, all sensitization tests show unsatisfactory diagnostic specificity (approximately 50 %) and limited positive predictive value (PPV) strongly, depending on the respective allergen source and the prevalence of food allergy in the cohorts investigated.

In of gastrointestinal allergic manifestations, local diagnostic measures can be considered, such as mucosal or endoscopic provocation tests and endoscopic lavage.

Recommendations/core statements

Specific tests for IgE sensitization should be guided by patient history.	strong consensus
IgE sensitization to foods and aeroallergens should be performed by means of specific IgE determination and/or skin prick testing.	consensus
Specific IgE determination and skin prick testing support the diagnosis of food allergy in conjunction with patient history and/or food challenge.	strong consensus
The detection of sensitization by means of specific IgE determination or skin prick testing does not prove the clinical relevance of the tested food and should not, in isolation, prompt its therapeutic elimination.	strong consensus
Failure to detect sensitization (negative specific IgE/skin prick test) often, but not always, excludes a clinically relevant IgE-mediated food allergy.	consensus

Kleine-Tebbe

4.1. Patient history and diet/symptom protocols

How important is the history of patients in suspected food allergy?

Which aspects of the patient history need to be considered in suspected food allergy?

4.1.1. Practical approach to history-taking

Allergy history-taking in suspected food allergy follows the general principles of interviewing. Providing patients with a special questionnaire prior to their initial appointment is helpful; patients should either bring the completed questionnaire to their appointment or complete it in the waiting room. History-taking (**Tab. 5**) includes family history, personal history and specific dietary history.

The times, places, and situations in which reported symptoms occur should be recorded. It is particularly important to establish whether the patient experiences periods of complete freedom from symptoms.

4.1.2. Supporting measures

A diet- and symptom diary helps patients to observe their habits and symptoms. Particularly if symptoms are permanently apparent, it is helpful for patients or their parents to keep a record over a period of 2–3 weeks Besides the intake of food, but also beverages, confectionery, chewing gum, etc., symptoms occurring in temporal relationship to this intake should be recorded. Recordings are evaluated by a dietician with experience in allergy, or an allergist.

Drug use should also be recorded in the diary. Symptoms should cover the type and intensity and date, time, duration it present and particular features (e. g., restaurant food). Once a diagnosis has been made, the further diagnostic and therapeutic approach is planned with the help of a follow-up patient history. In this way it is possible to qualify or confirm the relevance of existing (or absent) sensitizations and facilitate the decision-making process on challenge testing or other measures. It is also important to bear in mind that some medications [e. g., proton pump inhibitors (PPI) or alkylating drugs) can promote the development of sensitization [29].

4.1.3. Consideration of augmentation factors

Augmentation factors should also be taken into consideration in the patient history. These can magnify an allergic reaction and, in some cases, need to be present in order to facilitate the onset of symptoms occur (e. g., in wheat-dependent exercise-induced anaphylaxis). The most widely known augmentation factors include:

- physical activity and
- the use of non-steroidal anti-inflammatory drugs (NSAID)

Moreover, alcohol, pyrexia, acute infections and allergic symptoms during the pollen season have also been described as augmentation factors [30].

Recommendations	
A detailed patient history should build the basis for the diagnosis of food allergy.	strong consensus
A structured patient history should take: time course, symptoms, family history, comorbidities and the presence of other allergic diseases into consideration.	strong consensus
A diet- and symptom log is supportive.	strong consensus

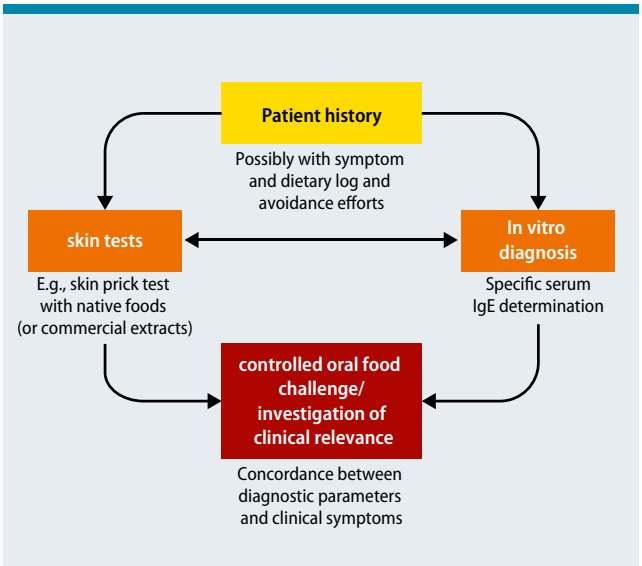

Fig. 2: Diagnostic approach in suspected food allergy: sensitization often detected in adults using skin tests (*left*), in children preferably using specific IgE determination (*right*; see text for additional details)

Tab. 5: Approach to history-taking

Patient history	
Personal patient history	Known allergic diseases Medications Physical exercise Acute infectious diseases Psychological stressors
Family history	Allergic diseases in first-degree relatives
Symptoms and specific triggers	When Where In response to what How long How often Repeatedly
Dietary history	Avoidance measures and extent thereof
Dietary and symptom diary	Documenting food and symptoms

4.2. Triggering allergens and in vitro diagnostics

How to determine the severity of a food-related allergic reaction?

What are helpful indications for sIgE determination?

How to classify the relevance of diagnostic methods using single allergens?
How relevant are sensitizations to specific allergens?
Which are the most important allergens in food allergy?
What needs to be taken into consideration in serological diagnosis?

4.2.1. Serological IgE determination to detect sensitization

Allergen-specific serum IgE to food allergens indicates sensitization. The absence of specific IgE (generally) excludes sensitization if the test covers all relevant allergens.
The results of logarithmically distributed specific IgE concentrations can differ from one another depending on:

- Manufacturer
- Test design
- Reagents
- Allergen(extract)s (most important)

The following allergens are used for IgE testing:

- Individual foods (allergen sources, **Tab. 6**)
- A combination of different foods (screening or panel test)
- Single allergens (**Tab. 7–9**, additional sources of information in **Tab. 10**) [32].

The diagnostic suitability is evaluated separately according to the allergen source and test procedure.

4.2.1.1. Indication for IgE determination

There are a number of different indications for in vitro diagnosis [33] depending on:

- age,
- symptoms and
- suspected allergen source (**Tab. 6**).

Suspicion/exclusion of a food allergy: Specific IgE determination is helpful if food allergy is suspected or should be excluded. This indication requires that the allergen sources or allergens used in the test are fully represented and are capable to detect potentially present IgE antibodies.

Panel tests for specific IgE (e. g., to peanut, fish, chicken protein, cow milk protein, soy, and wheat) make it possible to reasonably exclude as as basis for further or detect sensitization. Thus, they serve as a for a further detailed breakdown of single allergen sources. Broad screening panels in the absence of a reasonable suspicion of food allergy are not recommended.

Severe allergic reactions to foods: Determining specific IgE to the foodstuff suspected (or to be excluded) in severe anaphylactic reactions is preferred and skin testing should be performed after consideration of the individual risk:benefit ratio.

Suspected sensitization to foods suitable for skin testing: Specific IgE determination is recommended in such cases where skin testing is not suitable to detect sensitization (e. g., skin-irritating foods such as spices).

Conditions that preclude skin testing or its interpretation: Specific IgE determinations are helpful if skin testing is not suitable. Such cases involve urticaria factilia or active skin disease in the test area in a given Patient or the use of drugs that affect skin testing. Analysis of specific serum IgE to allergenic foods is often determined in infants and young children instead of performing skin tests.

Common food allergen sources with low potential risk: Mild clinical reactions (e. g., oropharyngeal symptoms in pollen-associated food allergy) can be tested in the usual diagnostic work up, i. e., patients history, skin testing, in vitro diagnosis. Sensitizations in birch pollen-associated food allergy should be tested by native prick-to-prick testing, since commercially available extracts do not contain the relevant allergens sufficiently. Screening (including serological tests) without specific suspicion of food allergy, e. g., of all fruit and vegetable types or the available single allergens in birch pollen-associated cross-sensitization, is not recommended [3].

Tab. 6: Important allergen sources in childhood and adult food allergies

Children	Adolescents and adults
cow's milk, hen's egg, peanut, wheat, soy, nuts, fish	pollen-associated food allergens (e.g., apple, nuts, soy, celery, carrot, bell pepper, spices), nuts and oilseeds (e. g., sesame), peanut, fish and crustaceans, cow's milk, hen's egg, latex-associated food allergens (e. g., banana, avocado, kiwi, fig), mammalian meat

4.2.1.2. Definitions and concepts for allergen selection

The potential advantages and disadvantages of in vitro diagnostics using extracts or single allergens need to be defined separately for each allergen source or single allergen [35] (see information in **Tab. 10**).

The following arguments support the use of single allergens (**Tab. 11**):

- Increased test sensitivity [lower limit of quantitation (LOQ)] [36] due to certain single allergens, particularly if they are underrepresented or absent in the (food) extract (examples: soy protein Gly m 4 [37], wheat gluten Tri a 19, apple protein Mal d 1, galactose-α-1,3-galactose, a sugar epitope of mammalian meat).
- Increased test discriminatory power (analytical specificity or selectivity) with single allergens from allergen sources made up of complex mixtures of multiple allergens and associated with increased clinical risk (examples: Ara h 2 from peanut, Pru p 3 from peach, Cor a 9 and 14 from hazelnut, Act d 1 from kiwi).
- The detection of IgE to typical cross-reactive allergen molecules facilitates interpretation in the case of low analytical specificity of extracts (cross reactivity) (examples: Bet v 1 or homologs, Phl p 12 or Pru p 4 as profilin, Pru p 3 as lipid transfer protein [LTP], cross-reactive carbohydrate determinant [CCD] components MUXF3).

Current reimbursement restrictions on IgE measurements can result in unacceptable limitations regarding a more extensive screening which may be needed in more complex cases of food allergy.

A lower LoQ when using single allergens in IgE diagnostics does not necessarily increase diagnostic sensitivity. Where this is the case diagnostic specificity can be lower. (**Tab. 11**).

Both parameters, diagnostic sensitivity and specificity, can result in difficulties regarding the interpretation of specific IgE diagnostic methods: A positive IgE finding, reflecting sensitization without information on previous history, cannot per se predict clinical reactions in food allergie individuals. Therefore , international guidelines on allergen-specific IgE test methods [38] no longer require diagnostic sensitivity and specificity to be given, but are replaced by analytical parameters. Thus, the use of single allergens for IgE determination is justified, most notably by their greater test sensitivity (lower LoQ) and analytical specificity: Where single allergens are capable of improving in vitro diagnosis, their use is helpful and recommended from an allergological perspective.

Tab. 7: List of definitions and abbreviations

Allergen	A molecule (protein, e. g., major allergen Gad c 1 from cod, more rarely a carbohydrate component) that elicits an allergic immune response
Allergen extract	A mixture of allergenic and non-allergenic components extracted from an allergen source (e.g., fish allergen extract)
Allergen source/carrier	Origin/source material of the allergens (e.g., fish)
α-Gal	Galactose-α-1,3-galactose, a disaccharide as the cause of severe anaphylaxis to mammalian meat, gelatin, and biologicals
Ara h 2	2S albumin, a peanut storage protein associated with severe systemic reactions in peanut allergy
Api g 1	Bet v 1-homologous celery allergen responsible for birch pollen-associated cross reactions
Bet v 1	Immunodominant major allergen in pollen and birch (*Betula verrucosa*)
Bet v 2	Birch pollen profilin which, as a panallergen in numerous pollen and plant-based foods, can be responsible for broad cross reactivity and hamper proper diagnostics
CCD	Cross-reactive carbohydrate determinants: N-glycan epitopes which, as panallergens, are responsible for broad cross-reactivity
Cor a 1.04	Bet v 1-homologous hazelnut allergen responsible for birch pollen-associated cross reactions
Dau c 1	Bet v 1-homologous carrot allergen responsible for birch pollen-associated cross reactions
Gad c 1	Major cod allergen (Ca2+ transport protein, parvalbumin, most important fish allergen)
Gly m 4	Bet v 1-homologous soy allergen responsible for birch pollen-associated, partially severe cross reactions
Cross reactive	Immunological response based on the similarity between molecular structures not responsible for the initial sensitization
LTP	Lipid transfer proteins: heat- and digestion-stable allergens of plant origin
Mal d 1	Bet v 1-homologous apple allergen responsible for frequent birch pollen-associated, mostly oropharyngeal cross reactions
MUXF3	Name given to the structure of a carbohydrate side chain made up of plant glycoproteins and allergens that can potentially be bound by IgE antibodies, a specific type of CCD (see above)
Oleosins	Lipophilic and heat-stable allergens in nuts and oilseeds
Pen a 1	Tropomyosin (muscle structure protein) in the shrimp with homologous proteins in other arthropods and the cause of cross reactions
PR-10	Pathogenesis-related protein family 10; bet v 1-homologous protein involved in plant defense (e.g., in tree pollen, foods)
Pru p 3	Peach LTP responsible for systemic reactions in patients in the Mediterranean region
Recombinant	Produced using genetically altered (micro-)organisms
Recombinant allergen	Allergenic protein frequently produced in *Escherichia coli* without the carbohydrate side chains found in native allergens
Sensitization	Susceptibility to allergy (only relevant in the presence of corresponding symptoms)
Tri a 19	ω-5-Gliadin in wheat responsible for systemic reactions and exercise-induced anaphylaxis in wheat allergy

Tab. 8: Selected food allergens and their sources of plant origin[a,b]

	Protein families							
						Storage proteins (protein families, structure)		
						Prolamins	Cupins	
	Bet-v-1 homologs	LTP	Profilins	Thaumatins	Oleosins	2S Albumins	7/8S Globulin (vicilin)	11S Globulin-(legumin)
Apple	Mal d 1	Mal d 3	Mal d 4	Mal d 2				
Peanut	**Ara h 8**	**Ara h 9**	Ara h 5		Ara h 10 (16 kD) Ara h 11 (14 kD)	**Ara h 2** Ara h 6 Ara h 7	**Ara h 1**	**Ara h 3**
Spices Bell pepper Parsley	Pet c 1	Pet c 3	Cap a 2 Pet c 2	Cap a 1				
Hazelnut	**Cor a 1**	**Cor a 8**	Cor a 2		Cor a 12 (17 kD) Cor a 13 (14/16 kD)	**Cor a 14**	Cor a 11	**Cor a 9**
Carrot	Dau c 1	Dau c 3	Dau c 4					
Cherry	Pru av 1	Pru av 3	Pru av 4	Pru av 2				
Kiwi	Act d 8		Act d 9	**Act d 2**				
Peach	**Pru p 1**	**Pru p 3**	**Pru p 4**					
Celery	**Api g 1**		Api g 4					
Sesame					Ses i 4 Ses i 5	Ses i 1 Ses i 2	Ses i 3	Ses i 6 Ses i 7
Soybean	**Gly m 4**	Gly m 1	Gly m 3				**Gly m 5**	**Gly m 6**
Wheat		Tri a 14	Tri a 12			**Tri a 19** (ω-5-gliadin)		

[a]Allergen sources (left column) with single allergens (table columns) and their protein families (table header)
*[b]**Bold**: already available for in vitro diagnosis; normal type: not yet available for differentiated diagnosis*

4.2.1.3. Foodstuffs as allergen sources and their allergens

Foodstuffs are complex allergen sources and contain a variety of (glyco)proteins, the actual allergens. A relationship is therefore formed by the biological taxonomy of the foodstuffs in question and via biochemical similarity of the allergens contained. The relevance of allergen sources (**Tab. 6**) is related to the age of the affected patient and depends on regional and personal dietary habits.

4.2.1.4. Important plant protein families and their allergens

Fruit, vegetables, legumes, tree nuts, oilseeds, and cereal contain allergens and can cause sensitization [39].

Tab. 9: Selected food allergens of animal origin[a,c]

	Protein families			
	Parvalbumins	**Tropomyosins**	**Lysozymes/α-lactalbumins**	**Other proteins (various families)**
Hen's egg			**Gal d 4** (lysozyme C)	**Gal d 1** (ovomucoid, trypsin inhibitor) **Gal d 2** (ovalbumin, serpin) **Gal d 3** (ovotransferrin, conalbumin)
Fish	**Gad c 1** **Cyp c 1**	Ani s 3[b]		
Crustaceans/ molluscs	**Hom a 6**	**Cha f 1** **Hom a 1** **Met e 1** **Pen a 1**		
Cow's milk			**Bos d 4** (α-lactalbumin)	**Bos d 5** (β-lactoglobulin, lipocalin) **Bos d 6** (bovine serum albumin) **Bos d 8** (casein)

[a]Allergen sources (left column) with single allergens (table columns) and their protein families (table header)
[b]Severe allergic reactions following the consumption of fish infected by the herring worm (Anisakis) have been described
*[c]**Bold:** already available for in vitro diagnosis, normal type: not yet available for differentiated diagnosis*

The most important protein families and single allergens in plant foods have now been identified (**Tab. 8**). These are increasingly used for IgE diagnostics (**Tab. 8**, **Tab. 12**).

Profilins: From a phylogenetic perspective, profilins are strongly conserved proteins and are considered to be clinically less relevant allergens. Sensitizations are, often caused primarily by grass-pollen exposure but, are potentially linked to all pollen and numerous plant foods (e. g., apple, carrot) due to cross reactions. Determination of sIgE against one profilin (e. g., grass pollen profilin Phl p 12, birch pollen profilin Bet v 2, or peach profilin Pru p 4) is usually sufficient for diagnostic purposes. Exotic fruits not belonging to the Bet-v-1 food allergen cluster (e. g., melon, banana, avocado, mango) have been reported to induce oropharyngeal symptoms [3].

Bet v 1-homologous PR-10 proteins: Birch pollen allergy in Central Europe is predominantly due to sensitization to the major allergen Bet v 1, a natural plant stress protein (pathogenesis-related protein family 10, PR-10).

Similar PR-10 proteins are found in hazel, alder, beech, and oak tree pollen, but also in various types of fruit and vegetables, as well as nuts and legumes (**Tab. 8**). They form the basis for birch pollen-asso-

Tab. 10: Freely accessible internet sources/databases and information on molecular allergology [34]

Web link	Short description
www.allergen.org	Official database of the IUIS Allergen Nomenclature Sub-committee with simplified search function
www.allergenonline.org	Food allergen database of the University of Nebraska in Lincoln, Food Allergy Research and Resource Program (FARRP); carefully maintained records sorted according to taxonomic affiliation of the allergen sources
www.allergome.org	Largest database of allergen molecules, initiated by the Italian allergologist, Adriano Mari, and his team; some of the identified single allergens were included prior to their official naming
www.meduniwien.ac.at/allergens/allfam/	Database of allergen families (protein families) of the Vienna Medical University, Institute for Pathophysiology and Allergy Research at the Center for Pathophysiology, Infectology, and Immunology
www.allergyeducation-ma.com	Short animated presentation made by a diagnostic manufacturer

Tab. 11: Influence of single allergens on the test characteristics of IgE diagnostics*

	Test sensitivity (LoQ)	Specificity
Analytical	+ Smallest quantity of a test substance that can be precisely determined (lower LoQ)	+ Ability of a test to measure a specific substance rather than others in a test (analytical selectivity)
	Sensitivity	**Specificity**
Diagnostic	(+) Proportion of affected individuals identified correctly (i.e., positive result) as affected prior to testing	(+) Proportion of healthy individuals identified correctly (i.e., negative result) as healthy prior to testing

**Components in IgE diagnostic testing increase test sensitivity (lower limit of quantitation, LoQ), particularly when they are underrepresented or absent in extracts. They increase analytical specificity, since only part of the allergen-specific IgE repertoire is identified and, e.g., cross reactivity due to extracts of complex composition is avoided. It is sometimes also possible to improve diagnostic test characteristics with regard to clinical symptoms (diagnostic sensitivity and specificity) (see text for more details).*

ciated cross reactions, e.g., to apple, cherry, peach, and hazelnut, among many others [3]. Due to the low proportion of PR-10 proteins in the total mass and their lack of heat and digestive resistance, symptoms are caused only by raw foods and generally remain restricted to the mouth and throat. In individual cases, severe systemic symptoms may occur, e.g., if large quantities of the food are consumed or due to matrix effects (the PR-10 protein is protected by other food components) (examples: Gly m 4 in soy, more rarely also Api g 1 in celery, Dau c 1 in carrots).

Tab. 12: Examples of clinical patterns and molecular diagnostic recommendations [40]

Clinical picture	Clinical suspicion	IgE diagnostics
Anaphylaxis following physical activity	Exercise-induced wheat allergy	Tri a 19 (ω-5-gliadin)
Pork-cat syndrome	Allergy to mammalian serum albumins	Fel d 2 or Bos d 6
Delayed meat allergy (e.g., urticaria)	Sensitization to galactose-α-1,3-galactose (α-GAL)	α-GAL (thyreoglobulin)
Allergy, e.g., to grapes	Sensitization to lipid transfer proteins (LTP)	Pru p 3 (peach LTP)
Oral allergy syndrome (OAS), frequently to nuts, pome and stone fruits, etc., systemic reactions to (native) soy possible	Sensitization to Bet-v-1 homologs (PR-10 proteins)	Bet v 1 and Gly m 4
OAS following uncommon plant foods (melon, exotic fruits such as lychee and citrus fruits)	Sensitization to profilins	Pru p 4 (or Bet v 2, Phl p 12, Hev b 8)

Lipid transfer proteins: Systemic reactions induced by fruit, vegetables, nuts, legumes, and cereals can be caused by LTP. Ripe peach can initiate primary sensitization, as described in the Mediterranean region. The structural similarity of peach LTP, Pru p 3, to other heat- and acid-stable LTP can cause cross reactions to other plant foods and to a certain extent independent from the Bet v 1 cluster described (e.g., wine grapes, blueberries, vegetables). The major allergen Pru p 3 is often sufficient to detect sensitization. The clinical relevance of LTP sensitization in terms of plant foods to be avoided in the future needs to be established with the patient on a case-by-case basis. This is achieved on the basis of the patient's previous history (clinical reaction) or, in cases of doubt, oral challenge with the suspected LTP-containing foods.

Seed storage proteins: Storage proteins are structurally related yet variable, stable and clinically relevant food allergens, e.g., in nuts, seeds, legumes, including peanut, soybean, lupin, and cereals.

A distinction is made between 2S albumins from the prolamin and globulins from the cupin superfamilies on the basis of their structure. The globulins contain vicilins (7S globulins) and legumins (11S globulins) (**Tab. 8**). Due to their stable structure and high proportion of the total protein, storage proteins rarely cause problems in extract-based diagnosis. They are associated with an increased risk for systemic symptoms due to their heat and digestive stability. The following storage proteins are well suited for a selective detection/exclusion of sensitization by analytical methods:

- Gly m 5 and 6 in soy allergy
- Ara h 1, 2, 3, and 6 in peanut allergy
- Cor a 9 and 14 in hazelnut allergy
- Jug r 1 and 2 in walnut allergy
- Ber e 1 in Brazil nut allergy

Serological cross reactions between storage proteins do not permit predictions of the onset of clinical symptoms.

4.2.1.4.1. Other allergens in plant derived foods

Cross-reactive carbohydrate epitopes: Numerous plant derived foods are glycoproteins containing CCD (Cross-reactive Carbohydrate Determinants) (e.g., in pollen, plant foods, articulates, molluscs, and certain pathogenic helminths).

Their IgE binding is generally clinically irrelevant [41]. Although they do not give rise to positive skin tests, they hamper IgE diagnosis with extracts or natural CCD-bearing single allergens. Specific tests against bromelain, horseradish peroxidase or the N-glycan MUXF (CCD single allergen component of bromelain with no peptide component) are well suited for CCD-specific IgE screening.

Oleosins: Oleosins are allergens which are present in high fat plant foods. As lipophilic proteins, they are underrepresented in aqueous extracts of legumes (e. g., peanut), seeds (e. g., sesame), and tree nuts (e. g., hazelnut) They can results in false-negative diagnostic results. In such settings, testing of the native foodstuff in skin tests is suggested.

Thaumatins and enzymes: Thaumatin-related proteins are thermo- and digestion-stable plant foods [40], i. e. from cherry (Pru av 2), apple (Mal d 2), kiwi (Act d 2), banana (Mus a 4), peach (Pru p 2), tomato, bell pepper and walnut. They are rarely available for diagnostics (Act d 2 from kiwi, ImmunoCAP ISAC®). The prevalence of sensitizations or clinically relevant reactions is unknown. A similar situation is present for a number of enzymes found in plant foods (e. g., exotic fruits).

4.2.1.5. Common animal food allergens

Animal proteins from a variety of allergen sources can also induce food sensitization. These are often heat- and digestion-stable and can cause systemic allergic reactions.

Their structural similarity induces serological cross reactions within a protein family. However the clinical relevance cannot be deduced from the test result. Due to complex sensitization patterns and good representation of the proteins, diagnosis using extracts is often sufficient.

Hen's egg: The most important hen´s egg allergens have been identified (Gal d 1, 2, 3, 4).

Sensitizations to the heat resistant major allergen Gal d 1 are frequently associated with persistent hen's egg allergy. The failure to detect IgE during the course of hen's egg allergy can indicate the development of tolerance. Despite clinically relevant hen's egg allergy (also in Gal d 1 sensitization), the majority of affected patients tolerate egg in cooked form.

Cow's milk: Complex sensitization patterns to predominantly stable cow milk proteins and the fact that these proteins are well represented in cow milk extracts are rationales to use the total extract for diagnostic purposes. Due to their stability, some single allergens, such as Bos d 8 (casein), are associated with persistent cow's milk allergy and reactions to processed milk (products). Decreasing or absent IgE may indicate the development of tolerance. Again, the majority of cow's milk allergics tolerate cow's milk in cooked form.

Meat: Allergies to mammalian meat, particularly after consumption of pluck, can be caused by sensitization to serum albumins. Due to high cross reactivity, determining IgE to one representative serum albumin (e. g., Fel d 2 from cat, Bos d 6 from cow) is sufficient.

A further source of allergic reactions following the consumption of meat is a carbohydrate epitope (CCD) found in mammals (but not primates): α-Gal. This carbohydrate side chain is responsible for delayed urticarial and severe anaphylactic reactions following the intake of red meat [42]; poultry, on the other hand, is tolerated. In suspected meat allergy, IgE determinations to albumins, α-Gal (o215, ImmunoCAP®, ThermoFisher), and the suspected meat type are helpful.

Fish: Reactions following fish consumption are often caused by a major allergen of the parvalbumin group (e. g., Gad c 1 from cod, Cyp c 1 from carp). Since additional species-specific fish allergens can

Tab. 13: Problems assessing specific IgE results

Technical and methodological errors
(Reasons for false-positive and false-negative results)
— Poor reagent quality (e.g., allergen extracts or their extraction, coupling, and stability)
— Laboratory errors
Interpretation errors
(Reasons for clinically irrelevant results)
— Markedly elevated total IgE and multiple sensitizations
— High detection sensitivity
— Cross-reactive IgE antibodies

IgE, immunoglobulin E

cause sensitization, extract-based diagnosis with the suspected fish type is recommended. The high stability of most fish allergens to heat and digestion, as well as the fact that they make up a large proportion of the total protein, explains their hazardous nature: Even small amounts can be sufficient to trigger systemic reactions.

Crustaceans and molluscs: Tropomyosin, a muscle protein with high cross reactivity, is considered an important major allergen in crustaceans and shellfish. In addition to determining this major allergen (e. g., Pen a 1, shrimp tropomyosin), the use of extracts from the suspected animal is recommended due to additional possible allergens. Shrimp can also trigger exercise-induced anaphylaxis. House dust mite allergy sufferers sensitized to tropomyosin, minor allergen Der p/f 10, can react to crustaceans.

4.2.1.6. Interpreting serological IgE diagnostic methods

Specific IgE to food allergens can only be reliably interpreted when the clinical reaction of the patient is known.

The following interpretation errors may occur:

- Sensitizations in the absence of corresponding symptoms are misinterpreted as an allergy.
- Allergens absent or barely present in the extract can cause false-negative or excessively low IgE values.
- Laboratory errors can cause both false-negative and false-positive findings.
- Total IgE needs to be considered when interpreting quantitative IgE concentrations: Very high total IgE (e. g., >2000 kU/l in patients with atopic eczema) is often associated with multiple sensitizations of questionable clinical relevance.
- In the case of low total IgE (e. g., < 20 kU/l), low specific IgE values can also be of diagnostic relevance and the detection or exclusion of sensitization can be hampered.

Conclusion: Specific IgE detection indicates IgE-mediated sensitization that is only of clinical relevance in conjunction with a corresponding patient history or positive controlled challenge.

4.2.2. Cellular techniques to detect IgE-dependent sensitization

IgE-mediated sensitization can also be detected indirectly using a basophil activation test (BAT). These tests are complex, costly, and only helpful in in vitro diagnosis in individual cases of suspected food allergy (e. g., in unusually low total IgE, < 20 < 10, < 5 kU/l).

Core statements/recommendations

The severity of a clinical reaction should be measured on the basis of the patients history and/or challenge testing rather than on quantitative test results.	strong consensus
Valid indications for IgE determination include: allergy testing	consensus
a) Justified suspicion of an IgE-mediated food allergy	
b) Targeted exclusion of an IgE-mediated food allergy	
c) A severe reaction to food	
d) Justified suspicion of sensitization to food not suitable for skin testing	
e) Conditions that preclude skin testing or the evaluation thereof (e. g., urticaria factitia, generalized skin disease, use of drugs that impair skin testing results)	
f) Very young patient age (infants or young children)	
g) Greater diagnostic value expected from molecular allergy diagnostics	
Total IgE should be measured to support interpretation.	consensus
IgE diagnostics using single allergens for the detection of sensitization should be used for specific diagnostic investigations.	strong consensus
In vitro diagnostics using single allergens can increase test sensitivity particularly in the case of unstable or underrepresented food allergens.	majority approval
Sensitization to certain allergen components (see tables in Sect. 4.2) can be associated with systemic allergic reactions. Determining these components increases analytical specificity compared with food extracts.	strong consensus

Kleine-Tebbe, Ballmer-Weber, Jappe, Saloga, Wagenmann

4.3. Skin testing

Which skin testing method is well suited to diagnose food allergy?

What should be given special attention in skin testing to diagnose food allergy?

Skin tests are a central component in food allergy diagnosis. The skin prick test is the preferred skin testing method. Diagnostic sensitivity and specificity can vary according to the material used (extract,

native foodstuff). The method is generally safe and results are available within 20 min.

4.3.1. Contraindications

Contraindications to skin testing include:

- Active skin disease in the test area
- Use of medications that affect test results (e. g. antihistamines)
- Presence of urticaria factitia
- Severe anaphylactic reaction in the patient history to the foodstuff to be investigated (relative contraindication)

4.3.2. Restrictions in the use of commercial extracts and criteria for their use

Numerous commercial food extracts are not standardized in terms of their allergen content. Skin tests have a greater diagnostic sensitivity and greater negative predictive value (NPV) but a limited PPV in children with atopic eczema and food allergy to, e.g., milk, egg, or peanut. Skin tests using extracts from plant foods (fruit, vegetables) often (if not always) have insufficient test sensitivity and diagnostic sensitivity. Endogenous enzymatic processes cause less stable allergenic proteins in the extract to degrade (e. g., Bet v 1-homologous food allergens). In addition, important allergenic components are sometimes present in lower concentrations. In such cases, prick-to-prick testing with fresh foodstuffs offers an alternative to commercial extracts (**Tab. 14**).

In practice, skin testing with pollen extracts is helpful in the case of suspected pollen-associated food allergy. Commercial solutions can be used for those foods that have been shown in studies to have high test sensitivity and diagnostic sensitivity in food allergy diagnosis, such as fish extract. In the case of fruit, vegetables and meat, prick-to-prick testing using native foodstuffs is considered more sensitive. Therefore these are more diagnostically sensitive, however less specific.

4.3.3. Advantages and disadvantages of testing with native material

Skin testing with native material can be helpful if original recipes are tested. A skin test, e. g., with a cooked, mixed original recipe, allows to assess whether the possible individual components should be investigated. Furthermore, skin testing offers to test the processed foodstuffs in a given meal and to assess any possible alterations to their allergenicity.

One drawback of skin testing with native material is in its lower diagnostic specificity. Thus, one may obtain e. g. false-positive results due to the irritant potential of native foodstuffs. In rare cases, native foodstuffs used for skin testing can cause

Tab. 14: An overview of the suitability of skin prick testing materials [43][c]

	Commercial extract	Suitable for native testing[a]	Limited suitability for native testing[b]
Foods of animal origin			
Fish	+	+	
Meat	(+)	+	
Hen's egg	+	+	
Seafood and snails	+	+	
Milk	+	+	
Foods of plant origin			
Pineapple			+
Apple		+	
Cereals	(+)	+	
Strawberries			+
Peanut	+	+	
Spices			+
Hazelnut	+	+	
Carrot		+	
Kiwi			+
Lychee		+	
Mango		+	
Oilseeds (e. g., poppy, sesame)		+	
Peach		+	
Celery	(+)	+	
Mustard			+
Soy	(+)	+	
Tomato			+
Grapes		+	
Sugar snap pea		+	

[a]Ideally, a control subject is tested due to irritant components (testing control subjects with non-approved test preparations is illegal in Germany according to the German Medicinal Products Act). [b]High irritant potential. [c]Data on extract quality is available only for individual foods; hence this table can only provide limited information. As a basic principle, testing with native foods generally has better diagnostic sensitivity at lower specificity.

systemic allergic reactions. Moreover, this test principle is not standardized.

4.3.4. Other skin testing methods and their diagnostic value

Intracutaneous tests using foods are not relevant in practice, since they bear a considerably higher risk of systemic reactions and may lead to false-positive reactions. Atopy patch tests using fresh foods, e. g., based on the suspicion that atopic eczema may be aggravated by food allergens, only rarely yield helpful additional information.

Greater emphasis will be placed on the use of fresh foods in skin testing in the future, since the number of commercially available extracts declines as these today need to be approved as medicinal products according to European legislation. Due to the high costs associated with this procedure manufacturers will only offer the most demanded allergen sources [2, 3, 44].

Recommendations/core statements	
The skin prick test is the preferred skin testing method in the diagnostic work up of IgE-mediated food allergy.	strong consensus
Scratch tests, rubbing tests, intracutaneous tests and closed epicutaneous tests (atopy patch test) are not recommended for the routine diagnosis of food allergy.	consensus
Tests should be conducted using commercially available test solutions or native foodstuffs, depending on the stability and safety of the food allergens.	strong consensus

Zuberbier, Szépfalusi

4.4. Diagnostic elimination diet and challenge testing

What is a diagnostic elimination diet and for how long should it be performed?
How important is food allergen challenge testing and how should it be performed?

4.4.1. Elimination diets

A diagnostic elimination diet comprises the controlled avoidance of foods for a certain period of time. In cases of chronic disease such as atopic dermatitis, the diet should not last longer than 1 to maximally 2 weeks, except in exceptional cases. Longer times (3–4 weeks) may be required for non-IgE-mediated reactions. There is evidence to suggest that long-term elimination in IgE-mediated food allergy increases the risk of immediate reactions upon reintroduction of relevant foods. It should therefore be avoided. A diagnosis can be supported or excluded by evaluating detailed (complete) documentation in the form of a diet and asymptom diary. This approach avoids unnecessary food restrictions.

Oral food challenge should be performed under medical supervision following a diagnostic elimination diet.

The extent of dietary measures needs to be reviewed if no symptom improvement is seen under diagnostic food avoidance. In such cases, either symptoms are non-food-related or not all potential triggers have been identified and hence eliminated, or augmentation factors are affecting reactivity.

4.4.1.1. Use of therapeutic infant formula during the diagnostic process

Non-breastfed infants with suspected cow's milk allergy require a cow's milk substitute in the form of an extensively hydrolyzed infant formula or an amino acid-based formula during the period of diagnostic elimination; formulas should be selected on a case-by-case basis (see also Sect. 5.3). Allergy to the avoided food is highly unlikely if symptoms fail to improve despite a carefully controlled elimination diet. In such cases, the food in question should be reintroduced into the infant's diet in order to ensure a varied diet and to avoid unnecessary dietary restrictions.

4.4.2. Oral food challenges

In general, controlled oral challenge testing is required for the diagnosis of a food allergy or to prove clinical tolerance (**Tab. 15**). Furthermore, it has been repeatedly shown that patient quality of life improves irrespective of the outcome of oral food challenge testing. The procedure for food challenge testing has been described in detail in national (GPA-Manual: https://www.gpau.de/fileadmin/user_upload/GPA/dateien_indiziert/Stellungnahmen/Manual_NMA_2009.pdf) and international guidelines (EAACI, PRACTALL consensus paper). The „food allergy due to immunological cross reactivity with inhalant allergens" guideline [3] describes the particular features of challenge testing in pollen-associated food allergy in greater detail.

4.4.2.1. Decision-making criteria and influencing factors

The recommendations include diverse variables that need to be taken into consideration in order to be able to perform challenge tests tailored to the individual patient:

- Patient selection
- Safety aspects
- Type and quantity of the food to be administered
- Time interval between individual administrations
- Assessment criteria
- Observation period
- Formulations

When performing challenge testing with cross reactive foods of inhalative allergens or challenge testing in adults need to consider further aspects such as:

- Possible cumulative effects during pollen season
- Altered response due to augmentation factors (physical exercise, infection, drug use, and alcohol consumption)
- Comorbidities (e. g., unstable bronchial asthma, mastocytosis)

4.4.2.2. Performing and interpreting oral food challenges

Open or blind food challenge tests can be performed (single- or double-blind format). Sequential mucosal and systemic challenge can be employed in the case of pollen-associated food allergy. Only a negative result represents a reliable finding in open oral challenge testing. Double-blind placebo-controlled food challenge (DBPCFC) is considered the gold standard for the diagnosis of food allergy.

A negative food challenge should be confirmed by a repeated administration of the cumulative dose the following day at the earliest. The time and personnel requirements for DBPCFC are significant. Thus, a negative open challenge may represent a reasonable first step towards excluding a food allergy. DBPCFC should be preferred over open challenge in patients with moderate or severe atopic eczema. This test format should also be performed in the case of subjective, delayed or atypical symptoms or if patients (or parents) are anxious. Furthermore, it is required to use DBPCFC in scientific investigations, e. g., to establish the clinical relevance or potency of certain allergens, but also if a threshold dose for defined food allergen is determined. The food should be administered in „blinded" form in terms of:

- Taste
- Aroma
- Texture
- Administration form (consistency, color and form)

Placebo and verum should be indistinguishable from each other.

In order to avoid severe reactions, patients receive the food to be tested in a titrated manner, generally in semi-logarithmic increments at time intervals of 20–30 min. Quantities between 3 mg and 3 g – based on the protein content of the administered food – have proven to be sufficient for many foodstuffs such as cow's milk, hen's egg, peanut and tree nuts.

Food challenges are generally discontinued as soon as a clinically detectable reaction occurs, or are ended if the final dose administered, as well as repetitive administration of the cumulative total dose (e. g., the following day) is tolerated without clinical symptoms. If subjective symptoms occur, the subsequent dose should be exposed or the previous dose repeated. Immediate-type reactions generally occur within 2 h of the last food intake. Since atopic dermatitis may worsen several hours (or

Tab. 15: Oral food challenge test procedure

Challenge design **open vs. blinded (single- or double-blind)** **titrated vs. single-step**		**Test design should be chosen according to the indication and purpose of challenge testing.**
Food challenge meal preparation		The food challenge meal should contain, as realistically as possible, the usual edible form of the food that elicits the reaction. Processing a food, as well as its incorporation in a matrix, can significantly affect its allergenicity (e.g., raw vs. cooked egg). Fresh fruit and vegetables should preferably be used in challenge testing to confirm pollen-associated food allergy, since triggering proteins are generally heat-labile.
Matrix selection		Careful attention should be paid to ensure that no other allergens to which the patient reacts are included in the meal. As few ingredients as possible should be used. Placebo meals should resemble the sensory characteristics of the test food as closely as possible.
Dosage	Number of doses	In most cases, titration in seven semi-logarithmic steps should be selected. A single dose may be adequate if negative challenge is expected and there are no safety concerns
	Initial dose	In clinical routine, an initial dose of 3 mg food protein is generally appropriate for most foods. Lower doses should used for threshold dose challenges and high-risk patients.
	Maximum dose	Corresponding to an age-adjusted portion, 3 g food protein is appropriate for most foods.
	Cumulative total dose	A cumulative total dose should be administered the following day or on another day, since some patients react only upon repeated administration.
	Time interval between doses	20–30 min, but should be adjusted according to previous history

even over the course of the following day) after food challenge, it is necessary to perform a skin examination on the following day. Although urticaria and/or angioedema are the most common immediate-type reactions, gastrointestinal, respiratory and cardiovascular symptoms may occur and patients require to be medically supervised upon provocation.

4.4.2.3. Safety aspects

For reasons of safety, oral challenges should only be performed in a setting where allergic reactions, including anaphylaxis, can be treated adequately and in an age-appropriate manner. Personnel should be trained and experienced in early recognition of symptoms and emergency management. Age- and weight-appropriate emergency medication that may potentially be required should be noted, e. g., in the patient's file prior to the challenge test and kept ready to use. In the case of non-IgE-mediated reactions, challenges should be tailored to the individual requirements of the patient.

Core statements

Oral food challenge (in particular DBPCFC) is the gold standard for the diagnosis of IgE-mediated food allergies.	strong consensus
Augmentation factors should be taken into consideration in challenge tests. Food challenges should be performed to confirm or exclude allergy.	strong consensus
Food challenges built the basis to safely determine the patient's range of tolerated food and enables counseling on appropriate allergen avoidance and risk assessment for severe reactions (anaphylaxis).	consensus
A negative oral challenge should be followed-up by a repeated administration on the following day at the earliest of the tested food in a quantity adjusted to age- and everyday eating habits.	strong consensus
Oral food challenges should be performed at specialized centers where emergency measures are available. In cases where challenge testing poses a high risk for severe allergic reactions, intensive care support should be available.	strong consensus

Rationale of food challenge testing

Indication	Rationale
Frequent indications for oral food challenge	1. Inconclusive diagnostic situation despite detailed patient history and test results (e.g., in patients with multiple food sensitizations due to sensitization to panallergens such as profilin or Bet v 1)
	2. Suspected allergic reaction for which the trigger remains unidentified despite allergy diagnostics (reaction following a composite meal)
	3. Sensitization detected, yet the relevant food has never been consumed, or only in small quantities
	4. To confirm clinical relevance following improvement in clinical symptoms, e. g., atopic dermatitis, during elimination diet
	5. To detect the development of natural tolerance (in persistent IgE reactivity)
	6. To prove the efficacy of causal therapy, e.g., oral immunotherapy in the context of clinical research

strong consensus

Lange, Reese, Schäfer, Niggemann, Bischoff, Beyer

4.5. Alternative diagnostic tests

Which alternative diagnostic methods are available? What is the relevance of alternative diagnostic tests in confirming food allergy?

Some physicians and alternative practitioners use a number of alternative diagnostic methods in the case of suspected food-related symptoms. These can be subdivided into two categories:

1. Tests based on dubious theoretical foundations, lacking validity and reproducibility. They include bioresonance, electroacupunture, hair analysis, iridology, kinesiology, and cytotoxic food testing (ALCAT test). These methods have not been successfully validated either technically or clinically to justify their use.
2. Tests that yield the measurement of data but resulting in a false interpretation: Immunoglobulin G (IgG) or IgG4 antibody determination and lymphocyte transformation tests with foods do not enable to distinguish between affected and healthy individuals [45] neither in food allergy or in food intolerance. Their lack of diagnostic specificity results frequently to positive findings in healthy individuals. Food-specific IgG or IgG4 merely indicates that an individual had repeated

contact with the according food and represents a physiological immune response to a foreign protein. Lymphocyte proliferation following food stimulation and serum IgG or IgG4 to food can be elevated in allergy sufferers. However, these tests are not suited for an individual diagnosis of food hypersensitivity due to their variance and poor specificity [46, 47, 48, 49, 50, 51, 52, 53].

The EAACI [52], the American Academy of Allergy, Asthma & Immunology (AAAAI), and the Canadian Society of Allergy and Clinical Immunology (CSACI) advise against testing for IgG/IgG4 against foods in suspected food allergy or intolerance.

Recommendations	
Other diagnostic test methods (e. g., bioresonance, electroacupunture, kinesiology, cytotoxic food tests (ALCAL test), as well as IgG/IgG4 determinations and lymphocyte transformation tests with foods, should not be used to diagnose food allergy or intolerance.	strong consensus

Niggemann, Kleine-Tebbe, Mahler

5. Course and treatment of food allergy

5.1. Natural course

Can food allergy develop into to tolerance?
To which food allergens are likely/unlikely to develop into tolerance?

Most primary IgE-mediated food allergies take the following course:

Onset in infancy or early childhood and spontaneous remission either by school age or adolescence [26] depending on the food and comorbidities [54]/cofactors.

Although rare, later onset at school age or adulthood is possible.

The natural course depends on the food source: cow's milk [55], hen's egg [56, 57], wheat [58], and soy allergies [59] tend to develop into spontaneous remission during the first years of life. Peanut [60, 61, 62, 63, 64], tree nut [65], but also fish and crab allergies [66], often persist. High specific IgE titers frequently correlate with clinical relevance and are less likely to develop into clinical tolerance. Specific IgE antibodies to food are often found as early on as in infancy and early childhood. Values can rise or fall later on. A decrease may be associated with tolerance development. There is evidence to suggest that the natural course of food allergy alters, resulting in slower tolerance development [25, 54, 67]. Recent data, primarily from the US, indicate that low specific IgE antibodies, low skin prick test diameter and mild atopic eczema tend to be associated more frequently with food allergy remission [25].

Food allergies in adulthood can represent either a persistent childhood form or a de novo sensitisation. Major triggers of food allergy in adulthood according to frequency are apple, peanut, kiwi, hazelnut, peach, cow's milk, hen's egg, wheat, fish, and shrimp [68]. Cross reactivity due to specific IgE to inhalant allergens are more frequent compared with primary food allergies – particularly in the form of birch pollen-associated food allergies in German-speaking countries (see Sect. 4.2). These adult-onset food allergies may persist [69].

Recommendations	
Due to the natural course of cow's milk, hen's egg, wheat and soy allergy in children, oral food challenges should be repeated at regular intervals (e.g., every 6, 12 or 24 months) to assess for tolerance development.	strong consensus
Provocation testing should be performed at longer intervals (e.g., every 5 years) in children with peanut and primary tree nut allergy, as well as fish and oilseed allergy.	consensus

Szépfalusi, Lepp, Lange

5.2. Treatment

5.2.1. Acute treatment of food allergy

What are the treatment forms available for food allergy?
When and how are they applied?

5.2.1.1. Core questions

How effective are pharmacological and non-pharmacological interventions in the treatment of acute, non-life-threatening reactions in food allergy?
How effective are pharmacological and non-pharmacological interventions in the long-term care of food-allergic patients?

5.2.1.2. Treatment of IgE-mediated food allergies

Food allergy treatment is based on:
a) Short-term management of acute reactions
b) Long-term strategies to reduce the risk of further reactions

The latter include dietary treatment and training programs. Training programs are designed to help affected individuals to avoid allergens and to learn how to react upon accidental allergen contact (e. g., use of emergency medicine). Sublingual or oral im-

munotherapy appear to offer new perspectives to achieve clinical tolerance.

5.2.1.3. Treatment of acute reactions

Assessing the risk of potentially severe reactions is an essential part of successfully caring for food allergy patients. This risk varies according to subgroup. Thus, patients with

- previous anaphylactic reactions,
- severe and/or uncontrolled bronchial asthmaor
- specific underlying diseases (mastocytosis)

are at greater risk.

The „Anaphylaxis" guidelines describe how to recognize and to treat anaphylactic reactions. In addition to emergency medical measures (e. g., administering fluids and oxygen, monitoring circulation, ABCD measures), emergency medication should be administered immediately. These are defined as immediate-action first-aid medications aimed at preventing the pathophysiological effects of anaphylaxis. They include adrenaline, bronchodilators, antihistamines and glucocorticosteroids [70]. Intramuscular administration of adrenaline is the first-line treatment in anaphylaxis [20].

A systematic overview of EAACI guidelines on the treatment of food allergies revealed only weak evidence for the efficacy of H1 antihistamines. This finding relates to three randomized and two non-randomized comparative studies in children and adults with acute non-life-threatening symptoms caused by food allergy [71].

There is no evidence to suggest that antihistamines are effective against respiratory or cardiovascular symptoms. However, the prophylactic use of antihistamines can mask early symptoms of anaphylaxis, thereby delaying the requisite use of adrenaline [70].

According to the guideline on the acute treatment of anaphylaxis [70], glucocorticosteroids also belong, alongside adrenaline and antihistamines, to the arsenal of acute treatments for food-related allergies, although there are no systematic clinical studies on this indication [72, 73, 74]. A nonspecific membrane-stabilizing effect following high-dose administration (500–1000 mg methylprednisolone) has been postulated in reviews. However, they are also effective at intermediate doses (1–2 mg/kg methylprednisolone) in the treatment of asthma and act against prolonged or biphasic reactions. All medical practice should have acute medication available.

5.2.2. (Long-term) Drug treatment of food allergy

Studies on the prophylactic use of mast cell stabilizers have yielded varying clinical results [77]. Four randomized studies and two non-randomized comparative studies showed that mast cell stabilizers are able to reduce symptoms, while three randomized studies found no effect. Thus, it is currently not possible to make a standard recommendation on the use of mast cell stabilizers; instead, a differentiated approach depending on the patient cohort investigated is required.

- The mode of action of mast cell stabilizers, such as cromoglicic acid or ketotifen, is not yet understood. While reduced disease activity has been described in intestinal symptoms due to its potentially positive effects on the intestinal barrier, there are negative reports on the efficacy of cromoglycate acid in the skin and extraintestinal manifestations.
- At present, there are no randomized treatment studies on budesonide in IgE-mediated food allergy. Existing recommendations are based on case and expert reports, and the extrapolation of data to patients with eosinophilic disease of which 50 % are associated with IgE-mediated allergy [85, 86, 87].

The above-mentioned treatment options using mast cell stabilizers and budesonide can be considered on an individual basis in the case of gastrointestinal symptoms alone. They should be critically reviewed, primarily by gastroenterologists, in terms of their efficacy.

Recommendations

Acute treatment

Patients at risk of severe reactions should be equipped with emergency medication, including an adrenaline autoinjector	strong consensus
Severe allergic reactions to food should be treated with intramuscularly administered adrenaline.	strong consensus
Antihistamines can be used in acute non-life-threatening symptoms, most notably to treat urticarial and mucosal reactions.	strong consensus
The prophylactic use of antihistamines is not be recommended.	consensus

Long-term treatment

Since cromoglycate acid and ketotifen exhibited no treatment effect when all patient cohorts were taken into consideration, it is currently not possible to make a standard treatment recommendation for all patient groups. Gastrointestinal symptoms require individual treatment decision-making and monitoring.	consensus

5.3. Long-term management of food allergy

How does one implement avoidance measures in everyday life?

5.3.1. Dietary treatment and allergen labeling

Long-term food allergy management includes:

- Avoidance of relevant foods
- Substitution with suitable foods
- The implementation of treatment measures in everyday life [4].

Avoidance is the most important intervention to prevent the onset of symptoms. Since, for ethical reasons, randomized controlled studies in non-food-allergic individuals, or in food-allergic individuals from whom dietary treatment is withheld in the control group, are critically viewed, valid data on the efficiency of avoidance measures are not available.

However, this lack of consistent data on the efficacy of avoidance [88, 89, 90, 91] can not be interpreted as evidence that elimination diets are ineffective.

Therapeutic elimination diets are tailored to the individual allergy and nutritional requirements of the affected individual. The requirements, aims, and expected results of dietary therapy vary considerably according to age and elicitating or causing allergen profile (primary vs. secondary food allergy).

Ideally, affected individuals receive treatment advice from a dietician with allergological experience. Individual tolerance to the eliciting food can vary between allergic individuals and may change on an individual basis. This applies to primary but also secondary food allergies. For dietary therapy it is important to take into consideration the aug-

Tab. 16: Lifetime prevalence of self-reported vs. oral food challenge-proven food allergies. Significance of spontaneous remission in young childhood

	Lifetime prevalence (self-reported; 95 % CI) [16]	Lifetime prevalence (oral food challenge-proven; 95 % CI [16]	Spontaneous remission (up to the age of)	Reference
Cow's milk	6.0 % (5.7–6.4)	0.6 % (0.5–0.8)	80 % (5 years)	[55]
Hen's egg	2.5 % (2.3–2.7)	0.2 % (0.2–0.3)	66 % (7 years)	[56, 57]
Wheat	3.6 % (3.0–4.2)	0.1 % (0.01–0.2)	29 % (4 years) 56 % (8 years) 65 % (12 years)	[58]
Soy	-	0.3 % (0.1–0.4)	25 % (4 years) 45 % (6 years) 69 % (10 years)	[59]
Peanut	0.4 % (0.3–0.6)	0.2 % (0.2–0.3)	0 % [63] to 57 % [64]	[60, 61]
Fish	2.2 % (1.8–2.5)	0.1 % (0.02–0.2%)	0 %	[66]
Crustaceans	1.3 % (0.9–1.7)	0.1 % (0.06–0.3)	0 %	[66]

CI, confidence interval

mentation factors for allergic reactions discussed in Sect. 4.1, „Patient history and diet/symptom protocols."

5.3.2. Cow's milk substitution

Cow's milk allergy with the onset before the age of 1 year requires special dietary treatment (extensively hydrolyzed amino acid-based formula) in order to ensure that infants grow and thrive in an age-appropriate manner. However, in such cases, the only means of providing an infant with sufficient nutrients is mainly via bottle-feeding.

The specific formula to be used is selected on a case-by-case basis: An extensive hydrolysate is generally the formula of first choice. Amino acid-based formulas can be beneficial in those affected by severe (notably also gastrointestinal) symptoms [90, 92, 93, 94, 95].

Soy formulas are not be recommended in infants aged under 12 months. Moreover, feeding with soy products in the first year of life is viewed critically due to their possible phytoestrogen, phytate and aluminum content. This is particularly relevant in the case of high intake per kilogram bodyweight, i. e., up to the age of 6 months. The risk:benefit ratio of soy formula in a predominantly milk substitute-based diet with low quantities of other foods is unfavorable.

Like sheep and goat milk, partially hydrolyzed infant formulas are not well suited for the treatment of cow's milk allergy [97, 98].

5.3.3. Food avoidance during breastfeeding

If a breastfed infant is affected by symptoms caused by the mother's intake of certain foodstuffs, the breastfeeding mother should eliminate the suspected triggering food(s) from her diet followed by dietary counseling. Mothers should receive dietary advice if milk and milk products need to be eliminated on a long-term basis. Supplements are required in cases where it is not possible to achieve sufficient intake, e. g. calcium.

5.3.4. Monitoring and re-evaluating clinical relevance

Extensive and long-term avoidance measures need to be monitored carefully. They may cause:

- Insufficient nutritional intake
- Impaired quality of life

Thus, counseling on dietary intake should include the calculation and possibly optimization of nutritional values to ensure a balanced and age-appropriate diet.

In order to ensure that avoidance measures are not maintained for longer than necessary, it is important to regularly review their clinical relevance. Cow's milk or hen's egg allergy should be re-evaluated by means of challenge testing at 6- to 12-month intervals in young children and 12- to 18-month intervals in older children.

The re-evaluation of prognostically unfavorable allergies, e. g. caused by nuts or peanuts, should be made on a case-by-case basis. Primarily such cases should be considered where no accidental allergic reactions have occurred. A follow-up patient history should be taken in case of pollen-associated food allergies to compile an accurate record of clinically relevant cross reactions over time.

5.3.5. Patient instruction and allergen labeling

Patient training is considered a key instrument of dietary intervention to achieve long-term elimination in everyday life.

Training programs are designed to teach patients, their families, relatives and caregivers

- to be aware of and to identify risk situations
- to be able to read lists of ingredients
- to completely avoid relevant triggers (in and outside the home (e. g., in restaurants))

Patients should be informed about the European Food Information Regulation (EU FIR):

1. The EU FIR requires that the 14 most important triggers of allergies and non-allergic intolerance need to be declared if they, or their associated products, have been included as an ingredient in a food (i. e., knowingly and as part of a recipe). These are the following:
   - Gluten-containing cereal: wheat (spelt, khorasan wheat), rye, barley, oats
   - Crustaceans, egg, fish, peanuts, soybeans, milk
   - Nuts: almonds, hazelnuts, walnuts, cashew nuts, pistachio nuts, pecan nuts, Brazil nuts, macadamia (Queensland) nuts
   - Celery, mustard, sesame seeds, lupine, and mollusks
   - sulfites

   Mandatory labeling applies to pre-packaged as well as non-pre-packaged foods.
2. There is no legal framework governing the labeling of allergens that occur unintentionally in packaged or loose products. Trace allergen labeling, which is voluntary, is not able to provide information at the level (allergen amount) of contamination or its true likelihood due to the lack of limit values, nor does its absence signify per se that a food is safe. Thus, it should always be interpreted on an individual basis.

Patients, their families, relatives and caregivers should be given the following informations:

- Substitute products
- Recipes to prepare their usual and preferred meals despite avoidance

5.3.6. Therapeutic use of pro- and prebiotics

Due to a lack of data the use of pre- and probiotics in the treatment of food allergy is not recommended.

Recommendations

An appropriate elimination diet is the keystone of food allergy management.	strong consensus
An elimination diet should be based on sound allergy diagnostic methods. Regular reviews regarding the indication are reqiuired.	strong consensus
Food-allergic individuals that adhere to long-term dietary elimination should receive advice from dieticians with proven allergological expertise.	strong consensus
Patients should be informed about allergen labeling (in accordance with the FIR), as well as the current gaps therein.	consensus
Extensive hydrolysate or, alternatively, amino acid-based formulas are recommended in cow's milk allergy, particularly in infants and, where appropriate, young children.	strong consensus
Soy-based formulas are the milk-substitute products of second choice in cow's milk allergy and are not recommended for infants below 12 months.	strong consensus

5.3.7. Gaps and important areas of research with regard to long-term management

- Long-term effect of elimination diets on nutrition and quality of life
- Effect of altered allergens (cooked milk/egg) on tolerance development
- Long-term drawbacks of rice- and soy-based formulas in terms of a balanced diet
- Strain-specific (relating to certain micro-organisms) effects on food allergy management using probiotics
- Determination of allergen-specific threshold values. Objective: To protect food-allergic individuals from severe reactions and to optimize food labeling in terms of ingredient and trace allergen labeling (unintended cross contact).

Reese, Schnadt, Schäfer, Fuchs

5.4. Immunotherapy in food allergy

Is it possible to perform effective immunotherapy in food-allergy patients?

5.4.1. The use of allergen-specific immunotherapy (AIT) in food allergy

Numerous attempts have been made to treat primary food allergy with:

- subcutaneous (SCIT),
- sublingual (SLIT) or
- oral (OIT) allergen-specific immunotherapy

using foods or food extracts.

Primary sensitizing pollen extracts have been used sublingually and subcutaneously to treat pollen-associated food allergy; in addition, oral and sublingual application of the food has also been investigated.

5.4.2. The use of SCIT in food allergy

Two studies showed evidence that treatment with verum is superior compared with placebo in SCIT using food allergen extracts for primary food allergy [100, 101]. Four other studies made similar observations on the efficacy of subcutaneously applied pollen allergens on pollen-associated food allergy [102, 103, 104, 105]. These studies investigated the effect of SCIT on birch-associated apple/hazelnut allergy. A randomized study found no effect for birch SCIT on birch-associated hazelnut allergy [106].

5.4.3. The use of SLIT in food allergy

SLIT with food allergens, as investigated in four randomized studies, improved tolerance and reduced allergic symptoms to peanut, hazelnut, and peach [107, 108, 109, 110]. No improvement was seen in apple-allergic subjects in a randomized study using birch-pollen allergens [111].

5.4.4. The use of OIT in food allergy

OIT using a wide variety of food allergens improved clinical tolerance in children and adults. This was shown in a number of randomized and non-randomized controlled studies – primarily with cow's milk, hen's egg, and peanut [112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128] – as well as in systematic reviews based partially on these studies [129, 130, 131, 132, 133]. However, (mostly mild but in rare case also severe) side effects were observed in many patients undergoing OIT with allergens.

A randomized study showed OIT with cow's milk or hen's egg to be not more effective than elimination dieting in terms of tolerance development; however, these studies were conducted in young children [134]. Although a further study showed OIT to be more effective in cow's milk allergy when compared directly with SLIT, it also caused more side effects [116]. One study showed that the regular consumption of apples in birch-associated food allergy resulted in tolerance [135].

While results for OIT appear to be promising the evidence is overall poor. Thus, OIT should be used only in controlled clinical studies [77]. There are no data on long-term effects yet. Due to conflicting data on efficacy, subcutaneous and sublingual immunotherapy with pollen allergens should only be used in pollen-associated food allergy provided the primary inhalation allergy also requires treatment [3].

Recommendations

Primary food allergy	
At present, specific oral, sublingual, or subcutaneous immunotherapy with food allergens should only be used in primary food allergy in the context of controlled studies.	strong consensus
Pollen-associated food allergy	
Pollen-associated food allergy should only be treated with subcutaneous or sublingual immunotherapy using pollen allergens in the case of concomitant pollen-related respiratory symptoms.	strong consensus
At present, oral immunotherapy with food allergens should only be used in pollen-associated food allergy in the context of controlled studies.	strong consensus

Vieths, Treudler, Beyer (modified from [77])

5.5. Everyday management of patients at risk of anaphylaxis

How can food-allergic patients deal with their disease successfully in everyday life?

5.5.1. Patient information and risk assessment

Patient information and training are the main tasks of food allergy management in everyday life. Risk assessment is essential in patients at increased risk of severe allergic reactions.

Patients, relatives and caregivers receive:

- A patient tailored management plan (see Sect. 5.3.1.)
- An anaphylaxis identification card
- An anaphylaxis emergency plan (see anaphylaxis guidelines [70].

5.5.2. Emergency plan

The emergency plan should take into consideration all the possible variables that could impact the identification and treatment of allergic reactions to food, including:

- Patient age
- Patient/family education level
- Type and extent of the food allergy
- Comorbidities
- Place of residence and access to medical assistance

The procedure management and in particular what should be done in the case of specific symptoms, should be easy to understand to a non-informed third party.

5.5.3. Instruction and anaphylaxis training

Training should include the following aspects:

- Patient-specific avoidance strategies at home and in their social environment
- Recognizing and interpreting warning signals
- When and how allergic reactions need to be treated
- When and how to use an adrenaline autoinjector

5.5.4. Who requires instruction?

Individuals professionally confronted with anaphylaxis patients should be considered in instruction programs. These include:

- general practitioners and pediatricians
- dieticians
- kitchen personnel
- teachers and caregivers
- first aiders in companies

Together, a multidisciplinary approach and the availability of written or online information on food allergies clearly improve knowledge and promote the correct use of adrenaline autoinjectors, thereby contributing to the reduction of allergic reactions [136].

In addition to direct family members other persons with whom the allergy sufferer comes into close contact in their social environment should also be informed e. g., childcare center, school or workplace, flight personnel etc..

5.5.5. Patient organizations

Referring patients to relevant patient organizations, such as the German Allergy and Asthma Association (Deutsche Allergie- und Asthmabund, DAAB; www.daab.de) for questions regarding everyday management is helpful. A standardized training program („AGATE," Arbeitsgemeinschaft Anaphylaxie – Training und Edukation, „German working group on anaphylaxis training and education"; www.anaphylaxieschulung.de) is available in Germany for severe allergic reactions (anaphylaxis).

Recommendations	
Patients, their relatives and caregivers should be informed about the foods to be avoided and practical information on avoidance measures, the recognition and self-management of future reactions should be given	strong consensus
The option to contact a patient organization should be communicated to patients.	consensus
Food-allergic patients at risk of anaphylaxis should receive an anaphylaxis identification card and should participate in patient/parent training.	strong consensus

Schnadt, Fischer, Schäfer

6. Current developments in the diagnosis and treatment of food allergies

What new diagnostic and therapeutic methods are currently under development?

6.1. Diagnostic methods

Molecular (synonym: component-based) diagnostic tests can determine specific IgE antibodies to single food allergens. This approach improves both the test sensitivity and the diagnostic sensitivity of in vitro tests, their analytical specificity, and (in a small number of food analyses) also their diagnostic specificity:

- Determining specific IgE to the major allergen Ara h 2 in peanut allergy increases diagnostic specificity to between 72% and 96% [137, 138, 139, 140].
- An Ara h 2 greater than 40 kU/l yields a 95 % likelihood of a positive oral challenge in children with peanut allergy.
- ω-5-Gliadin-specific IgE is of high diagnostic relevance in exercise-induced food allergy to wheat [141].
- Specific IgE to rGly m 4 in soy milk allergy in birch pollen-sensitized patients considerably increases test sensitivity (lower LoQ) and diagnostic sensitivity compared with extract-based diagnostic methods.

Reagents for molecular diagnostic methods are available for certain fruits (apple, peach, and kiwi), hazelnut and peanut, soy, fish, and molluscs to detect specific sensitization profiles. Further studies are needed to confirm the clinical usefulness of molecular-based IgE diagnostics. At present, whilst the determination of IgE to single allergens can contribute to risk assessment, it can not substitute placebo-controlled challenge testing.

Small clinical studies have investigated basophil activation assays for the diagnosis of cow's milk, hen's egg, and peanut allergy [140, 142, 143] and for the diagnosis of pollen-associated food allergy [144, 145, 146]. The basophil activation test (BAT), which generally shows exceptional analytical sensitivity, has greater diagnostic specificity and a better negative predictive value compared with skin testing and specific IgE without influencing the diagnostic sensitivity or the positive predictive value. Since the BAT requires a special laboratory setting and since large clinical studies on diagnostic sensitivity and specificity in the area of food allergy are lacking, this test is and will continue to be recommended primarily for research in food allergy.

Novel diagnostic options are emerging with the determination of specific IgE against overlapping synthetic linear peptides. Although this approach has been described to date for milk [147, 148, 149], peanut [150, 151], egg [152], shrimp [153, 154], and celery [155], there are currently no peptide-based tests available on the market that can currently be recommended for routine practice.

6.2. Treatment

Specific immunotherapy approved for the treatment of food allergy is currently not available (see Sect. 5.3.2). Independent of oral and sublingual immunotherapeutic approaches [156], the efficacy and tolerability of epicutaneous allergen immunotherapy in peanut allergy is currently being investigated in a multicenter study [157, 158].

Food allergies are generally IgE mediated and attempts were performed to establish anti-IgE therapy to prevent the onset of symptoms. Despite promising results [159], this approach has not pursued further for the time being. Recently a combined approach (anti-IgE antibodies plus OIT) was investigated in peanut-allergic patients [160] and suggested promising results. Considering such positive reports and studies in the literature, one should assess on an individual basis whether anti-IgE treatment is an option in patients with IgE-dependent severe repetitive life-threatening food allergic reactions.

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7. Food as an occupational allergen

How common is occupational allergy and what are the triggers?

How is occupational allergy diagnosed and what is the impact for an individual's ability to work?

7.1. Epidemiology and triggers

IgE-sensitization to food allergens in an occupational setting can be acquired via the skin or the respiratory tract. Manifestations mainly occur in, but can also develop outside the workplace in form of [3]:

- (Occupational) allergic rhinopathy and/or allergic asthma
- Contact urticaria (CU) and/or protein contact dermatitis (PCD) (predominantly on the hands) [161, 162] (**Tab. 17**).

Inhalant symptoms to food allergens can cause occupational disease (OD) No. 4301 , while IgE-mediated skin manifestations cause OD No. 5101.

Although CU and PCD to food allergens are extremely rare in the general population, their prevalence is significantly higher (1.5 %–20 %) in the food-processing industry depending on the occupation and cohort studied [161, 163, 164]. The prevalence of occupational asthmatic diseases in exposed employees ranges between 1 % and 20 % and is particularly high among bakers [165, 166, 167]. Flour allergy to wheat and rye is the most frequent cause of occupational allergic obstructive airway disease in Germany [166, 167].

Food allergens from a wide variety of allergen sources have been described as triggers [161, 167, 168, 169]. Asthmatic bakers sensitized following inhalation exposure to wheat flour exhibit other allergen profiles compared with individuals to orally acquired wheat-induced food allergy [166, 167]. In how far certain food allergens are able to trigger specific allergic symptoms depending on the exposure route (oral, inhalant, or cutaneous) (**Tab. 18**) has not been clarified for most allergen sources until to date [166, 170].

7.2. Prevention

It is essential to protect employees from allergen exposure and sensitization by minimizing occupational health risks [167, 178]. Extensive occupational dermatological and occupational medicine guidelines and recommendations are available. In order to optimize preventive measures, the relevant insurance should be informed even if a possible occupational disease is suspected:

- Dermatological report (Hautarztbericht) in the case of skin manifestations
- Occupational disease notification in the case of airway symptoms

7.3. Symptoms and differential diagnosis

Occupational skin disorders of varying origin on the hands are common in the food-processing industry, whereby eczematous skin disorders predominate. Hand eczema can be of irritant, allergic and endogenous origin. Specific occupational and non-occupational triggers need to be investigated in the patient history and by means of patch testing [3, 163, 178].

Tab. 17: Forms, symptoms, and characteristics of occupational food allergies

Immuno-pathology	Disease/symptoms	Clinical characteristics	Typical age group	Prognosis
IgE-mediated	Contact urticaria syndrome (grade I–IV)	Triggered by predominantly occupation-related skin contact	Adults, occupationally exposed individuals	Dependent on the triggering food and possible avoidance measures
	Occupational obstructive airway disease (including allergic rhinopathy) caused by allergenic substances	Predominantly workplace-related airway symptoms due to inhalation allergen exposure	Adults, occupationally exposed individuals	Dependent on the triggering food and possible avoidance measures
Mixed IgE- and cell-mediated	Protein contact dermatitis	Triggered on the hands predominantly by work-related skin contact	Adults, occupationally exposed individuals	More severe effects and less favorable prognosis compared with skin disorders of other origin
Non-immunological	Non-immunological contact urticaria	Triggered on the hands predominantly by work-related skin contact with benzoic acid, sodium benzoate, sorbic acid, abietic acid, nicotinic acid ester, cinnamic acid, cinnaminic aldehyde, and balsam of Peru	Adults, occupationally exposed individuals	In contrast to IgE-mediated contact urticaria, generally restricted to the area of contact

IgE-mediated contact urticaria to food allergens is to be distinguished from non-immunological contact urticaria (e.g., elicited by benzoic acid, sodium benzoate, sorbic acid, abietic acid, nicotinic acid ester, cinnamic acid, cinnaminic aldehyde, balsam of Peru) [163]. The latter generally remains restricted to the area of contact, while IgE-mediated contact urticaria may cause systemic manifestations [184]. Non-occupational forms of urticaria should be considered in the differential diagnosis [184].

7.4. Diagnostic

In the case of suspected IgE-mediated allergic diseases related to the workplace, in particular work-related rhinopathy/asthma, the diagnostic process should be initiated early on, when the patient has not yet left the workplace [165].

Stepwise diagnosis includes history-taking, skin prick testing (additional epicutaneous testing in PCD), specific IgE determination and challenge testing [161, 162, 167, 171, 180, 181]. In vivo and in vitro diagnosis are challenging, because the extracts for occupationally relevant food allergens are often lacking relevant allergens or are insufficiently standardized. The diagnostic sensitivity and specificity may vary considerably with the currently available occupational allergens depending on the allergen source and test solution [182, 185]. For the time being, parallel testing of skin prick test solutions from different manufacturers is recommended [182]. To detect CU and PCD against food allergens, skin prick tests should be performed with fresh material [161, 186].

Skin prick tests to diagnose occupational type-1 allergies should be performed using a metal lancet if possible using double determinations. Where reproducible, wheals of even small diameters (≥ 1.5 mm) when controls are negative should be considered as positive and confirmed serologically [182]. Medically monitored allergen avoidance and re-exposure, as well as workplace-related challenge testing may be required to establish the diagnosis. The specific inhalation challenge test is considered the gold standard for many triggers of occupational allergy. However, a negative result in this test or following exposure at the workplace is not sufficient to exclude the diagnosis of occupational asthma in the presence of otherwise good evidence [165, 167, 180]. Further diagnostic measures are given in „Prevention of occupational obstructive airway disease" guidelines [165, 180].

7.5. Course and treatment

Efforts should be made to achieve early allergen avoidance in occupational IgE-mediated allergies in order to avoid symptom exacerbation and the onset of OD 5101 (in the case of allergic skin disorders) or OD 4301 (in the case of allergic airway symptoms) [165, 179, 187]. Treatment measures as well as the benefits of various management options for occupational allergic rhinopathy and obstructive airway disease are discussed in the „Prevention of occupational obstructive airway disease" guidelines [165].

Although allergen avoidance by avoiding exposure or by using suitable protective gear can result in the improvement or resolution of IgE-mediated skin disorders caused by food allergens, these measures are not always successful [162]. In the food-processing industry, individuals affected by PCD exhibit a more severe course and have a less favorable prognosis compared with patients with skin disorders of the hands of other origin. Significant differences were seen in terms of:

- The need to consistently wear protective gloves at work
- The duration of absence to work
- The frequency of occupational changes [164]

In cases where it is not possible to achieve a symptom control with allergen avoidance or a reduced exposure by means of technical/organizational measures or the use of personal protective gear, individuals affected by occupationally acquired IgE-mediated food allergy may be forced on objective grounds to cease the relevant occupation. When assessing reduced capacity to work, it is important to take into consideration not only the severity of clinical disorders [183], but also the proportion of jobs on the general labor market precluded due to allergy [179, 187].

It is possible for food allergens to elicit concomitant occupational skin and airway symptoms. Since this represents a uniform allergic disease involving symptoms in various organs, this particular constellation should be treated as one insured loss – based on OD No. 5101 and OD No. 4301 – thereby necessitating an assessment of the overall reduction in capacity to work while taking the impact of the allergy into consideration [187, 188].

Recommendations/core statements	
The diagnostic work-up in suspected IgE-mediated occupational allergic disease should be initiated promptly, assuming the patient has not yet left the job, in order to perform, e.g., workplace-related measurements and exposure challenge testing in addition to specific stepwise diagnostic tests.	strong consensus
Allergen avoidance has priority also in occupational food allergies using appropriate protective measures. Where this is not possible the need to cease the relevant occupation should be assessed.	strong consensus

Tab. 18: Allergen profiles and occurrence as occupational allergens (examples)

Allergen source	Allergens relevant in food consumption	Occupational allergens	Occupation	Source
Wheat	ω-5-Gliadin (Tri a 19), among others: wheat-dependent, exercise-induced anaphylaxis (WDEIA); Profilin (Tri a 12), nsLTP (Tri a 14); agglutinin isolectin 1 (Tri a 18), ω-5-gliadin (Tri a 19), γ-gliadin (Tri a 20), thioredoxin (Tri a 25), high-molecular-weight (HMW) glutenin (Tri a 26), among others	α-amylase-trypsin inhibitors (e.g., Tri a 28, Tri a 29.0101, Tri a 29.0201, Tri a 30, Tri a 15); thiol reductase (Tri a 27); thioredoxin (Tri a 25), triose-phosphate isomerase, α-/β-gliadin, 1-Cys peroxiredoxin (Tri a 32), dehydrin (Tri a DH, serpin, glyceraldehyde 3-phosphate dehydrogenase (GA3PD), ω-5-gliadin (Tri a 19), nsLTP (Tri a 14); acyl-CoA oxidase, fructose-bisphosphate aldolase, serin protease inhibitor (Tri a 39), among others	Bakers	[166, 167, 169, 171]
Cow	Beef: Bos d 6 and α-GAL	Bovine dander Bos d 2 (lipocalin)	Farmers	[172]
Soy	Gly m 4 (PR-10 homolog), Gly m 5 (β-conglycinin), Gly m 6 (glycinin) among others	Soy flour: high-molecular-weight allergens (Gly m 5 and 6)	Bakers	[173, 174]
Fisc	Gad m 1.0101 Gad m 1.0102 Gad m 1.0201 Gad m 1.0202 Sal s 1.0101 Enolase, e.g., Gad m 2.0101 Sal s 2.0101 Aldolase Gad m 3.0101 Sal s 3.0101	Skin and inhalation Parvalbumin, glyceraldehyde 3-phosphate dehydrogenase	Fish-processing industry, professional chefs	[175, 176, 177]

nsLTP, non-specific lipid transfer protein

Method report

Guidelines initiation and interest group participation

The S2k-guideline „Management of IgE-mediated food allergies" [German Association of Scientific Medical Societies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaft) register number 061–031] was initiated by the German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und Klinische Immunologie, DGAKI). Prof. Dr. med. Margitta Worm, from the Charité Allergy Center, was responsible for coordinating the guidelines project. The Division of Evidence Based Medicine (dEBM), PD Dr. med. Alexander Nast, provided methodological supervision.

In all, 15 specialist societies, professional associations, and other organizations participated in the preparation of the guideline and nominated official representatives for the guideline group (**Tab. 19**). The German Allergy and Asthma Association (Deutsche Allergie- und Asthmabund) represented patient interests.

Formulation of the recommendations and structured consensus-finding

Drafts of the text and recommendations in the guidelines sections were elaborated by the authors and then submitted via email to the guidelines group. A distinction was made in the derivation of the guidelines between three levels of recommendation that express the strength of recommendation (**Tab. 1**).

Consensus was reached on the proposed recommendations and core statements using a nominal group technique during two consensus conferences held on 11 April 2014 and 4 July 2014 in Berlin, Germany. PD Dr. med. Alexander Nast (AWMF guideline advisor) acted as facilitator of the structured consensus-finding process. Once the recommendations

on which consensus was sought had been presented, each group member was invited to share their comments on the draft. Divergent proposals were noted. This was followed by: a discussion of each point, a preliminary vote, debating/discussion, and a final vote. Each member of the expert group had one vote. Strong consensus (> 95 % agreement) was generally sought. Where this could not be reached despite discussion, recommendations were approved by consensus (> 75 % agreement). For one recommendation, it was possible to reach only a „majority approval" (50 %–74 % agreement). The respective strengths of consensus were documented. A Delphi procedure was conducted for those recommendations or core statements for which no consensus could be reached during the consensus conference.

Approval by the board members of participating organizations

The guidelines manuscript was sent to the board members of all participating specialist societies, professional associations, and patient organizations on 27 March 2015 for their information and with the request for formal approval.

The approval process took place between 27 March 2015 and 28 May 2015.

Financing of the guidelines

The travel expenses of participating DGAKI members, as well as hospitality costs during the consensus meeting and facilitator costs totaling 10,000 Euro (to the Charité, Working Group of PD Dr. med. Alexander Nast) were borne by the DGAKI.

Disclosure and handling of conflicts of interest

In order to disclose potential conflicts of interest, all members of the guidelines group completed the „declaration of conflicts of interest" form. Declarations were presented during the consensus conference and discussed. No significant conflicts of interest were identified.

A summary of conflicts of interest declarations is available on the AWMF website under http://www.awmf.org/leitlinien/detail/061-031.html.

Period of validity and review procedure

Valid until 31 June 2018, the review of these guidelines should be initiated by the responsible person at the DGAKI, currently the guidelines coordinator, Prof. Margitta Worm.

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Tab. 19: Participating organizations

Organization	Representatives
German Medical Association of Allergologists (Ärzteverband Deutscher Allergologen, AeDA)	Prof. Dr. med. Thomas Fuchs Dr. med. Ute Rabe
German Professional Association of Pediatricians (Berufsverband der Kinder- und Jugendärzte, BVKJ)	Dr. med. Peter J. Fischer
German Allergy and Asthma Association (Deutscher Allergie- und Asthmabund, DAAB)	Sabine Schnadt
German Dermatological Society (Deutsche Dermatologische Gesellschaft, DDG)	Prof. Dr. med. Regina Treudler
German Society for Allergology and Clinical Immunology (Deutsche Gesellschaft für Allergologie und klinische Immunologie, DGAKI)	Prof. Dr. med. Margitta Worm Prof. Dr. med. Uta Jappe Prof. Barbara Ballmer-Weber Prof. Dr. med. Thomas Werfel Prof. Dr. med. Torsten Zuberbier Prof. Dr. med. Joachim Saloga PD Dr. med. Jörg Kleine-Tebbe
German Society for Nutrition (Deutsche Gesellschaft für Ernährung, DGE)	Prof. Dr. Bernhard Watzl
German Society for Gastroenterology, Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, DGVS)	Prof. Dr. med. Stephan C. Bischoff Prof. Dr. med. Martin Raithel
German Society for Oto-Rhino-Laryngology, Head and Neck Surgery (Deutsche Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie)	Prof. Dr. med. Ludger Klimek PD Dr. Martin Wagenmann
German Society for Pediatric and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin, DGKJ)	Prof. Dr. med. Berthold Koletzko
German Society for Pediatric Allergology and Environmental Medicine (Gesellschaft für Pädiatrische Allergologie und Umweltmedizin, GPA)	Prof. Dr. med. Bodo Niggemann Prof. Dr. med. Kirsten Beyer Dr. med. Lars Lange
German Society for Pneumology (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin, DGP)	Dr. med. Ute Lepp Prof. Dr. med. Jens Schreiber
German Society for Pediatric Gastroenterology and Nutrition (Gesellschaft für pädiatrische Gastroenterologie und Ernährung, GPGE)	Dr. med. Martin Claßen
German Contact Allergy Group (Deutsche Kontaktallergie-Gruppe, DKG) in the DDG	Prof. Dr. med. Vera Mahler
Austrian Society for Allergology and Immunology (Österreichische Gesellschaft für Allergologie und Immunologie, ÖGAI)	Prof. Dr. med. Zsolt Szépfalusi Dr. med. Isidor Huttegger
German Professional Association of Nutritional Sciences (BerufsVerband Oecotrophologie e.V., VDOE)	Dr. rer. medic. Imke Reese Dipl. oec. troph. Christiane Schäfer
Methodology/AWMF Guidelines Advisor	PD Dr. med. Alexander Nast

Conflicts of interest

The authors' disclosures are available in a table on the AWMF-page www.awmf.org/leitlinien/detail/061-031.html.

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