



Food intolerances—a diagnostic challenge

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Abstract

Background Food-associated complaints in the gastrointestinal tract can be signs of an intolerance of different etiology, which is reported by almost a quarter of the population. Due to the unspecific symptoms, a whole range of different triggers and immune reactions can be considered for the differential diagnosis, which cannot always be determined unambiguously and quickly.

Differentiation and diagnosis of disease entity The time course in connection with the clinical picture already allows a rough estimation of the underlying pathomechanism and points the diagnostic way. Thus, immune-mediated clinical pictures such as allergy must be distinguished from nonimmune-mediated intolerances. An allergic reaction can be IgE-mediated or cellularly induced. Secondary food allergies are triggered by other allergens than primary allergies, differ in their sensitization routes and course of disease. Non-immunological intolerance reactions also play a not insignificant role, including carbohydrate utilization disorders and histamine intolerance in addition to toxic reactions. Often difficult to identify

are also those food components which trigger a non-specific mast cell activation. Due to their particular clinical relevance, wheat intolerances of different pathogenesis are also discussed. As a consequence of their complexity with regards to disease-causing proteins, target organ manifestations, pathomechanisms and diagnostic clarification, these require a particularly differentiated approach.

Purpose This review article presents the current recommendations regarding the diagnosis of food intolerance and food allergy, with a separate focus on the specifics in the interpretation of different tests including IgE diagnostics.

Keywords Adverse reaction · Histamine · Lactose · Celiac disease · IgE-mediated

Abbreviations

α -Gal	Galactose- α -1,3-galactose
DD	Differential diagnoses
EGID	Eosinophilic gastrointestinal disorder
EoE	Eosinophilic esophagitis
FA	Food allergy
FPIES	Food protein-induced enterocolitis syndrome
HIT	Histamine intolerance
HWP	Hydrolyzed wheat protein
IBD	inflammatory bowel disease
IBS	Irritable bowel syndrome
IFN γ	Interferon γ
Ig	Immunoglobulin
nsLTP	Nonspecific lipid transfer protein
OAS	Oral allergy syndrome
WDEIA	Wheat-dependent exercise-induced anaphylaxis

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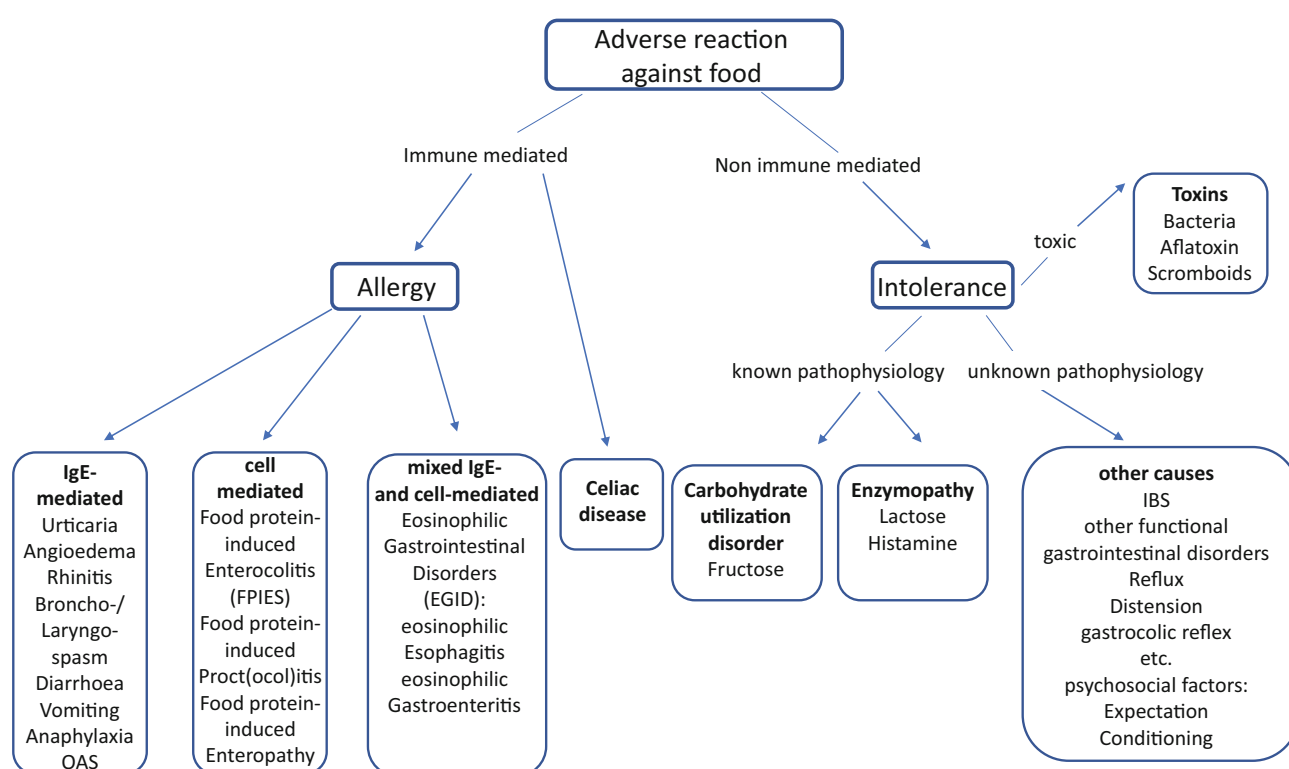


Fig. 1 Classification of food intolerances. *EGID* eosinophilic gastrointestinal disorder, *FPIES* food protein-induced enterocolitis syndrome, *GI* gastrointestinal, *IBS* irritable bowel syn-

drome, *IgE* immunoglobulin E, *OAS* oral allergy syndrome. Adapted from Turnbull, Adams, Gorard [4], Worm et al. [5]

Introduction

Numerous patients are referred to the allergist for clarification of questionable “allergic” diseases with complaints in various organ systems, with manifestations mainly in the skin, eyes, upper and lower respiratory tract, and gastrointestinal tract. The clinical picture ranges from acute, transient to chronic symptoms and from mild to life-threatening clinical presentations.

Over 20% of the general population report suffering from food allergy, but only about one tenth of these can be verified as IgE-mediated allergy [1]. Food intolerance may be far more common but is more difficult to diagnose because diagnosis is primarily clinical with the aid of a dietary and symptom diary as well as provocation testing, and clinical complaints are dose-dependent and modified by cofactorial influences [2].

Since the clinical picture is often nonspecific and the trigger cannot always be identified with certainty, it usually takes years until a reliable diagnosis with corresponding targeted therapy can be made. In addition, the number of foods suspected of triggering the symptoms is almost inexhaustible and the underlying pathomechanisms are also manifold. The most common pathologies are presented and discussed in this review.

Delimitation

In general, a distinction is made between immune-mediated and non-immune mechanisms in the diagnosis of food intolerances [3, 4]. For example, a patient may be allergic to cow’s milk due to an immunologic reaction to milk protein or intolerant to milk due to an inability to digest lactose, resulting in increased bacterial fermentation and fluid retention in the intestine. The clinical presentation in either case may remain nonspecific with abdominal pain and diarrhea. In terms of differential diagnosis, it is not only important to consider the age and the triggers: in lactose intolerance, lactose-free dairy products, but also cheese and butter, are usually tolerated without any problems [5].

Non-immune-mediated intolerances to foods are basically divided into carbohydrate utilization disorders, enzymatic, toxic, and undefined/idiopathic food intolerances (Fig. 1), although overlaps can certainly be found with regards to symptoms. A first clue to distinguish between food allergies and food intolerances may be the dose dependence. In food intolerances, small doses are usually tolerated, and symptoms develop only with consumption of increasing amounts or the combination of different triggers. This may mean, for example, that consumption of cheese alone is without discomfort, but combination with tomatoes, red wine/beer, and salami causes problems. In

the case of food allergies, the dose-symptom correlation is not present to the same extent: Here, too, co-factors can influence the severity of the reaction, but patients can also develop severe systemic reactions to even the smallest traces of the intolerant food.

Clinical manifestations

The specific symptomatology described in more detail for the individual clinical pictures often allows an estimation of the underlying pathomechanism and is summarized in Table 1 as an example.

It is important to know that the triggers of urticaria are basically the same regardless of age; they differ only in the frequency of their occurrence: Thus, unlike in adults, urticarial exanthema in children is most frequently triggered by infections [7]. Moreover, in children, chronic idiopathic urticaria is more likely to be triggered by physical factors (cold, pressure, sun exposure) than by food [8, 9]. The diagnostic procedure can be handled uniformly for all age groups according to the current guideline [10].

Immune-mediated food intolerances

Immune-mediated intolerances can be classified as allergic and nonallergic, with the former distinguished between IgE-mediated, mixed IgE-dependent, and cell-mediated and purely cell-mediated reactions (Fig. 1; [3, 4]).

An allergy is a reproducible specific immune response to a food component (allergen). Allergens are usually proteins, with the exception of allergies to galactose- α -1,3-galactose (α -Gal), an oligosaccharide found in red meat, among other foods [11]. In food allergies (FA), primary FA are distinguished from secondary FA [5]. Most primary FAs occur in infancy and early childhood and are usually caused by gastrointestinal (and less commonly epicutaneous) sensitization to genuine and usually stable food allergens.

Further classifications can be made depending on the time course, immune mechanisms and organ manifestations: In cow's milk allergies, for example, an IgE-mediated immediate-type allergy is distinguished from a non-IgE-mediated late-type reaction [12]. In immediate-type reactions, the skin and gastrointestinal tract are primarily affected within minutes of exposure. Life-threatening anaphylaxis is possible. Older children increasingly show a quantity-dependent and often strongly delayed IgE-mediated reaction. In the case of delayed purely gastrointestinal symptoms, specific IgE sensitization is usually not detectable—in this case, diagnosis is performed clinically by means of a symptom diary, time-limited abstinence, and oral provocation testing [12].

Secondary FA develops in the wake of sensitization to inhalant allergens (e.g., pollen) with consecutive reactions to structurally related, i.e., cross-reactive, and often unstable allergens in foods [5].

Secondary FAs are far more common than primary FAs: nearly 60% of all FAs in older childhood, adolescence, and adulthood are related to inhalant allergy [13].

Mixed IgE- and cell-mediated entities, not discussed in detail here, include food allergy-associated atopic dermatitis and eosinophil-associated diseases of the gastrointestinal tract (EGID), such as eosinophilic esophagitis and other eosinophilic syndromes. Non-IgE-mediated conditions include food protein-induced enterocolitis syndrome, proctocolitis, and food protein enteropathy, respectively, the former exclusively and the latter predominantly affecting infants and young children, who usually develop tolerance after some time (period first months to years of life) [5, 13].

IgE-mediated food allergies

IgE-mediated food allergies can be divided into primary and secondary food allergies. Primary, genuine food allergies are triggered by stable food allergens (class I allergens). In contrast, secondary food allergies are caused by more unstable cross-reacting allergens (class II allergens), which, to take the example of seasonal allergies, are present in pollen as well as in raw fruits, vegetables, or some nuts [6].

In general, proteins can be classified according to their sensitization route. Class I proteins are considered true food allergens, induce sensitization via body surfaces with non-intact barrier function, i.e., the gastrointestinal tract and less commonly the skin, and are characterized by linear sequence epitopes. These proteins are heat stable and resistant to enzymes of the gastrointestinal tract and therefore tend to induce very severe systemic reactions [14].

In comparison, class II proteins are considered cross-reactive molecules with primary sensitization via the respiratory tract, where protein structures play a major role. These are often more sensitive to heat and enzymatic digestion and are more likely to lead to milder and often localized symptoms, such as an oral allergy syndrome; however, stable proteins such as tropomyosins or nsLTs (nonspecific lipid transfer proteins) can also lead to secondary food allergies via the inhalation sensitization route [15–17].

In childhood, the most common food allergies are against allergens of milk and chicken egg whites, soy, wheat, peanut, and tree nuts [5]. 60–75% of pediatric patients develop tolerance to these foods by 7 years of age [18, 19]. However, allergic reactions to peanuts, tree nuts, and shellfish usually persist into adulthood [19]. In allergic adults, fish and seafood are the main triggers of allergic food reactions, in addition to wheat, tree nuts, and peanuts [5, 20]. Prevalence figures on food allergy vary widely depending on the source and geographic region and are likely to be around 3–4% globally in adults and up to 6% in children [1, 19, 20], with recent data from the EuroPrevall cohort show-

ing a much lower percentage of 1.4–3.8% for primary school children in the participating eight European countries [21]. This survey also confirmed the historical finding that approximately 10% of anamnestically reported food intolerances are diagnostically verifiable as IgE-mediated FA [22]. The severity of IgE-mediated food allergy ranges from mild unpleasant symptoms such as itching in the oral cavity, erythema, sneezing to severe reactions such as vomiting, abdominal cramps, urticaria, angioedema and asthma attacks and finally life-threatening anaphylactic reactions. All these symptoms show a prompt onset with the exception of delayed meat allergy, which is caused by a reaction to the above-mentioned carbohydrate galactose- α -1,3-galactose (α -Gal) and is readily manifested several hours after meat consumption in association with augmenting factors such as physical exertion (sports), alcohol consumption, hormonal factors, etc. [11, 23, 24].

Secondary food allergy usually manifests as an oral allergy syndrome and is a relevant clinical problem for up to 70% of all patients with inhalant allergy [13, 25]. Typical symptoms after consumption of raw or unprocessed cross-reactive foods are oral pruritus, swelling of lips, tongue, throat, and larynx. Itchy ears and perioral urticaria are sometimes reported. Symptoms are usually self-limiting and localized; anaphylactic reactions have been described only in isolated cases. Affected individuals can often eat the food, which is intolerable in raw form, in cooked form because the proteins are denatured during the heating process [26], but exceptions have also been described in the literature [27, 28]. However, inactivation of the IgE epitopes does not affect T-cell reactivity, which may result in a worsening of the skin condition in patients with atopic dermatitis [26].

In Northern and Central Europe, the most common pollen-associated secondary food allergy is directed against birch pollen-associated plant foods. Clinical symptoms are usually reduced to an oral allergy syndrome, which, however, is sometimes severe and may lead to relevant respiratory distress, especially if laryngeal swelling occurs. Systemic reactions to cross-reactive PR10 proteins have been described for soy (Gly m 4) [28, 29], carrot (Dau c 1) [30], hazelnut (Cor a 1), celery (Api g 1) [31, 32], Sharon fruit [33], and jackfruit [34].

Another major source of secondary food allergies is mugwort pollen allergy, with the majority of sufferers in northern and central Europe being sensitized to the major allergen, “Art” v 1. The nsLTP from mugwort, “Art” v 3, is another pollen allergen that is also suspected to be responsible for cross-reactive reactions with pome and stone fruits and also various vegetables. However, this allergen is only predominant in southern Europe and plays a minor role in central Europe [35]. It is questionable whether food allergies with positive Art v 3 findings may be interpreted in terms of a mugwort-associated food allergy: It is

now believed that the primary sensitization is not to Art v 3 but to Pru p 3 or other LTPs [36]. The incidence of mugwort pollen-associated food syndromes is thought to be around 10% [37], but clinical reactions can be consistently severe [13].

Mite allergy, the most common year-round inhalant allergy, also causes associated symptoms in less than 10% of patients when eating crustaceans [38], molluscs [39], and edible insects, which are probably caused mainly by the muscle protein tropomyosin [40, 41] and can be quite severe. A role of other proteins such as arginine kinases [40, 42] or troponin C [43, 44], which is mainly found in cockroaches, is suspected but currently not confirmed.

Latex allergies are tending to decline but can still be the cause of secondary food allergies to tropical fruits such as kiwi, banana, pineapple, papaya, mango, but also chestnut, cassava, curry, and avocado [45, 46]. Allergens with sequence homologies to the latex allergens Hev b 2, 6, 7, 8, and 11 [13, 47] may be the causative agents for these secondary food allergies. In the rare inhalant Ficus allergies, patients complain (in up to 35% of cases) of associated food allergies, here especially to fig or papaya (papain; mainly contained in barbecue spice mixtures) [48, 49].

In the literature, secondary food allergies in furry animal allergy sufferers are repeatedly described as the so-called “cat–pork syndrome” or as the “bird–egg syndrome” in bird allergy sufferers [5, 13]. The “cat–pork syndrome” is triggered by primary sensitization to the serum albumin in cat dander (Fel d 2) and affects about 1–3% of cat allergic individuals, mainly older children, and adults [50, 51].

“Bird–egg syndrome” is due to cross-reactivity between serum albumin in pet birds and hen’s egg (Gal d 5). The clinical picture after consumption of raw or soft-boiled egg yolk ranges from OAS to systemic reactions. Egg allergy in the “bird–egg syndrome”, in contrast to the primary egg allergy of early childhood, often occurs and persists later in life [52].

The most common inhalant allergens and their cross-reactive foods are summarized in Table 2.

Celiac disease and other wheat intolerances

Celiac disease

Among non-IgE-mediated wheat intolerances, celiac disease is the most important and one of the most common autoimmune diseases, with a prevalence of about 1% of diagnosed patients. As a non-atopic immune-mediated disease, celiac disease plays an important role in the differential diagnosis of adverse reactions to wheat. This malabsorption disorder is caused by the gluten fraction present in wheat and other cereals. Furthermore, genetic factors (genetic markers HLA-DQ2 or HLA-DQ-8) are characteristic for the disease.

Antibodies (IgG, IgA) are produced against gliadins, endomysium, and tissue transglutaminase. The production of IFN- γ (interferon gamma) by TH1 cells leads to damage of the epithelial tissue in the small intestine with consecutive villous atrophy, which is a main feature of celiac disease. Depending on the existing pathological mucosal changes and the clinical picture, we now distinguish potential, subclinical, symptomatic, classic, and refractory forms [59]. The clinical picture is quite nonspecific with the typical gastrointestinal symptoms of nausea, vomiting, diarrhea, flatulence or constipation, and failure to thrive, but also extragastrointestinal abnormalities such as liver dysfunction, iron deficiency anemia, and affections of bone and skin. The majority of patients with celiac disease has no symptoms at all and is classified as “subclinical” if celiac disease-specific serology and typical changes are detectable in small intestinal biopsies or as “potential” if small intestinal pathology is absent. Today, due to improved diagnostic possibilities and a significantly increased awareness, far more affected persons are diagnosed than 30 years ago; however, the number of unreported cases is probably more than double due to the high percentage of subclinical and symptom-free cases [60]. This is critical, as the continuous exposure of undiagnosed patients to gluten significantly increases the risk of further autoimmune diseases [61]. The cutaneous manifestation of celiac disease is dermatitis herpetiformis Dühring. This blistering autoimmune dermatosis with subepidermal blistering indicates an underlying (subclinical) celiac disease in almost all affected patients [59]. Functional intestinal diseases such as irritable bowel syndrome [62], carbohydrate intolerance or malabsorption syndromes, or other wheat-associated diseases should be evaluated (Fig. 2), as well as motility disorders and nutritional abnormalities [63].

Celiac disease is detected by serological detection of celiac disease-specific antibodies according to recent guideline recommendations. The diagnosis is confirmed by duodenal mucosal biopsies. Since the findings normalize under gluten abstinence, both serology and biopsy must be performed under a gluten-containing diet, i.e., celiac disease must be reliably ruled out before initiating a gluten-free diet [59, 63].

IgE-mediated wheat allergy

Wheat allergies are differentiated between food allergy and inhalant allergy, which are clearly distinguished by different allergens.

The alcohol-soluble gluten fraction, which contains mono- and polymeric gliadins and is considered a marker for severe nutritive wheat allergies, accounts for the largest proportion of allergens present in wheat (80%) [66]. These manifest as urticaria with or with-

out angioedema, anaphylaxis, or wheat-dependent exercise-induced anaphylaxis (WDEIA).

Primary wheat allergy affects 0.4–1% of infants in the first year of life and often occurs together with allergy to milk and hen's egg [17]. Clinical symptoms range from worsening of an existing eczema condition to food protein-induced gastrointestinal disorders and anaphylaxis. In children, foods are the most important triggers of anaphylaxis, and wheat ranks seventh in frequency [67]. Most children outgrow the condition by school age, with only a small proportion persisting into adolescence [68]. In adults, wheat is an important trigger of wheat-dependent exercise-induced anaphylaxis (WDEIA) or baker's asthma. Statistically, food anaphylaxis in adults is listed third after insect venom and drug anaphylaxis, but wheat being the most important trigger [67].

Given the cross-reactivity indicated above and the poor predictive value of skin test and sIgE level, clinical reactivity can only be verified by provocation testing.

It is important to know that wheat-allergic patients develop immune reactions to almost all domestic cereals and all wheat subspecies [69]. Only millet, corn, the millet subspecies teff and sorghum, as well as amaranth and quinoa and gluten-free produced oats are actually gluten-free [70].

Another source of wheat allergy, which is still unclear in terms of its clinical significance, is allergy to hydrolyzed wheat proteins, which are added to food as a source of vegetable protein and are used in cosmetics. Industrial hydrolysis processes generate additional IgE epitopes, which can lead to urticaria in gliadin-sensitized patients, but also to severe symptoms such as anaphylaxis [71].

Non-IgE mediated wheat allergy

Wheat is also a major trigger of conditionally or non-IgE-mediated, cell-mediated allergic clinical pictures, which include the eosinophilic gastrointestinal disorders such as eosinophilic esophagitis. Eosinophilic esophagitis (EoE) was first described in the 1970s and is characterized by chronic esophageal dysfunction, presumably mediated by topical allergen exposure and other exogenous cofactors. Endoscopically, esophageal epithelial inflammation is found with more than 15 eosinophils per high-power field (Eos/HPF) in the biopsy specimen [72]. The overall incidence and prevalence has increased in recent decades and is currently reported to be as high as 50/100,000 in adults with wide geographic variations and higher numbers [73, 74]. The disease can occur in all age groups, with incidence peaks described in older adolescents and in 30- to 50-year-olds. The risk of disease is two- to threefold higher in men [75]. Eosinophilic esophagitis often manifests nonspecifically as dysphagia to compact foods such as steak, which is then suspected as the trigger. However, only

Table 1 Clinical symptoms (classification modified acc. to [6])

Likely IgE-mediated response	Likely not IgE-mediated response	No intolerance
One or more of the following symptoms ≤ 2 h: – Skin symptoms: rash, urticaria, pruritus, flush – Angioedema – Rhinitis or rhino conjunctivitis – Bronchospasm (chest tightness, shortness of breath, wheezing, cough, cyanosis) – Hemodynamic instability (presyncope, syncope, arrhythmia, seizures, cardiac arrest) – OAS	Isolated gastrointestinal symptoms: – Stomach pain – Nausea – Vomiting – Diarrhea – Flatulence – Reflux symptoms	– No temporal relationship between symptoms and food intake (<i>Caution:</i> can take up to 12 h with α -Gal reaction!) – Subsequent exposure to the same food without reaction – Symptoms that are no indication for an immune-mediated reaction (e.g., headache, obstipation, hypertension, blurred vision) – Temporal relationship between food consumption and the appearance of symptoms is vague/unknown. – Vague history without details (e.g., “childhood food allergy”!)
α -Gal galactose- α -1,3-galactose, IgE immunoglobulin E, OAS oral allergy syndrome		

Table 2 Important inhalative allergens and their cross-reactive foods

Inhalative allergen source	Cross reactive foods	Protein group	Frequency of severity	References
Tree pollen (birch and homologues)	Apple, cherry, nectarine, peach, hazelnut, carrots, celery, soybeans, kiwi, sharon, jackfruit	PR-10	Up to 70% OAS, up to 50% systemic reactions in carrots, celery, soy, sharon, jackfruit	[13, 26–30]
Mugwort	Umbelliferae (celery, carrot, parsley, fennel, coriander, anise, cumin/curry), daisy family (chamomile, sunflower seeds, black salsify, lettuce, Jerusalem artichoke), nightshade family (tomato, paprika), Piperaceae (pepper, Anacardiaceae, Lychee) and Liliaceae (garlic, onion), cruciferous vegetables (mustard, broccoli, cabbage, cauliflower), nuts, legumes, rose fruits, corn, honey	Unclear Art v 1? nsLTP?	Occasionally, OAS to severe systemic reactions	[13, 34–36, 52–54]
House dust mite	Crustaceans, mussels, mollusks, edible insects	Tropomyosin Troponin C? Arginine kinase?	Rarely (less than 10%), partly severe	[37, 38, 42, 43]
Latex	Pineapple, avocado, banana, potato, tomato, kiwi, chestnut, passion fruit, papaya, mango, pepper	Hevein Endochitinase 1,3- β -glucanase Hev b 2, 6, 7, 8 and 11	21–58%, partly severe	[13, 46, 55, 56]
Ficus benjamina	Fig, kiwi, papaya, avocado, pineapple, banana	Thiol protease?	–	[47, 48, 57, 58]
Avian allergens	Egg yolks, poultry meat, offal	Serum albumin	Rarely, partly severe	[51]
Animal epithelia	Cow's milk, meat, offal	Serum albumin	Rarely (1–3%), partly severe	[50]
OAS oral allergy syndrome, nsLTP nonspecific lipid transfer protein				

a few foods are likely to be responsible for the majority of food-associated inflammation in patients with eosinophilic esophagitis; these include milk, wheat, egg, and soy [76, 77], with milk and wheat likely to be prominent in children. However, specific sensitization cannot be demonstrated in all patients, and dietary measures also lead to limited clinical and histologic improvement [73–75].

Non-celiac wheat sensitivity

Non-celiac wheat sensitivity is postulated to be an intolerance reaction to amylase trypsin inhibitors (ATIs) that occurs relatively quickly after consumption of gluten-containing wheat products and is thought to lead to activation of the innate immune system without the formation of any antibodies [78]. That so-called FODMAPs (fermentable oligo-, di- and monosaccharides and polyols) play a not insignificant role in this context is suspected, but has not yet

been definitively clarified [59, 65]. Since validated diagnostic criteria are still lacking, a careful differential diagnosis is recommended, which should include a differentiated anamnesis with the keeping of a dietary and symptom diary, an allergological diagnosis and the reliable exclusion of celiac disease [65].

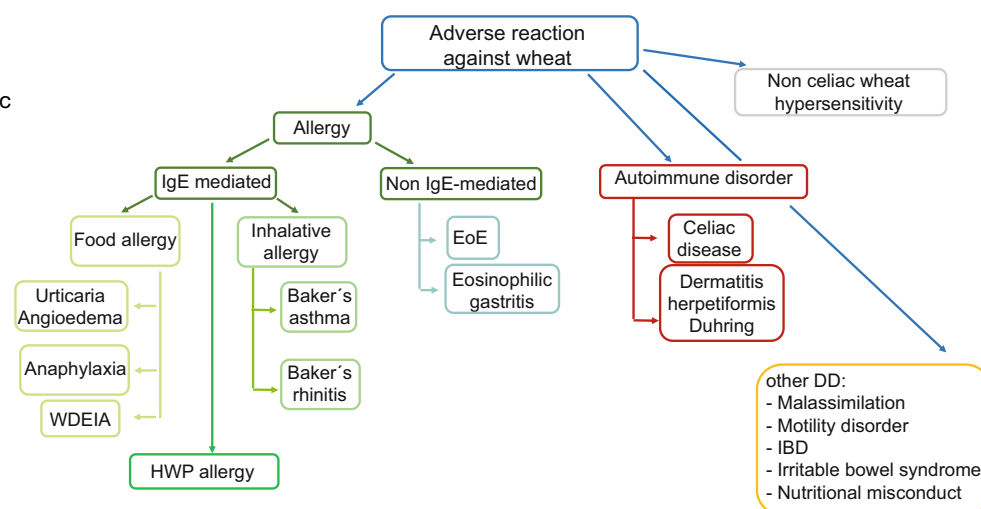
Intolerances

Carbohydrate-induced reactions: malabsorption versus intolerance

Carbohydrate utilization disorders Carbohydrate utilization disorders are among the most important nonimmunological food intolerances. One example is lactose intolerance with hypolactasia, i.e., a deficiency of lactase, the enzyme that breaks down lactose ingested with milk into galactose and glucose.

The clinical picture of lactose intolerance is based on lactose malassimilation, a mismatch between en-

Fig. 2 Wheat intolerances. *IBD* inflammatory bowel disease, *DD* differential diagnosis, *EoE* eosinophilic esophagitis, *HWP* hydrolyzed wheat protein, *WDEIA* wheat-dependent exercise-induced anaphylaxis. Adapted from Gianferoni [64], Reese et al. [65]



zyme and substrate, by which undegraded lactose is taken up and processed by intestinal bacteria, producing bacterial degradation products such as methane, carbon dioxide and hydrogen, and triggering symptoms such as osmotic diarrhea, flatulence, cramps, etc. The most common cause in adolescents and adults is lactase nonpersistence. The most common cause in adolescents and adults is primary (genetic) lactase nonpersistence. Prevalence rates vary considerably globally with a south–north and east–west gradient and are as high as 100% in some regions, especially Africa and Asia [79, 80]. This should be distinguished from congenital lactase deficiency, a very rare pediatric disorder associated with severe symptoms and failure to thrive in infants [81].

With prevalence rates of about 20%, fructose malabsorption is also common [82] and should be distinguished from the very rare autosomal recessive hereditary fructose intolerance. It occurs because more fructose is supplied with food than can be absorbed by GLUT-5 and GLUT-2 transporters in the small intestine, whereby unabsorbed fructose is bacterially fermented in the large intestine and induces symptoms similar to lactose intolerance [83].

Histamine intolerance A different pathomechanism is suspected in the disease pattern of histamine intolerance, which has been insufficiently documented and controversially discussed to date: Thus, a deficiency or insufficient enzyme(s) diamine oxidase (DAO) and histamine N-methyltransferase (HNMT) are supposed to lead to the fact that dietary histamine and other biogenic amines cannot be metabolized sufficiently and therefore cause allergy-like symptoms after enteral absorption [84, 85]. The hypothesis is supported by data showing that DAO supplementation significantly mitigates clinical symptoms in affected individuals [86]. On the other hand, histamine-induced symptoms have limited reproducibility [86], and subjects with positive and negative histamine

provocation, respectively, do not differ in their DAO levels, nor is an increase in plasma histamine levels detectable with positive provocation [87]. However, the oral histamine tolerance threshold varies considerably from individual to individual and depends on cofactors. The transition to toxic reactions (e.g., when eating spoiled fish) is fluid, and it remains unclear to what extent the symptomatology is caused by endogenous histamine liberation [84].

The clinical picture of these disorders is extremely variable and nonspecific and includes symptoms such as sudden facial erythema (flush), pruritus, and skin rashes, as well as gastrointestinal symptoms such as nausea and/or vomiting, diarrhea, and abdominal pain. Respiratory symptoms, migraine, and cardiovascular symptoms such as hypotension, dizziness, or tachycardia are less common, but are recurrent and also require differential diagnosis.

Pseudoallergies To date, so-called “pseudoallergies”, are also postulated, assuming that other substances in food cause nonspecific mast cell activation with consecutive allergy-like reactions or chronic spontaneous urticaria [88]. However, experimental evidence for such mechanisms is scarce [89]. This area includes food additives, which, due to their ubiquitous use in the food industry, are still present in quite a few nonnatural preparations and are correspondingly difficult to be identified as triggers of intolerance reactions. Among the 316 currently approved food additives are flavor enhancers such as glutamate (E 620), sweeteners (including E 951=aspartame, E 952=cyclamate, E 954=saccharin), preservatives (including E 200=sorbic acid, E 210=benzoic acid, E 214=PHB ester, E 280=propionic acid) and azo dyes as well as antioxidants [17].

For all food additives, specific abstinence measures have not yet been shown to improve symptoms [17, 86].

On the contrary, there are even considerations regarding protective effects of salicylic acid [90, 91], which is found in high concentrations in spices such as bell pepper or spice mixtures such as curry, paprika powder, rosemary, thyme, oregano, and Worcester sauce, but also in ketchup and tomato paste, red berries, and green olives, and has historically been suspected of causing pseudoallergic reactions.

Diagnostics

The diagnostic procedure is carried out according to the recommendations of the guidelines of the involved professional societies in the respective valid version and is based on the clinical suspected diagnosis—a differentiated anamnesis is therefore indispensable! The plausibility check, which includes the question of reproducibility and the assignment of the complaints to the trigger, also in relation to age, is decisive for the further procedure. In Fig. 3, the diagnosis of food intolerances of different pathogenesis is illustrated.

In cases of suspected IgE-mediated food allergy, the diagnosis is based on several complementary measures, the most important of which is the patient's medical history (possibly with a dietary and symptom protocol), without which subsequent in vivo or in vitro analyses cannot be interpreted. Diagnostically, the specific anamnesis of the patient is therefore in the foreground since it represents the essential criterion for the therapy decision. A sensitization per se does not mean an allergy, only the corresponding clinical

symptoms result in the disease value and thus the therapy indication for the IgE-mediated allergy. Sensitization can remain without clinical correlate, i.e., mute, and thus does not result in therapy. Since positive sensitization evidence is found in a very high percentage of the population without clinically manifest allergy, the positive predictive value of the test result is manageable [55, 93]. In practice, the skin prick test is the most commonly used test method for the detection of IgE-mediated sensitization because it is simple, rapid, inexpensive, and safe to perform and has good sensitivity and specificity when interpreted correctly.

Commercial extracts of good quality are available for fish, seafood, egg, milk, peanut, and hazelnut. However, not all allergens relevant to the patient are always available in sufficient quantity in the extracts, making false-negative test results possible. When good quality commercial extracts are not available, prick-to-prick testing (PPT) with native allergens can be considered. There is better diagnostic sensitivity in prick-to-prick testing with the native food, which is in principle suitable for all types of food. In the case of potentially irritating foods (Table 3), control subjects should be tested as well. Irritative reactions have been described for tomato, mustard, kiwi, spices, strawberries, and pineapple ([5, 17]; Table 3).

In the in vitro diagnostics of IgE-mediated food allergies, the detection of allergen-specific IgE antibodies is particularly important. These can be determined qualitatively and quantitatively using tests based either on extracts of the allergen sources or on native purified or recombinantly produced single allergens.

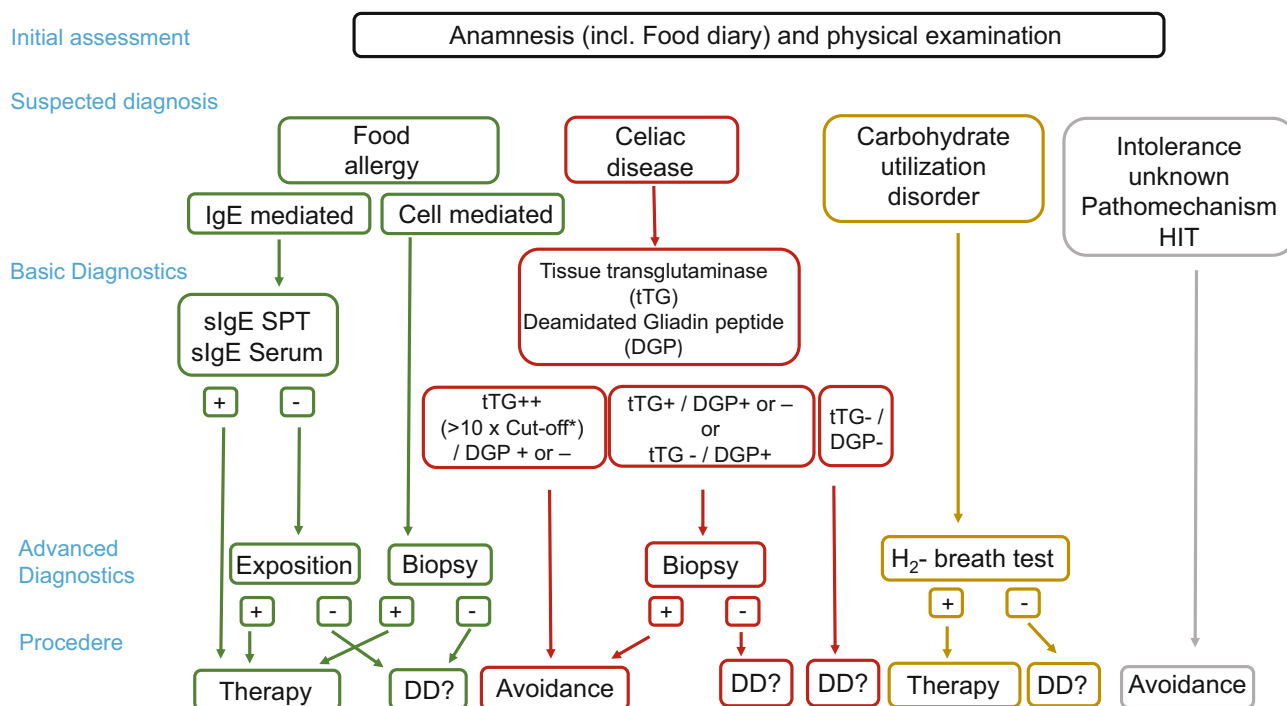


Fig. 3 Diagnostic algorithm for the clarification of food intolerances of different pathogenesis. DD differential diagnosis, HIT histamine intolerance, sIgE specific immunoglobulin E, SPT skin prick test. Husby et al. [92]

Table 3 Overview of the suitability of prick test materials. From [5], with the kind permission of Springer^c

	Commercial extract	Suitable for native testing ^a	Conditionally suitable for native testing ^b
<i>Food of animal origin</i>			
Fish	+	+	∅
Meat	(+)	+	∅
Chicken egg	+	+	∅
Seafood and snails	+	+	∅
Milk	+	+	∅
<i>Food of plant origin</i>			
Pineapple	∅	∅	+
Apple	∅	+	∅
Cereals	(+)	+	∅
Strawberry	∅	∅	+
Peanuts	+	+	∅
Spices	∅	∅	+
Hazelnuts	+	+	∅
Carrot	∅	+	∅
Kiwi	∅	∅	+
Lychee	∅	+	∅
Mango	∅	+	∅
Oil seeds (e.g., poppy seeds, sesame seeds)	∅	+	∅
Peach	∅	+	∅
Celery	(+)	+	∅
Mustard	∅	∅	+
Soy	(+)	+	∅
Tomato	∅	∅	+
Grape	∅	+	∅
Sugar snap	∅	+	∅

+ very good, (+) good

^aIdeally, test control persons for possible irritative components (testing control persons with non-approved test preparations is not legal in Germany according to the „Arzneimittelgesetz“ (German Pharmaceuticals Act))

^bHigher irritative potential

^cData on the quality of the extracts are only available for individual foods, so this table can only provide limited information. In principle, testing with native foods usually has better diagnostic sensitivity with low specificity

Molecular diagnostics are particularly indicated when possible cross-reactions play a role and the risk of severe reactions such as anaphylaxis and resulting emergency measures must be assessed. Especially in patients with multiple allergies, knowledge of the sensitization pattern as well as knowledge of the significance of the respective allergens for the clinical symptomatology only enables sensible and specific therapy planning. In individual cases, molecular allergy diagnostics with a multiplex method, i.e., the simultaneous quantification of a whole series of allergens, can be helpful. Various quantitative or semi-quantitative assays from commercial suppliers are now available on the market. Especially for patients with polysensitization, severe atopic dermatitis, very high total IgE values, unclear anaphylaxis or with low available serum volume, the preparation of a differentiated sensitiza-

tion profile considerably facilitates the interpretation of the test results with regards to the assignment to a clinical symptomatology and the consecutive therapy planning [94].

For the assessment of the clinical relevance of sensitization, a diagnostic elimination diet for a maximum period of 2 weeks may also be useful, ideally involving a nutritionist in its planning and implementation [5]. This should be followed by food provocation under controlled conditions according to the guideline recommendations to confirm the diagnosis of food allergy or to prove clinical tolerance [5, 95, 96, 97]. This will not be done if an anaphylactic reaction has been recently experienced or if the diagnosis is clear. The procedure depends on the age of the patient, clinical picture, and purpose of the provocation [17]. Oral food provocation is performed in a standardized manner, double-blind placebo-controlled provocation corresponds to the current gold standard and is recommended with increasing age whenever nonspecific or atypical as well as late-type reactions are described, the outcome of the provocation is unclear or uncertainties exist in patients and their families. Here, the provocation meals are given titrated at 30 min intervals, with semilogarithmic increases to avoid severe reactions (e.g., 3 mg, 10 mg, 30 mg, 100 mg, 300 mg, 1000 mg, 3000 mg peanut protein) [93]. Placebo and allergen are given on different days in randomized order. Cumulative administration, in which the total amount of food is applied once on a different day, is useful because approximately 10% of patients only respond to this total amount and not to titrated provocation [17, 96]. In case of an immediate-type reaction, open provocation is recommended, especially in very young children.

If celiac disease is suspected, primary serological tests are indicated. Tissue transglutaminase IgA antibodies (tTG IgA antibodies), determined by ELISA, and endomysium IgA antibodies (EmA IgA antibodies), detected by indirect immunofluorescence, have a specificity of at least 75 and 83%, respectively, and a sensitivity of almost 100% in the diagnosis of celiac disease [64]. A total IgA level is always collected, since IgG antibodies against tissue transglutaminase (tTG) or IgG antibodies against deamidated gliadin peptides (dGP) must also be tested in the case of IgA deficiency. Since a gluten-free diet can lead to a negation of the test results within one month, serological diagnostics are only useful under gluten exposure [97].

In the diagnosis of carbohydrate utilization disorders, H₂ breath tests are of great importance. Here, the concentration of hydrogen (H₂) in the exhaled air is measured in ppm (parts per million) over a period of 3 h after the patient has drunk a carbohydrate solution (lactose, fructose). The fermentation gases (hydrogen gas = H₂ and methane) produced by the bacterial degradation of carbohydrates in the intestine, which pass by diffusion through the intestinal wall into the bloodstream and from there to the alveoli, are exhaled

and can thus be measured [82]. To date, there are no validated test systems for intolerance reactions to histamine and food additives [84, 89]. In individual studies, the concentration or functionality of DAO in serum and intestine as well as histamine in serum, stool, and urine (methylhistamine) were determined, but a correlation with the clinical symptoms of the patients could not be found in any of the studies [84, 87]. There are recommendations for re-exposure after previous abstinence, but no standardized procedure. The recommendations of the guideline [84] are to perform a titrated exposure test under controlled conditions to determine the individual tolerance limit, which, however, may vary considerably depending on cofactors.

Management

Since the present review primarily deals with the diagnosis, the further therapeutic procedure can only be briefly discussed. Often, regardless of the underlying pathomechanisms, avoidance of the symptom-causing food is an important therapeutic pillar after the diagnosis has been confirmed. However, this does not always lead to freedom from symptoms and must be handled in a very restrictive and targeted manner in order to prevent malnutrition. Restriction measures are implemented and regularly re-evaluated depending on the results of the oral provocation test in collaboration with trained nutritionists after nutritional counseling [5]. Especially in the case of histamine intolerance, this is more likely to be understood as a change in diet with optimization of nutrient intake [84]. Due to the natural development of tolerance in childhood food allergies, the measure should be reviewed every second year in any case. As noted above, in eosinophilic esophagitis, for example, dietary measures lead to a significant clinical improvement in only about half of the patients, which can be objectified histologically only in some cases [75]. Here, supportive therapy plays an important role: modern oral corticosteroid formulations with budesonide or fluticasone induce better clinical effects than proton pump inhibitors or other antiallergic or anti-inflammatory agents [75]. In any case, in the event of anaphylaxis, after patient education has been provided, an emergency kit is carried that includes an oral antihistamine, an oral or rectal corticosteroid, and an epinephrine autoinjector [98]. The availability of standardized specific therapeutic options for the induction of clinical tolerance in food anaphylaxis will be available in the near future, at least for peanut: Here, an oral preparation will be available from fall 2021, and clinical development has already been completed for at least one other formulation for epicutaneous use. For enzyme supplementation in the case of enzyme deficiencies such as DAO insufficiency, the data currently do not permit any recommendations.

Conflict of interest U. P. Zieglmayer discloses that she was employed by Thermo Fisher Scientific until September 2019. There is no conflict of interest with the present work. S. Wieser states that she is employed by MacroArray Diagnostics. There is no conflict of interest with the present work. W. Hemmer and K. Hoffmann-Sommergruber declare that they have no competing interests.

References

1. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, et al. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy*. 2014;69:992–1007.
2. Zopf Y, Baenkler HW, Silbermann A, Hahn EG, Raithel M. The differential diagnosis of food intolerance. *Dtsch Arztebl Int*. 2009;106:359–69.
3. Boyce JA, Assa'ad A, Burks WA, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1–S58.
4. Turnbull JL, Adams HN, Gorard DA. The diagnosis and management of food allergy and food intolerances. *Aliment Pharmacol Ther*. 2015;41:3–25.
5. Worm M, Reese I, Ballmer-Weber B, Beyer K, Bischoff SC, Claßen M, et al. Guidelines on the management of IgE-mediated food allergies. S2K-Guidelines of the German Society for Allergology and Clinical Immunology (DGAKI) in collaboration with the German Medical Association of Allergologists (AeDA), the German Professional Association of Pediatricians (BVKJ), the German Allergy and Asthma Association (DAAB), German Dermatological Society (DDG), the German Society for Nutrition (DGE), the German Society for Gastroenterology, Digestive and Metabolic Diseases (DGVS), the German Society for Oto-Rhino-Laryngology, Head and Neck Surgery, the German Society for Pediatric and Adolescent Medicine (DGKJ), the German Society for Pediatric Allergology and Environmental Medicine (GPA), the German Society for Pneumology (DGP), the German Society for Pediatric Gastroenterology and Nutrition (GPGE), German Contact Allergy Group (DKG), the Austrian Society for Allergology and Immunology (ÖGAI), German Professional Association of Nutritional Sciences (VDOE) and the Association of the Scientific Medical Societies Germany (AWMF). *Allergo J Int*. 2015;24:256–93.
6. Sooriyakumar K, Mohamed O, Osborne T, Beck SC, Melchior C, Heslegrave J, et al. Suspected food allergy in adults: mapping 208 open food challenges with allergy tests and risk stratification. *J Clin Pathol*. 2021;74:133–6.
7. Ricci G, Giannetti A, Belotti T, Dondi A, Bendandi B, Cipriani F, et al. Allergy is not the main trigger of urticaria in children referred to the emergency room. *J Eur Acad Dermatol Venereol*. 2010;24:1347–8.
8. Chinthrajah RS, Tupa D, Prince BT, Block WM, Rosa JS, Singh AM, et al. Diagnosis of food allergy. *Pediatr Clin North Am*. 2015;62:1393–408.
9. Sackesen C, Sekerel BE, Orhan F, Kocabas CN, Tuncer A, Adalioglu G. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol*. 2004;21:102–8.
10. Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, et al. The EAACI/GA2LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868–87.

11. Steinke JW, Platts-Mills TAE, Commins SP. The alpha-gal story: Lessons learned from connecting the dots. *J Allergy Clin Immunol*. 2015;135:589–96.
12. Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. *Clin Exp Allergy*. 2014;44:642–72.
13. Werfel T, Asero R, Ballmer-Weber BK, Beyer K, Enrique E, Knulst AC, et al. Position paper of the EAACI: Food allergy due to immunological cross-reactions with common inhalant allergens. *Allergy*. 2015;70:1079–90.
14. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: Food allergy. *J Allergy Clin Immunol*. 2012;129:906–20.
15. Nowak-Węgrzyn A. Food allergy to proteins. *Nestle Nutr Workshop Ser Pediatr Program*. 2007;59:17–31.
16. Harrer A, Egger M, Gadermaier G, Erler A, Hauser M, Ferreira F, et al. Characterization of plant food allergens: an overview on physicochemical and immunological techniques. *Mol Nutr Food Res*. 2010;54:93–112.
17. Worm M, Reese I, Ballmer-Weber B, Beyer K, Bischoff SC, Bohle B, et al. Update of the S2k guideline on the management of IgE-mediated food allergies. *Allergol Sel*. 2021;5:195–243.
18. Sampson HA. Update on food allergy. *J Allergy Clin Immunol*. 2004;113:805–19.
19. Savage J, Sicherer S, Wood R. The natural history of food allergy. *J Allergy Clin Immunol Pract*. 2016;4:196–203.
20. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol*. 2006;117:S470–S5.
21. Grabenhenrich L, Trendelenburg V, Bellach J, Yürek S, Reich A, Fiandor A, et al. Frequency of food allergy in school-aged children in eight European countries—The Euro-Prevall-IFAAM birth cohort. *Allergy*. 2020;75:2294–308.
22. Osterballe M, Hansen TK, Mortz CG, Høst A, Bindslev-Jensen C. The prevalence of food hypersensitivity in an unselected population of children and adults. *Pediatr Allergy Immunol*. 2005;16:567–73.
23. Dunkman WJ, Rycek W, Manning MW. What does a red meat allergy have to do with anesthesia? Perioperative management of alpha-Gal syndrome. *Anesth Analg*. 2019;129:1242–8.
24. Platts-Mills TAE, Schuyler AJ, Hoyt AEW, Commins SP. Delayed anaphylaxis involving IgE to galactose-alpha-1,3-galactose. *Curr Allergy Asthma Rep*. 2015;15:1–6.
25. Poncet P, Sénéchal H, Charpin D. Update on pollen-food allergy syndrome. *Expert Rev Clin Immunol*. 2020;16:561–78.
26. Bohle B, Zwölfer B, Heratizadeh A, Jahn-Schmid B, Antonia YD, Alter M, et al. Cooking birch pollen-related food: divergent consequences for IgE- and T cell-mediated reactivity in vitro and in vivo. *J Allergy Clin Immunol*. 2006;118:242–9.
27. Vieths S, Scheurer S, Ballmer-Weber B. Current understanding of cross reactivity of food allergens and pollen. *Ann NY Acad Sci*. 2002;964:47–68.
28. Kleine-Tebbe J, Vogel L, Crowell DN, Haustein UF, Vieths S. Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1-related PR-10 protein in soybean, SAM22. *J Allergy Clin Immunol*. 2002;110:797–804.
29. Berneder M, Bublin M, Hoffmann-Sommergruber K, Hawranek T, Lang R. Allergen chip diagnosis for soy-allergic patients: Gly m 4 as a marker for severe food-allergic reactions to soy. *Int Arch Allergy Immunol*. 2013;161:229–33.
30. Ballmer-Weber BK, Wüthrich B, Wangorsch A, Fotisch K, Altmann F, Vieths S. Carrot allergy: double-blind, placebo controlled food challenge and identification of allergens. *J Allergy Clin Immunol*. 2001;108:301–7.
31. Ballmer-Weber BK, Vieths S, Luttkopf D, Heuschmann P, Wüthrich B. Celery allergy confirmed by double-blind, placebo-controlled food challenge: a clinical study in 32 subjects with a history of adverse reactions to celery root. *J Allergy Clin Immunol*. 2000;106:373–8.
32. Ballmer-Weber BK, Hoffmann A, Wüthrich B, Luttkopf D, Pompei C, Wangorsch A, et al. Influence of food processing on the allergenicity of celery: DBPCFC with celery spice and cooked celery in patients with celery allergy. *Allergy*. 2002;57:228–35.
33. Bolhaar ST, van Ree R, Ma Y, Bruijnzeel-Koomen CA, Vieths S, Hoffmann-Sommergruber K, et al. Severe allergy to sharon fruit caused by birch pollen. *Int Arch Allergy Immunol*. 2005;136:45–52.
34. Bolhaar ST, Ree R, Bruijnzeel-Koomen CA, Knulst AC, Zuidmeer L. Allergy to jackfruit: a novel example of Bet v 1-related food allergy. *Allergy*. 2004;59:1187–92.
35. Scheurer S, van Ree R, Vieths S. The role of lipid transfer proteins as food and pollen allergens outside the mediterranean area. *Curr Allergy Asthma Rep*. 2021;21:7.
36. Skypala IJ, Asero R, Barber D, Cecchi L, Diaz Perales A, Hoffmann-Sommergruber K, et al. Non-specific lipid-transfer proteins: Allergen structure and function, cross-reactivity, sensitization, and epidemiology. *Clin Transl Allergy*. 2021;11:e12010.
37. Egger M, Mutschlechner S, Wopfner N, Gadermaier G, Briza P, Ferreira F. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. *Allergy*. 2006;61:461–76.
38. Lopata AL, Kleine-Tebbe J, Kamath SD. Allergens and molecular diagnostics of shellfish allergy: Part 22 of the series molecular allergology. *Allergo J Int*. 2016;25:210–8.
39. Taylor SL. Molluscan shellfish allergy. *Adv Food Nutr Res*. 2008;54:139–77.
40. Kamath SD, Abdel Rahman AM, Voskamp A, Komoda T, Rolland JM, O'Hehir RE, et al. Effect of heat processing on antibody reactivity to allergen variants and fragments of black tiger prawn: A comprehensive allergenomic approach. *Mol Nutr Food Res*. 2014;58:1144–55.
41. Gámez C, Zafra MP, Sanz V, Mazzeo C, Ibáñez MA, Sastre J, et al. Simulated gastrointestinal digestion reduces the allergic reactivity of shrimp extract proteins and tropomyosin. *Food Chem*. 2015;173:475–81.
42. Abdel Rahman AM, Kamath SD, Lopata AL, Robinson JJ, Helleur RJ. Biomolecular characterization of allergenic proteins in snow crab (*Chionoecetes opilio*) and de novo sequencing of the second allergen arginine kinase using tandem mass spectrometry. *J Proteomics*. 2011;74:231–41.
43. Ruethers T, Taki AC, Johnston EB, Nugraha R, Le TTK, Kalic T, et al. Seafood allergy: A comprehensive review of fish and shellfish allergens. *Mol Immunol*. 2018;100:28–57.
44. Pascual M, Grishina G, Yang AC, Sánchez-García S, Lin J, Towle D, et al. Molecular diagnosis of shrimp allergy: Efficiency of several allergens to predict clinical reactivity. *J Allergy Clin Immunol Pract*. 2015;3:521–9.
45. Brehler R, Theissen U, Mohr C, Luger T. "Latex-fruit syndrome": frequency of cross-reacting IgE antibodies. *Allergy*. 1997;52:404–10.
46. Beezhold DH, Sussman GL, Liss GM, Chang NS. Latex allergy can induce clinical reactions to specific foods. *Clin Exp Allergy*. 1996;26:416–22.
47. Ebo DG, Bridts CH, Rihs HP. Hevea latex-associated allergies: piecing together the puzzle of the latex IgE reactivity profile. *Expert Rev Mol Diagn*. 2020;20:367–73.
48. Focke M, Hemmer W, Wöhrl S, Götz M, Jarisch R. Cross-reactivity between *Ficus benjamina* latex and fig fruit in patients with clinical fig allergy. *Clin Exp Allergy*. 2003;33:971–7.

49. Hemmer W, Focke M, Götz M, Jarisch R. Sensitization to *Ficus benjamina*: relationship to natural rubber latex allergy and identification of foods implicated in the Ficus-fruit syndrome. *Clin Exp Allergy*. 2004;34:1251–8.
50. Hilger C, Kohnen M, Grigioni F, Lehnert C, Hentges F. Allergic cross reactions between cat and pig serum albumin. Study at the protein and DANN levels. *Allergy*. 1997;52:179–87.
51. Faber MA, Van Gasse AL, Decuyper II, Sabato V, Hagedorens MM, Mertens C, et al. Cross-reactive aeroallergens: which need to cross our mind in food allergy diagnosis? *J Allergy Clin Immunol Pract*. 2018;6:1813–23.
52. Hemmer W, Klug C, Swoboda I. Update on the bird-egg syndrome and genuine poultry meat allergy. *Allergo J Int*. 2016;25:68–75.
53. Gao ZS, Yang ZW, Wu SD, Wang HY, Liu ML, Mao WL, et al. Peach allergy in China: a dominant role for mugwort pollen lipid transfer protein as a primary sensitizer. *J Allergy Clin Immunol*. 2013;131:224–6.
54. Skypala IJ, Bartra J, Ebo DG, Faber MA, Fernández-Rivas M, Gomez F, et al. The diagnosis and management of allergic reactions in patients sensitized to non-specific lipid transfer proteins. *Allergy*. 2021; <https://doi.org/10.1111/all.14797>.
55. Berghi ON, Vrinceanu D, Cergan R, Dumitru M, Costache A. Solanum melongena allergy (A comprehensive review). *Exp Ther Med*. 2021;22:1061. <https://doi.org/10.3892/etm.2021.10495>.
56. Alessandri C, Zennaro D, Zaffiro A, Mari A. Molecular allergology approach to allergic diseases in the paediatric age. *Ital J Pediatr*. 2009;35:29.
57. Barre A, Culerrier R, Granier C, Selman L, Peumans WJ, Van Damme EJM, et al. Mapping of IgE-binding epitopes on the major latex allergen Hev b 2 and the cross-reacting 1,3 β -glucanase fruit allergens as a molecular basis for the latex-fruit syndrome. *Mol Immunol*. 2009;46:1595–604.
58. Cox AL, Eigenmann PA, Sicherer SH. Clinical relevance of cross reactivity in food allergy. *J Allergy Clin Immunol Pract*. 2021;9:82–99.
59. Felber J, Aust D, Baas S, Bischoff S, Bläker H, Daum S, et al. Results of a S2k-consensus Conference of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS) in conjunction with the German Coeliac Society (DZG) regarding Coeliac disease, wheat allergy and wheat sensitivity. *Z Gastroenterol*. 2014;52:711–43.
60. Crawley C, Sander SD, Nohr EA, Lillevang ST, Andersen AN, Murray J, et al. High prevalence of celiac disease among Danish adolescents—A population-based study. *J Pediatr Gastroenterol Nutr*. 2021; <https://doi.org/10.1097/MPG.0000000000003247>.
61. Cosnes J, Cellier C, Viola S, Colombel JF, Michaud L, Sarles J, et al. Incidence of autoimmune diseases in celiac disease: protective effect of the gluten-free diet. *Clin Gastroenterol Hepatol*. 2008;6:753–8.
62. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, et al. ACG clinical guideline: management of irritable bowel syndrome. *Am J Gastroenterol*. 2021;116:17–44.
63. Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: diagnosis and management of celiac disease. *Am J Gastroenterology*. 2013;108:656–77.
64. Gianferoni A. Wheat allergy: diagnosis and management. *J Asthma Allergy*. 2016;9:13–25.
65. Reese I, Schäfer C, Kleine-Tebbe J, Ahrens B, Bachmann O, Ballmer-Weber B, et al. Non-celiac gluten/wheat sensitivity (NCGS)—A currently undefined disorder without validated diagnostic criteria and of unknown prevalence. *Allergo J Int*. 2018;27:147–51.
66. Nilsson N, Sjölander S, Baar A, Berthold M, Pahr S, Vrtala S, et al. Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. *Pediatr Allergy Immunol*. 2015;26:119–25.
67. Worm M, Eckermann O, Dolle S, Aberer W, Beyer K, Hawranek T, et al. Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria and Switzerland. *Dtsch Arztebl Int*. 2014;111:367–75.
68. Sievers S, Rawel HM, Ringel KP, Niggemann B, Beyer K. Wheat protein recognition pattern in tolerant and allergic children. *Pediatr Allergy Immunol*. 2016;27:147–55.
69. Sievers S, Rohrbach A, Beyer K. Wheat-induced food allergy in childhood: ancient grains seem no way out. *Eur J Nutr*. 2020;59:2693–707.
70. Woormer JS, Adedeji AA. Current applications of gluten-free grains—A review. *Crit Rev Food Sci Nutr*. 2021;61:14–24.
71. Laurière M, Pecquet C, Bouchez-Mahiou I, Snégoff J, Bayrou O, Raison-Peyron N, et al. Hydrolysed wheat proteins present in cosmetics can induce immediate hypersensitivities. *Contact Derm*. 2006;54:283–9.
72. Furuta GT, Katzka DA, Ingelfinger JR. Eosinophilic esophagitis. *N Engl J Med*. 2015;373:1640–8.
73. Wilson JM, Li RC, McGowan EC. The role of food allergy in Eosinophilic Esophagitis. *J Asthma Allergy*. 2020;13:679–88.
74. Leigh LY, Spergel JM. An in-depth characterization of a large cohort of adult patients with eosinophilic esophagitis. *Ann Allergy Asthma Immunol*. 2019;122:65–72.
75. Miehke S, Schlag C, Storr M, von Arnim U. Eosinophilic Esophagitis update: new guidelines of the European study group EUREOS. *Z Gastroenterol*. 2018;56:139–50.
76. Lucendo AJ, Molina-Infante J, Arias A, von Arnim U, Brede-noord AJ, Bussmann C, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J*. 2017;5:335–58.
77. Kagalwalla AE, Wechsler JB, Amsden K, Schwartz S, Makhija M, Olive A, et al. Efficacy of a 4-food elimination diet for children with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*. 2017;15:1698–707.
78. Barbaro MR, Cremon C, Wrona D, Fuschi D, Marasco G, Stanghellini V, et al. Non-celiac gluten sensitivity in the context of functional gastrointestinal disorders. *Nutrients*. 2020;12:3735.
79. Storhaug CL, Fosse SK, Fadnes LT. Country, regional, and global estimates for lactose malabsorption in adults: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2017;2:738–46.
80. Catanzaro R, Sciuto M, Marotta F. Lactose intolerance: An update on its pathogenesis, diagnosis, and treatment. *Nutr Res*. 2021;89:23–34.
81. Misselwitz B, Butter M, Verbeke K, Fox MR. Update on lactose malabsorption and intolerance: pathogenesis, diagnosis and clinical management. *Gut*. 2019;68:2080–91.
82. Born P. Carbohydrate malabsorption in patients with non-specific abdominal complaints. *World J Gastroenterol*. 2007;13:5687–91.
83. Tuck CJ, Muir JG, Barrett JS, Gibson PR. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols: role in irritable bowel syndrome. *Expert Rev Gastroenterol Hepatol*. 2014;8:819–34.
84. Reese I, Ballmer-Weber B, Beyer K, Fuchs T, Kleine-Tebbe J, Ludger Klimek L, et al. German guideline for the management of adverse reactions to ingested histamine: Guideline of the German Society for Allergy and Clinical Immunology (DGAKI), the German Society for Pediatric Allergy and Environmental Medicine (GPA), the German Association of Allergologists (AeDA), and the Swiss Society for Allergy and Immunology (SGAI). *Allergo J Int*. 2017;26:72–9.

85. Lehane L, Olley J. Histamine fish poisoning revisited. *Int J Food Microbiol.* 2000;58:1–37.
86. Komericki P, Klein G, Reider N, Hawranek T, Strim�tzer T, Lang R, et al. Histamine intolerance: lack of reproducibility of single symptoms by oral provocation with histamine: a randomised, double-blind, placebo-controlled cross-over study. *Wien Klin Wochenschr.* 2011;123:15–20.
87. Wöhrl S, Hemmer W, Focke M, Rappersberger K, Jarisch R. Histamine intolerance-like symptoms in healthy volunteers by oral provocation with liquid histamine. *Allergy Asthma Proc.* 2004;25:305–11.
88. Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy.* 2018;73:1393–414.
89. Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. *Clin Transl Allergy.* 2015;13:34.
90. Paterson JR, Srivastava R, Baxter GJ, Graham AB, Lawrence JR. Salicylic acid content of spices and its implications. *J Agric Food Chem.* 2006;54:2891–6.
91. Dölle-Bierke S, Plank-Habibi S, Schäfer C, Ahrens B, Ballmer-Weber B, Beyer K, et al. Diätetische Implikationen bei ASS-Unverträglichkeit. Stellungnahme der AG Nahrungsmittelallergie der Deutschen Gesellschaft für Allergologie und klinische Immunologie (DGAKI). *Allergo J.* 2020;29:93–6.
92. Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. *J Pediatr Gastroenterol Nutr.* 2012;54:136–60.
93. Roberts G, Ollert M, Aalberse R, Austin M, Custovic A, DunnGalvin A, et al. A new framework for the interpretation of IgE sensitization tests. *Allergy.* 2016;71:1540–51.
94. Passalacqua G, Melioli G, Bonifazi F, et al. The additional values of microarray allergen assay in the management of polysensitized patients with respiratory allergy. *Allergy.* 2013;68:1029–33.
95. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber S, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol.* 2012;130:1260–74.
96. Niggemann B, Lange L, Finger A, Ziegert M, Müller V, Beyer K. Accurate oral food challenge requires a cumulative dose on a subsequent day. *J Allergy Clin Immunol.* 2012;130:261–3.
97. Husby S, Murray JA, Katzka DA. AGA clinical practice update on diagnosis and monitoring of celiac disease-changing utility of serology and histologic measures: expert review. *Gastroenterology.* 2019;156:885–9.
98. Ring J, Beyer K, Biedermann T, Bircher A, Fischer M, Fuchs T, et al. Guideline (S2k) on acute therapy and management of anaphylaxis: 2021 update. S2k-Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Medical Association of German Allergologists (AeDA), the Society of Pediatric Allergy and Environmental Medicine (GPA), the German Academy of Allergology and Environmental Medicine DAAU, the German Professional Association of Pediatricians (BVKJ), the Society for Neonatology and Paediatric Intensive Care (GNPI), the German Society of Dermatology (DDG), the Austrian Society for Allergology and Immunology (ÖGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Anaesthesiology and Intensive Care Medicine (DGAI), the German Society of Pharmacology (DGP), the German Respiratory Society (DGP), the patient organization German Allergy and Asthma Association (DAAB), the German Working Group of Anaphylaxis Training and Education (AGATE). *Allergo J Int.* 2021;30:1–25.