

Food Allergies

Stephan C. Bischoff, MD

Corresponding author

Stephan C. Bischoff, MD
Department of Medicine, Nutritional Medicine and Prevention,
(140b), University of Hohenheim, Stuttgart, Fruwirthstr. 12, 70593
Stuttgart, Germany.
E-mail: bischoff.stephan@uni-hohenheim.de

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Food incompatibilities affect approximately 20% of the general population in Western countries. In about one quarter of the affected children and one tenth of affected adults, the incompatibility is based on an allergy, that is, on an immunologically generated incompatibility reaction. Gastrointestinal symptoms occur in a third of these cases. Food allergies are caused by IgE-dependent or IgE-independent immunologic reactions, which lead to an inflammatory reaction, in which mast cells, eosinophilic granulocytes, and other cells are involved. Both genetic and environmental causes are under consideration. New findings concerning the interaction between the innate immune system and intestinal microflora have generated innovative therapeutic concepts, including the use of probiotics to prevent food allergies. The development of recombinant allergens and varieties of allergens will improve diagnostic possibilities and bring new therapeutic options, such as hyposensitization and induction of immunologic tolerance. Food intolerances (non-immunologic food incompatibilities often caused by specific enzyme deficiencies) must be diagnostically differentiated from food allergies.

Introduction

Food allergies frequently develop in the early stages of childhood and disappear spontaneously with increasing age, up to about 6 or 7 years. Sometimes these infantile food allergies are replaced by allergies to aeroallergens such as pollen, mites, or animal epithelia. Very few children retain their food allergies until adulthood. However, some adults suffer from food allergies without ever having been affected as children. The prevalence of food allergies is 4% to 8% among children and 1% to 2% in adults [1–3]. In comparison, approximately 20% of all adults in

industrialized nations complain of food intolerance [4••,5]. The majority of food intolerances are not immunologic in origin; lactose intolerance represents the most frequent form of food intolerance in Western countries.

Analogous to the development of allergic illnesses in general, food allergies have also increased significantly during the past decades. However, specific numbers indicating an increase in the prevalence of food allergies are only available for allergy to peanuts [6]. The reasons behind this growth are not clear, although epidemiologic studies have suggested that a rise in hygienic standards in Western countries is associated with the amplified incidence of allergies [7]. Sufficient exposure to bacterial lipopolysaccharide (LPS) could have a protective effect with regard to the development of allergic illnesses within the first years of life [8]. These observations, which have led to the definition of the “hygiene theory,” indicate that the innate immune system is fundamental to the development of allergic illness, whereas the manifestation of allergic reaction is triggered by the specific immune system. The hygiene theory refers to the increased incidence not only of allergic diseases but also of other immunologic diseases, such as rheumatic arthritis, type 1 diabetes mellitus, and chronic inflammatory intestinal disorders [9].

Definition of Food Allergy and Intolerance

Food allergy and food intolerance represent two subsets of adverse reactions to food. Food allergy is based on an immune pathogenesis [10], whereas food intolerance stems from other pathomechanisms.

Food allergies manifest themselves, depending upon age, in up to 50% of all patients in the form of gastrointestinal symptoms. Many of these patients consult their gastroenterologist, who is not usually sufficiently acquainted with the pathologic symptoms [4••,11]. The symptoms are then frequently labeled as being “psychosomatic” or the complaints classified as “functional” or as “irritable bowel syndrome” (IBS), without the actual problem ever being defined. However, IBS and food intolerance are frequently associated, and food allergies are sometimes an underlying mechanism for symptoms in a subgroup of patients with IBS [12,13]. The relevance of food allergy is also related to the discovery that allergic reaction to food is the most common cause of life-endangering anaphylaxis [14].

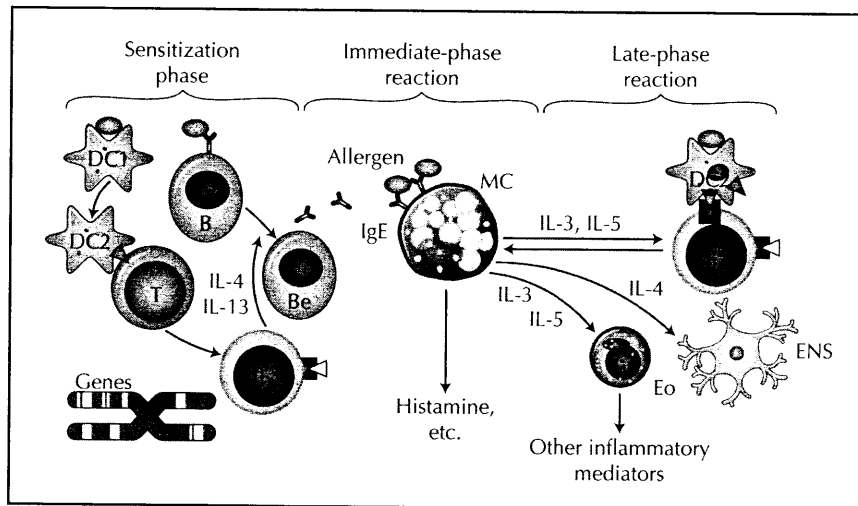


Figure 1. Phases of allergic reaction. DC—dendritic cells; ENS—enteric nervous system; Eo—eosinophilia; IL—interleukin; MC—mast cells

Immune Pathogenesis of Allergic Conditions

Immunologic hypersensitivity reactions are divided into types I, II, III, and IV based on antigen-revealing molecule (eg, IgE, IgG, immune complexes, T-cell receptor) [10]. The best characterized hypersensitivity reaction to food is the IgE-mediated type I reaction, which is also a basis for many cases of bronchial asthma, seasonal rhinitis, urticaria, and atopic eczema. Some people develop a delayed reaction after the initial acute IgE-reaction, which is distinguished by an amplified cellular infiltration of the affected tissue with inflammatory cells and is later characterized by a tissue dysfunction (Fig. 1). Such mechanisms play a role in milk- and soy protein-induced enteropathy and in celiac disease. Immunologic reactions to food can also be caused by a combination of IgE-dependent and IgE-independent reactions. Type IV hypersensitivity reactions to food proteins can be expected due to the presence of food antigen-specific Th cells and cytotoxic T cells [4••,15••].

For an allergic intestinal inflammation to develop, a sufficient quantity of allergens is required in the intestine, along with a hyper-reactive mucosal immune system. The increased presence of antigens may result from a genetically defined alteration to or immaturity of key molecules of the intestinal wall, an acquired disorder of the innate intestinal immune system, a bowel infection, or any combination of these. Nonspecific inflammation, caused by bacteria, virus, or toxins, can trigger the loss of an immunologic tolerance and induce development of hypersensitivity of the mucosal immune system toward luminal antigens. Similar mechanisms have been described for other inflammatory diseases of the gastrointestinal tract, including inflammatory bowel diseases (IBD), in which bacterial rather than food antigens appear to be the cause [9].

A delayed development of the protective IgA system within the gut-associated lymphoid tissue (GALT) in the postnatal phase, or a particularly pronounced switch to IgE-producing B lymphocytes, is associated with an enhanced risk for the development of allergic diseases.

IgA synthesis is induced mainly by transforming growth factor (TGF)- β from Th3 cells and external triggers, whereas IgE synthesis is dependent on CD40 ligands and cytokines interleukin (IL)-4 and IL-13, which are produced by the Th2 cells, and inflammatory cells (mast cells, basophils) [15••]. In contrast, Th1 cytokines, such as interferon (IFN)- γ , inhibit the activity of Th2 cells, which explains how a controlled Th1-dominant immune response triggered, for example, by certain bacterial products, can contribute to restriction of a primary pre-existing Th2 response in the bowel and thus prevent overproduction of IgE. Such procedures support the previously mentioned "hygiene theory."

Innate and specific immune system

Both the innate and the specific immune system are involved in immunologic hypersensitivity reactions. The characterization of key molecules belonging to the innate immune defense mechanism, such as defensins, mucin, or synactin, and their possible mutation in people with allergies, is therefore important for an understanding of the mechanisms and the development of new therapeutic concepts [16]. Disorders of the innate immune system can also be responsible for deviations of the specific immune system, which lead, for example, to an overproduction of specific IgE.

During an allergic reaction, naïve lymphocytes of the GALT give rise to the production of Th2 cytokines, such as IL-4 and IL-13, which encourage the development of IgE-producing plasma cells. Allergen-specific T cells, which, apart from IL-4 and IL-13 also produce IL-5, can actually be isolated in the blood, skin, and mucosa of patients with food allergies. These cytokines not only regulate the IgE synthesis (IL-4, IL-13) but also regulate the colonization and activation of inflammatory cells, such as mast cells (IL-4) and eosinophilic granulocytes (IL-5) [4••,15••].

Because IgE is produced locally in the respiratory and gastrointestinal mucosa, serum IgE evaluations and skin

tests do not correlate closely with mucosal allergic reactions in the intestines. In atopic patients, the increased IgE levels are closely related to IL-13, the gene of which is attributed to a polymorphism, which is associated with atopy. The IgE-induced, allergic immune response can therefore be divided into three phases: the clinically silent sensitization phase, usually during infancy or childhood; the symptomatic effector phase, which is composed of an acute and a facultatively delayed reaction; and the chronic, organ-destroying phase, which can be the outcome of recurring delayed reactions [4••].

Inflammatory cells and the enteric nervous system

Inflammatory mediators derived from mast cells and eosinophils are primarily responsible for the clinical symptoms of patients with food allergies. These patients have an increased level of histamine (or methylhistamine), tryptase, eosinophilic cationic protein (ECP), IL-5, and tumor necrosis factor (TNF)- α in serum, urine, intestinal lavage, and stool samples [4••,17]. Histologic examinations show that mast cells and eosinophils degranulate in the intestinal mucosa after localized provocation testing and that they release mediators such as cytokines [18]. These cells are no longer understood to be solely inflammatory cells but are also seen as immune modulatory cells, which contribute to homeostasis in the intestines and to the suppression of bacteria and parasites [4••].

It has become apparent in recent years that the enteric nervous system (ENS) plays a role in regulating allergic inflammatory cells, such as lymphocytes, mast cells, and eosinophils. The morphologic, functional association between immune cells and nerve cells has been described mainly for mast cells [19] and in some cases has been extended to include eosinophils [20]. Not only is the GALT innervated, but conversely, the ENS is also regulated in a crucial manner by mediators derived from mucosal immune cells [4••,20]. Such neuroimmune interactions may explain the frequent psychological and functional accompanying symptoms that characterize many patients with allergic and other chronic bowel disorders.

Structural and functional characteristics of food allergens

The structural and biochemical characteristics of the provoking allergens determine the type of immune response to food allergies. However, to date, the factors necessary for an antigen to function as an allergen remain unidentified. This topic is especially important in predicting whether an article of food may act as an allergen and in testing new foodstuffs for their allergen potential. In general, soluble proteins are more tolerogenic than particulate or globulous proteins. Other biochemical characteristics determine the rate of absorption and the stability of the allergen in the intestines. For example, the peanut protein Ara h1 is highly resistant to degradation in the gastrointestinal tract due to the formation of stable homodimers, which contribute a

great deal to the relevance of this form of food allergy. The allergen dose also plays a role because lower doses tend to activate regulatory T cells (Th3), whereas higher doses lead to anergy or apoptosis [15••].

Although many food proteins can function as allergens, 90% of food allergies are actually caused by only a few foodstuffs. The "top ten" of food allergens is dependent on eating habits, which can vary greatly according to age (infancy, childhood, adulthood) and cultural factors. Cross reactions between differing food allergens derived from related botanical families, and especially among food allergens and pollen, mites, or latex allergens, are of particular significance [21,22]. Knowledge of such cross allergies is valuable in formulating a precise medical history, diagnosis, and elimination diet and also facilitates new insight into the "functional anatomy" of the allergen molecules. During the past decade, so-called "major allergens" or "epitopes," which can be found within related groups of food allergens and in foodstuffs and pollen, among other sources, have helped to explain and molecularly categorize the phenomenon of cross allergies. The first major epitopes to be cloned were Bet v1 and Bet v2 (profilin), which occur in birch pollen and in numerous articles of food, such as fruit and celery. The specific IgE of patients with allergies to birch pollen and foodstuffs is directed mainly toward Bet v1, which underlines the implication of this allergen structure as a main B-cell epitope and IgE epitope for the activation of mast cells. So far, more than 1000 epitopes, of which 50 to 100 are major epitopes, have been cloned and sequenced (details can be viewed at <http://www.allergome.org>). The recombinant allergens that have consequently been made available unveil new possibilities for the diagnosis and treatment of allergic conditions and are currently being tested in clinical studies [23••].

Clinical Picture of a Food Allergy or Intolerance

Allergy symptoms range from minor impairments to life-threatening shock reactions. Approximately one third of patients with real food allergies suffer from gastrointestinal symptoms, such as nausea, vomiting, cramps, flatulence, and diarrhea. Others complain of skin problems (urticaria, Quincke edema, atopic dermatitis), respiratory symptoms (rhinitis, bronchial asthma), shock symptoms, or less clearly defined systemic ailments (eg, migraine, fatigue syndrome, edema, hypotension, arthritis) [24–27]. Whereas dermatologic, respiratory, and systemic signs of allergies are sufficiently well-known and established, this is not the case for gastrointestinal manifestations, which are frequently caused by food antigens and are difficult to diagnose and treat [4••].

The most important clinical symptoms of food allergies inside and outside the gastrointestinal tract are summarized in Table 1. Food allergy is typically a condition of

Table 1. Clinical symptoms of food allergies

Organ	Disorder	Affected individuals
GI tract	Oral allergy syndrome (OAS)	All
	Eosinophilic inflammation	All
	IgE-independent inflammation	Children
	Celiac disease	All
	Irritable bowel syndrome	Adults
Airways	Hay fever, asthma	All
	Otitis serosa	Children
Skin	Urticaria	All
	Neurodermatitis	Children
Joints	Arthritis, etc.	Adults
Nervous system	Migraine headaches	Adults
	Chronic fatigue	Adults
	Psychiatric disturbances	Adults
	Hyperactivity syndrome	Children
Heart-circulation	Vasculitides	All
	Edema	All
	Anaphylactic shock	All

GI—gastrointestinal.

the skin, the airways, the gastrointestinal tract, or a combination thereof. Occasionally, additional symptoms such as migraine, arthritis, generalized edema, hypotension, and chronic fatigue appear; however, these symptoms are more typical for intolerance that is not immunologically induced, such as histamine intolerance [24]. Food allergies, unlike food intolerance, can lead to life-threatening anaphylaxis. Indeed, food allergy is considered to be the main cause of anaphylaxis in the United States and Europe [14]. The prevalence of peanut allergy (0.5% to 7% of adults in the United States and UK) and its potential fatal consequences have already made an impact on regulations in institutions ranging from school cafeterias to airlines. Occasionally, the anaphylaxis only appears under simultaneous physical effort, for example, if triggered by a cereal and induced by exercise. Acetylsalicylate and other nonsteroidal anti-inflammatory drugs can likewise contribute to an increase in allergic symptoms.

Intestinal manifestations of food allergy

Gastrointestinal manifestations of food allergy in children are typically food protein-induced proctitis or enteropathies, possibly combined with atopic dermatitis [11]. More recently, eosinophilic esophagitis and allergic constipation have also been described as symptoms of food allergy [28••]. Oral allergy syndrome (OAS) is the most common form of food allergy in teenagers and adults, although other manifestations, such as eosinophilic enteropathies and celiac disease, also occur [4••]. OAS is typically triggered by plant proteins, which produce cross reactions with particular respirable

antigens, especially birch tree, ragweed, and mugwort pollen. Exposure to cross-reactive foods can lead to pruritus, tingling, and swelling of the tongue, the lips, the palate, or the pharynx, and occasionally also to bronchospasm or even systemic reactions, which usually appear within minutes of allergen ingestion. Because these reactions are almost exclusively IgE induced, the diagnosis can usually be confirmed with a prick test or measurement of specific IgE in the blood. In contrast, gastrointestinal symptoms (nausea, vomiting, abdominal pains, and diarrhea) are typically triggered by such allergens as milk, egg, peanuts, fish, and shellfish, depending on which eating habits are predominant [4••].

The latex-food allergy syndrome, also called the latex-fruit syndrome, is a form of food allergy that is increasingly prevalent. In 21% to 58% of cases it appears together with food allergy [29]. Banana, avocado, walnut, and kiwi are the most common triggers of food-associated symptoms in latex allergy worldwide. These foods can induce the same symptoms as does latex, which may include pruritus, eczema, OAS, asthma, gastrointestinal complaints, and generalized anaphylaxis.

Food-induced enteropathy is a childhood illness and is characterized by protracted diarrhea and vomiting, leading to a clinical picture of malabsorption. Protein-losing enteropathy can lead to edema, abdominal distention, nausea, vomiting, diarrhea, and anemia. Infectious and metabolic diseases, lymphangiectasia, and celiac disease should be diagnostically differentiated. Underlying mechanisms include the formation of immune complexes and abnormal T-cell reactions after the consumption of milk,

soy, and other foods, such as egg, fish, cereals, rice, vegetables, and meat [11]. Normally, there is no detectable specific IgE against these foods. The diagnosis is based on endoscopic and histologic findings (increased intraepithelial lymphocytes and eosinophilic granulocytes, villous atrophy) and on elimination diets and re-exposure.

Celiac disease affects approximately 1% of the population, which far exceeds earlier estimates of its occurrence. Orally consumed gliadin, which is contained in cereals and rice, instigates enteropathy in genetically predisposed individuals. Normalization of the bowel anatomy and function can be achieved with an elimination diet, and the symptoms (diarrhea and weight loss as well as fatigue, lethargy, and dyspepsia) can be reduced or even terminated. Usually gluten must be eliminated on a permanent basis [30].

Eosinophilic esophagitis and gastroesophageal reflux disease

Investigations involving milk elimination in children with reflux symptoms have shown that approximately one third of reflux conditions are caused by cow's milk [11]. In such cases, classical antireflux treatment does not lead to improvement, and histologic investigation shows a marked infiltration with eosinophilic granulocytes, which give the illness its name. Typical symptoms include vomiting, retrosternal pains, and dysphagia due to strictures, sometimes also signs of asthma. Recent studies have demonstrated that this illness is by no means limited to children but can also affect adults to a still largely undefined extent [28••].

Eosinophilic gastroenteritis is characterized by eosinophilic infiltration of the gastroenteric mucosa, muscularis, or serosa. Abdominal pains, vomiting, and diarrhea occur simultaneously in over 50% of patients. Ascites are seen in patients with serosa infiltrations. More than two thirds of these patients also show eosinophilia in the peripheral blood. The differential diagnosis of eosinophilic gastroenteritis in children includes parasites, IBD, connective tissue diseases, tumors, and drug allergies. The eosinophilic gastroenteritis itself is closely associated, in 50% to 70% of cases, with food allergies and other atopic diseases [4••,28••].

Clinical characteristics of food intolerance

The majority of abnormal reactions to food are not immunologic in origin but are relevant due to their rate of recurrence. These reactions are called food intolerances, and they include bacterial food poisoning, post-infectious irritable bowel symptoms, and chronic intolerance reactions. In these instances, pseudoallergic and pharmacologic reactions are induced by food, and these reactions imitate the IgE-dependent mast cell degranulation by independently activating IgE. Triggers are mostly such food additives as sulfide, tartrazine, and glutamate, which cause bowel symptoms and can be accompanied by asthma. Pharmacologic

reactions to food or additives are also frequent forms of intolerance to food, although the symptoms are mostly localized outside the gastrointestinal tract. Biogenic amines, such as histamine, serotonin, or tyramine, can cause food allergy-like symptoms such as headaches, hypotension, erythema, and gastrointestinal symptoms. The pathophysiology of the histamine intolerance includes an accumulation of histamine due to a faulty histamine degradation process, which in turn increases sensitivity to relatively small quantities of histamine in food. The origin is a deficiency of diamine-oxidase (DAO), the most important decomposing enzyme for histamine, or a DAO coenzyme such as vitamin B₆, and possibly vitamin C [24].

Lactose malabsorption, also incorrectly described as lactose intolerance, represents the most common form of a food intolerance and is mostly attributable to a diminishing release of lactase in the intestines with increasing age, but in some cases it can also be primarily genetic in origin. The degree of such symptoms as flatulence and diarrhea is usually dependent on the dose. A secondary lactase deficiency can occur with viral gastroenteritis, Crohn's disease, and celiac disease [31]. Lactose malabsorption and other food intolerance reactions should be distinguished from psychological causes for food intolerance, a rare type of intolerance that cannot be confirmed in provocation tests [32].

Physiologic food intolerance may be the most common form of food intolerance to a particular food component or additive. For example, vegetable or cereal starch can lead to gas production in the colon. Other food elements are known for reducing the tonus of the lower esophageal sphincter or causing a delayed emptying of the stomach, resulting in dyspepsia. Such physiologic reactions to food are reported particularly in patients with respiratory distress syndrome. The investigation of food intolerance is thus relevant in this group of patients because it can be demonstrated that a targeted elimination diet really leads to improvement in the list of complaints [33].

Diagnostics

Recently, the American Gastroenterological Association (AGA) and the German Association for Allergology and Immunology (DGAI) have published guidelines and position papers on the diagnosis and treatment of food allergies [34•,35]. The basis of the diagnosis should be a thorough medical history with respect to the foodstuffs that are not tolerated and that correlate with specific symptoms. Open provocation tests are helpful, although they are subjective in nature and require confirmation through objective testing before a permanent elimination diet can be recommended. Because no test can clearly confirm the probable diagnosis of food intolerance, a thorough diagnosis by exclusion is necessary and must be more extensive for adults than for children (Table 2). The allergy tests discussed in the following text can serve either as proof of the intolerance to certain foods or of the immunologic mechanism of the

Table 2. Elimination diagnostics

Adults
Non-immunologic food intolerances (eg, lactose intolerance)
Reflux, ulcers, gastritis, celiac disease, Whipple disease, IBD, microscopic colitis
Infections
Tumors
Children
Infections
Celiac disease
IBD—inflammatory bowel disease.

Table 3. Requirements for diagnosis of food allergies

Confirmation of the intolerance/allergy
Medical history
Open provocation tests
Controlled provocation tests (oral, DBPCF; localized, COLAP)
Release tests (BHRT, CAST, TABOX, etc.)
Confirmation of the immunologic mechanisms
Skin tests, RAST
Quantification of inflammation mediators ($\pm$ controlled provocation)
Visualization of mast cell degranulation ($\pm$ controlled provocation)

BHRT—basophile histamine-releasing test; CAST—chemilluminescence allerge-sorbent test; COLAP—colonoscopic allergen provocation; DBPCF—double-blind placebo-controlled food challenge; RAST—radio-allergo-sorbent test; TABOX—provocation test of mucous membrane biopsies.

intolerance. Evidence of both should be furnished for a complete diagnosis (Table 3). Although all allergy tests can neither confirm nor exclude the probable diagnosis due to limited sensitivity and specificity, they attain satisfactory predicted values when applied to a carefully preselected group of patients. This means that patients with suspected food allergy should be diagnosed according to a flow chart after standardized steps have been taken (Fig. 2).

Allergy skin tests

Allergy skin tests, so-called prick tests, are simple, inexpensive methods for evaluating sensitization in children and adults. However, their positive prognostic value is restricted, which is a limitation. A further drawback of the prick test stems from the insufficient standardization and stability of many food allergen extracts used in these tests. This problem could be diminished through use of recombinant allergens, which are available in increasing amounts, or by means of a prick-to-prick test with native foods. Here, the food is given first and then the patient's skin is pricked with

the same lancet. Recently, the epicutaneous test for delayed reactions has also become available and is being evaluated in clinical studies.

In vitro allergy diagnostics

An alternative or complementary technique to skin tests is the measurement of specific IgE in the serum, a laboratory procedure with a higher specificity and, due to its independence from the tester, greater reliability. This test, which is also known by the acronym "RAST" (radio-allergo-sorbent test), used to be gauged radioactively, but it can also be carried out in patients with skin symptoms, such as atopic dermatitis, in which skin tests are not recommended. A possible cause for the frequently reported discrepancy between results from anamnesis skin tests and measurement of specific IgE can be explained by the fact that food allergy in the gastrointestinal tract is induced by locally produced IgE, which does not lead to altered IgE serum level. Finally, the measurement of IgE-independent parameters is recommended, using such eosinophilic mediators as eosinophil granule proteins (ECP and EPX) in the serum and feces. With this practice, IgE-independent allergic reactions can also be registered [4•,17]. Due to the limitations of all of these laboratory methods, the diagnosis of gastrointestinal food allergy is based, in essence, on exclusion of infectious, chronic, inflammatory, and malignant stomach-bowel diseases.

Allergen-provocation procedure

As a rule, a supervised provocation test, in the form of a "double-blinded placebo-controlled food challenge" (DBPCFC), is necessary in ambiguous cases. Using this strategy, food antigens are taken either orally, in the form of a gelatin capsule, or fed directly into the intestines by means of a tube. The DBPCFC method is viewed as the gold standard for confirmation of the diagnosis of food allergy and should be an obligatory component of the diagnosis in all uncertain cases [4•,34•,35]. Nevertheless, even this procedure has weaknesses, especially in regard to the clarification of a food allergy with gastrointestinal manifestations. These tests are not standardized and validated with respect to gastrointestinal symptoms, making them subjective rather than objective. In addition, no immunologic reaction is verified, which means that the test checks for an intolerance to food but not for an allergy [4•]. Several attempts have been made to develop a gastrointestinal equivalent of the allergy skin test in which food allergens would be administered to the stomach or bowel mucosa and reactions such as reddening or swelling of the mucous membrane could be detailed. This approach was conceived in the 1930s and later developed in the form of gastric, duodenal, and, most recently, colonic provocations. The colonoscopic allergen provocation (COLAP) test, in particular, has been validated as a localized procedure in clinical studies,

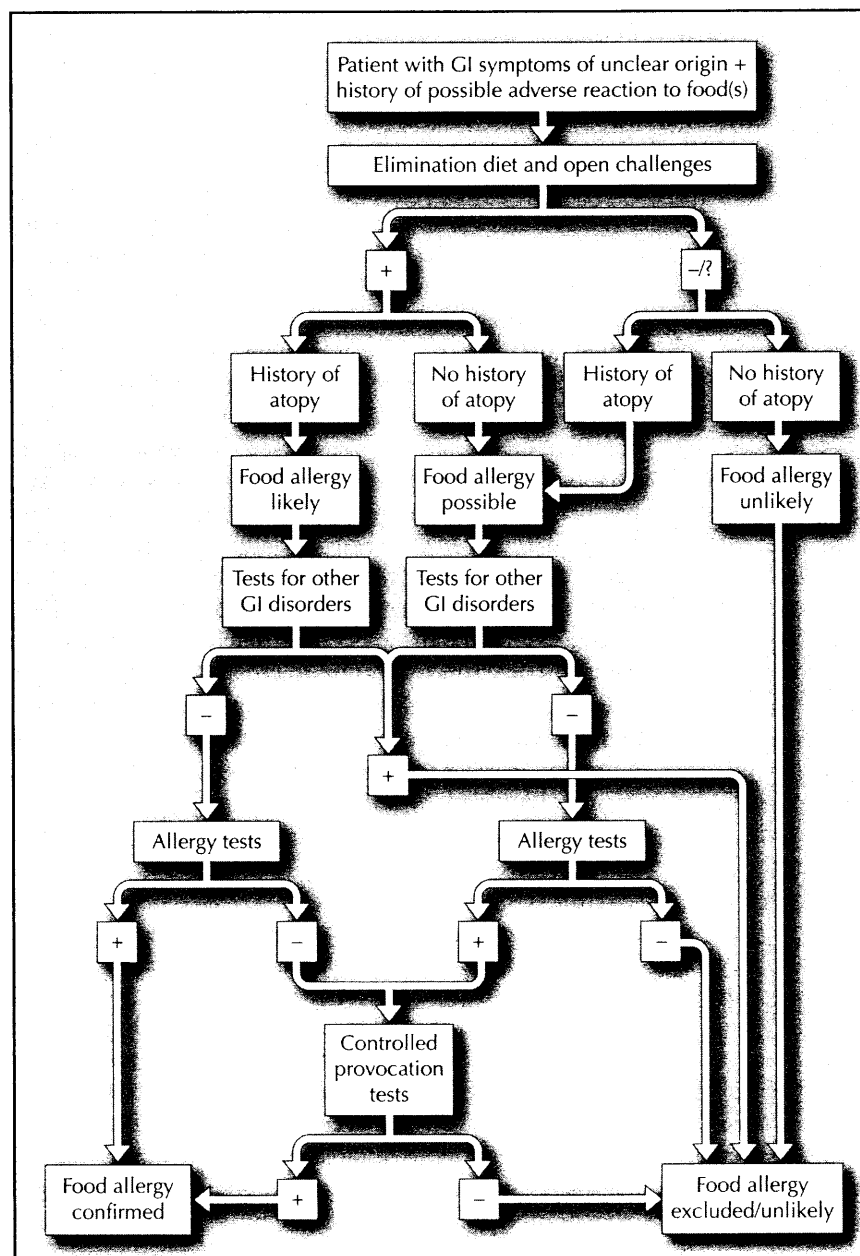


Figure 2. Flow chart for the diagnosis of food allergies. GI—gastrointestinal. (Adapted from Bischoff and Crowe [4••].)

and it offers an alternative to oral provocation tests for patients with gastroenterologic disorders [18]. Despite the obvious advantages of localized testing, this type of test is not routinely used in clinics due to its expense and the necessity of endoscopic expertise. However, endoscopic examination and histology represent the basis for the diagnosis of other immunologic reactions of the gastrointestinal tract to food, such as celiac disease, food-protein-induced gastroenteropathy in children, or eosinophilic gastroenteritis.

Diagnostics of food intolerances

Very few objective and certified testing techniques are available for the diagnosis of food intolerances. Consequently, patient history, elimination diets, and especially provocation methods are of central impor-

tance. The breath test procedures, which are used after provocation for the diagnosis of carbohydrate malabsorption (eg, lactose, fructose) should be emphasized. These tests have been described elsewhere [36,37]. Furthermore, it is possible to measure enzyme activity and polymorphism for enzyme-coded genes. Enzyme activity in the intestinal mucosa can be determined for lactose malabsorption (although this is not established as a routine procedure). Moreover, polymorphisms of the lactase gene are described that correlate with the probability of lactose malabsorption in the course of life. However, these tests do not reflect actual disease activity and can in no way replace the lactose- H_2 breath test. The histamine-destroying enzyme DAO, or cofactors of DAO, such as vitamin B_6 , can be determined for the diagnosis of histamine intolerance; these

laboratory values, in combination with anamnesis and provocation procedures, facilitate a reliable diagnosis in most patients [24].

Treatment

Treatment of food intolerance

Because the underlying mechanisms of food intolerances have to a large extent not been identified and therefore specific therapeutic intervention is not generally available, the most relevant method of treatment for food intolerance is at present an elimination diet. This practice requires thorough individual counseling and education of the patient, who must learn to read labels and to convert from ready-made products to primary foods. Apart from an elimination diet, specific treatment of enzyme deficiencies can be considered in patients with lactose malabsorption using lactase.

Treatment of food allergies

Elimination diet

The basis for treating food allergy is the avoidance of exposure to the allergen(s) that cause(s) the symptoms. This is particularly important in peanut allergy, in which even tiny traces of allergens can initiate substantial reactions. However, the practicality of such elimination diets is limited. They necessitate well-trained counselors, time, and a great deal of motivation on the part of the affected persons.

Supplementary medical treatment

If an elimination diet cannot be implemented thoroughly or if all of the provocative foodstuffs are not clearly identifiable, supplementary medicinal treatment becomes necessary. In such cases, a bowel-friendly compound of chromoglycate is available [38]. In more complicated cases (short-term), treatment with corticosteroids may be unavoidable. To date, corticosteroid treatment has not been investigated in controlled studies to determine the extent to which locally effective steroids, such as budesonide, are suitable for the treatment of gastrointestinal food allergies [4••]. No data exist to support the application of oral or systemic desensitization or for prophylactic medicinal treatment and similar approaches to manage food allergy.

Medical emergency treatment

Because an undesired exposure to food antigens cannot always be avoided, patients with an anaphylactic history must be equipped with a so-called "emergency kit." The chief component of this kit is adrenaline, the application of which must be carefully learned by affected persons to be used in emergency situations. The kit should also include a corticosteroid (2×100 -mg prednisolone equivalent), and an antihistamine (eg, 2×2 mg clemastine). People with food allergies should also learn to read and

understand the labels on foodstuffs with respect to hidden or cross-reactive allergens [39].

Prevention

A hypoallergenic diet is recommended for atopic mothers during pregnancy and during the lactation period to reduce the incidence of food allergies in their children. Foodstuffs with an especially high allergy potential should be introduced into the diet of an endangered baby later in order to minimize the likelihood of a food allergy arising. Recently published studies indicate that such probiotics as *Lactobacillus rhamnose* GG are capable of reducing the incidence of allergies in children from high-risk families. For example, the prevalence of food-induced atopic dermatitis can be reduced by approximately 50% through treatment with *Lactobacillus* GG during and immediately after pregnancy based on results of studies conducted 2 or 4 years after birth of the child [40].

New approaches to treatment

An interesting field of modern allergy research is the development of new treatments, such as tolerogen peptides, recombinant epitopes for hyposensitization, anti-IgE antibodies, and DNA-vaccination with allergen DNA, anticytokine antibodies, or cytokine-receptor antagonists against Th2 cytokines, such as IL-4 and anti-c-kit-antibodies functioning as anti-mast cell medications [12]. In addition, methods have been developed for the genetic or chemical modification of antigen structures of food allergens with the aim of reducing the allergen potential [30]. Antibodies against the Fc part of IgE, which bonds to the high-affinity IgE receptor, were successfully employed in animal experiments and clinical studies with patients suffering from asthma. These agents also offer potential for the treatment of food allergy. Anti-IgE treatment has already been used effectively in patients with peanut allergy [41].

Conclusions

Food incompatibilities affect approximately 20% of the general population in Western countries. In about one quarter of the affected children and one tenth of affected adults, the incompatibility is based on an allergy, that is, on an immunologically induced incompatibility reaction. Gastrointestinal symptoms occur in one third of these cases. Food allergies are caused by IgE-dependent or IgE-independent immunologic reactions. The diagnosis is founded on meticulous self and family history, a symptom-orientated eliminatory diagnosis, specific allergy tests, and, in problem cases, a controlled provocation procedure. Although none of these methods can lead to confirmation or exclusion of a "food allergy" in their own right, the combination of the various testing processes offers a reliable means of diagnosis.

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- Of major importance

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