

New visions for food allergy: An iPAC summary and future trends

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The spectrum of food allergy consists of a variety of different clinical pictures including immunoglobulin (Ig)E, and non-IgE food allergy as well as mixed, IgE and non-IgE disorders. In addition, eosinophilic diseases of the gastrointestinal (GI) tract with occasional IgE-type sensitization are increasingly recognized. As a consequence, the clinical picture of food allergy is pleomorphic and can range from chronic GI symptoms to severe anaphylaxis. The diagnosis of food allergy is mostly hampered by the lack of reliable *in vitro* tests for non-IgE-mediated diseases, and in most cases relies on a reoccurrence of symptoms upon re-exposure to the antigen; in general during a standardized food challenge. Currently, there is no safe and efficient treatment for food allergy and the treatment relies on avoidance diets. Priorities for research have been identified by iPAC (international Pediatric Allergy and Asthma Consortium) and outlined in this review. They include studies to better identify the pathogenesis of food allergy, including genetic aspects; studies to develop diagnostic and follow-up tests; studies for standardization of food challenges; as well as studies addressing a safe and efficient treatment of food allergy.

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Food allergy is a common disease that affects children more often than adults. Food allergic reactions typically develop in early childhood. The reason why oral tolerance fails to develop is still not completely understood (1). A large part of food allergic reactions are immunoglobulin (Ig)E-mediated and involve the skin, gastrointestinal (GI) and respiratory systems, with reactions ranging from mild skin symptoms to severe anaphylactic reactions. Patients with non-IgE-mediated food allergy suffer mostly but not exclusively from GI symptoms. They can include diarrhea, abdominal cramping, nausea, vomiting, failure-to-thrive, chronic reflux and/or dysphagia. Mechanisms of non-IgE-mediated food allergy are not well characterized, but are known to include, T-cell- or eosinophil-mediated disorders.

For the diagnosis of food allergy, obtaining a proper history is critical. In addition, several *in vitro* and *in vivo* measurements are available. The gold standard is still a standardized oral provocation test or food challenge (2). Recently, novel diagnostic criteria for the diagnosis of food allergy and the predication of its time course have become available. With regard to therapy, new concepts are under discussion which focus on the (re)establishment of oral tolerance. However, in the mean time, elimination diets and proper education of patient remain the key aspects of medical management of food allergy. Because dietary 'failures' (accidental exposure to allergens) are not uncommon (3), many patients require an emergency kit including self-injectable epinephrine for emergency management. This manuscript will highlight the current knowledge on the pathogenesis of food allergy in children, methods of food allergy diagnosis and therapy and future research directions.

Epidemiology

Recognition of food allergy in the community is largely based on symptoms reported by patients or parents. While IgE-mediated food allergy is relatively easy to diagnose, identification of non-IgE-mediated food allergy relies on suggestive symptoms, frequently mimicked by various other adverse reactions to foods and other pediatric diseases. Prospective data have been obtained on the prevalence of cow's milk allergy in a cohort of Danish infants followed for their first three years of life. Of 1749 newborns, the diagnosis of cow's milk allergy was proven in 2.2% (39 infants), of which 18 had non-immediate symptoms with negative IgE tests (4). Children presented with cutaneous symptoms (urticaria and/or atopic

eczema) in 64% of the cases, GI symptoms (infantile colic, vomiting, diarrhea and failure to thrive) in 59% or respiratory symptoms (wheezing and/or rhinitis) in 33%. A majority of children (72%) had symptoms involving two or more organ systems. Other relevant epidemiologic studies providing figures on non-IgE-mediated food allergy are mostly transectional population studies. A large German survey, based on a questionnaire, was analyzed specifically for the pediatric population (0–17 yr) (5). Of 739 subjects contacted by phone, 38.4% (284) reported a reproducible adverse reaction to foods. Food challenges elicited symptoms in 31 patients, with five negative IgE tests. Symptoms suggesting IgE-mediated food allergy included oral pruritus, urticaria and rhinitis in 3.5% of the total population, and other symptoms possibly evoking non-IgE-mediated food allergy or intolerances were seen in 0.7%. In another cross-sectional Danish study, symptoms suggestive of IgE-mediated food allergy during food challenges were seen in 2.3% of the children at 3 yr of age (mostly to hen's egg), and only one child in this age group had a typical non-IgE-mediated reaction, accounting for a prevalence of 0.5% (6). Finally, a recent meta-analysis provided data for specific foods with regard to reported symptoms and sensitization, suggesting a global prevalence of 'food allergy' of between 2% and 5%. However, clear figures on non-IgE-mediated food allergy unfortunately could not be assessed (7). Eosinophilic diseases related to food allergy have been reported in various American, European and Asian countries. The disease prevalence is less well defined than that of IgE-mediated food allergy and might be different in various geographical areas (8). It has been estimated to be around 1–3 per 10,000 inhabitants (9). An increasing prevalence has been reported in the Midwest United States between 2000 and 2003 (10).

Definitions

Food allergies can be divided into three categories: (i) IgE-mediated reactions; (ii) mixed IgE-mediated and non-IgE-mediated disorders and (iii) non-IgE-mediated diseases (11). IgE-mediated disorders can be classified as either an immediate GI hypersensitivity reaction or an oral allergy syndrome. The immediate hypersensitivity syndrome is a disorder that typically involves the skin, respiratory tract, GI tract or generalized reactions, i.e. anaphylaxis. In most of these patients, serum food-specific IgE antibodies can be measured in conjunction with positive skin

tests, confirming the IgE-mediated pattern of the reaction.

The oral allergy syndrome is a form of IgE-mediated allergy based on contact of food antigens with the mucosal surface; it rarely involves other organ systems. Symptoms of these types of food allergy typically occur within minutes to hours of the ingested food.

Non-IgE-mediated GI diseases are often classified as dietary protein enteropathies. Dietary protein enterocolitis and celiac disease are the most common forms. Celiac disease is characterized by villous atrophy, crypt hyperplasia, increased intraepithelial lymphocytes and a mixed inflammatory infiltrate. Dietary protein enterocolitis and enteropathy are typically caused by cow's milk or soy protein and cause variable small and/or large bowel injury associated with non-specific villous atrophy and inflammation.

The mixed IgE and non-IgE-mediated disorders include the eosinophilic gastroenteropathies: eosinophilic proctocolitis, eosinophilic gastroenteritis and eosinophilic esophagitis (EE). These diseases are characterized by infiltration of the GI tract with eosinophils with an absence of other inflammatory cells. While eosinophilic proctocolitis involves only the distal colon, eosinophilic gastroenteritis may involve any portion of the GI tract; the eosinophils may infiltrate the mucosa, the muscular layer and the serosa (12). Finally, EE has recently gained a large amount of attention. It is a clinico-pathologic diagnosis best defined as the presence of more than 15 eosinophils per high power field (HPF) isolated strictly to the esophageal mucosa that is unresponsive to acid blockade and associated with clinical symptoms of the upper GI tract (8).

Clinical pictures and mechanisms

IgE-mediated food allergy

Skin symptoms are reported most frequently in IgE-mediated food allergy. Urticaria with or without angioedema occurs generally within 2 h and may be present alone or may be associated with other reactions. Flares of atopic eczema might be caused by ingestion of foods. Several studies involving standardized exposure to food by double-blind, placebo-controlled food challenges (DBPCFC) have carefully characterized these manifestations of food allergy occurring in up to 40% of children with moderate to severe atopic dermatitis (13–15). Food-induced flares of atopic eczema may occur within minutes; however, some patients may manifest symptoms after

a prolonged period of observation (16–18). Respiratory reactions range from mild symptoms with a feeling of dyspnoea without bronchoconstriction to severe symptoms, such as acute asthma, leading to severe hypoxia. Up to two-thirds of patients undergoing food challenges develop respiratory symptoms, which generally co-exist with skin or GI symptoms (19, 20). Respiratory reactions are a hallmark for the potential severity of a food-induced allergic reaction, in particular in patients with pre-existing asthma. Several series describing fatal, or near fatal reactions to foods have highlighted that the vital prognosis of severe reactions are clearly linked to acute manifestations of asthma (21–23). Anaphylaxis has been defined as a severe, life-threatening generalized or systemic hypersensitivity reaction (24). Food-induced anaphylaxis is the leading cause of anaphylactic reactions, particularly in children. It is estimated that there are 30,000 anaphylactic reactions to foods treated in emergency departments as well as 150–200 deaths each year in the United States; similar numbers have also been reported in Europe (25).

Food hypersensitivity reactions mostly occur after ingestion. However, it must be highlighted that a significant number of patients also describe manifestations of food allergy after skin contact or inhalation. Anaphylaxis has been reported, although infrequently, in children after skin contact with peanut butter (26, 27) or after inhalation of fish vapors (28). Standardized food challenges with inhalation of aerosolized foods may reproduce patient-reported symptoms (29).

The complete mechanism of IgE-mediated food allergy remains unknown. In particular, little is known about the molecular or cellular events leading to the loss of tolerance or to reacquisition of tolerance in a specific patient; however, the mechanisms underlying specific IgE production have been largely studied (30). While allergic diseases have been shown to develop in genetically predisposed individuals exposed to potentially allergenic foods, a defined set of genes predisposing an individual to food allergy has not yet been identified. According to current knowledge, a breach in tolerance mechanisms is favored by up-regulation of Th2 cytokines, i.e. interleukin (IL)-4, IL-13 and IL-5 and by down-regulation of regulatory mechanisms involving among others, T-regulatory cells and IL-10 and/or transforming growth factor (TGF) β (31, 32). As a consequence, patients with IgE-mediated food allergy will usually have food-specific IgE antibodies detectable in their serum and in their mucosal surfaces, bound to Fc ϵ receptors on

mast cells, leading to degranulation and liberation of vasoactive mediators and the development of immediate-type symptoms of food allergy following ingestion of the offending food.

Non-IgE-mediated food allergies

Food protein-induced enterocolitis syndrome (FPIES) in infants caused by cow's milk and/or soy protein has been recognized for decades. Symptoms typically begin in the first several months of life, including vomiting, colicky abdominal pain and diarrhea. In severe cases, FPIES may be associated with failure to thrive which could progress to acidemia and shock (33, 34). Symptoms typically resolve after the causal protein is removed from the diet but return with a characteristic symptom pattern on re-exposure. Approximately 2–4 h after reintroduction of the protein, vomiting ensues, followed by an elevation of the peripheral blood polymorphonuclear leukocyte count, diarrhea and hypotension (35). These children may present to medical care with symptoms of severe lethargy and shock. The disorder is generally not associated with detectable food-specific IgE antibody (36). Approximately half of the infants react to both milk and soy (37). There are increasing reports of additional causal foods, including rice or poultry (38), prolonged clinical courses and onset outside of early infancy. The disorder poses numerous diagnostic and therapeutic challenges.

Colonic biopsies in symptomatic patients reveal crypt abscesses and a diffuse inflammatory cell infiltrate with prominent plasma cells. Small bowel biopsies reveal edema, acute inflammation and mild villous injury. In some cases, focal erosive gastritis and esophagitis is found with prominent eosinophilia and villous atrophy (39). The immune process that causes milk-induced FPIES results partly from elaboration of the cytokine tumor necrosis factor (TNF) α by milk-responsive T cells (40).

According to Sampson and Anderson's classification (11), non-IgE-mediated syndromes of food allergy also include *dietary protein proctocolitis* and *enteropathy*. Dietary protein proctocolitis has been described in infants, mostly breast-fed, presenting with isolated rectal bleeding in otherwise healthy infants. This syndrome is described further in the section on eosinophilic disease (see next). *Dietary-induced enteropathy* is a pleomorphic disease. In the past, it was mostly diagnosed in early infancy in patients with recurrent vomiting or diarrhea and/or failure-to-thrive (41). Recently, the disease has been suspected in school-age children with recurrent

abdominal pain or diarrhea (42). Atopic features such as a history of earlier food allergy or atopic eczema was common. Endoscopy reveals mostly lymphonodular hyperplasia of the duodenal bulb, but also gastritis and esophagitis. These findings suggest an immune mechanism as the cause of the symptoms.

Eosinophilic food allergies

The eosinophilic gastroenteropathies are an interesting, yet somewhat poorly defined set of disorders that by definition include the infiltration of at least one layer of the GI tract with eosinophils. Within the broad classification of these disorders lie at least three clinical entities that are defined in large part by the presence of abnormal numbers of eosinophils in various GI sites: eosinophilic proctocolitis (EP), eosinophilic gastroenteritis (EG) and EE.

Through the process of endocytosis by the enterocyte, food antigens are generally degraded into non-antigenic proteins (43). Although the GI tract serves as an efficient barrier to ingested food antigens, this barrier may not be mature for the first few months of life (44). As a result, ingested antigens may have an increased propensity for being presented intact to the immune system. These intact antigens have the potential for stimulating the immune system, and driving an inappropriate response directed at the GI tract. It is felt that up to 7.5% of the population in developed countries might exhibit cow's milk allergy, although there is wide variation in the reported data (4). Over 50% of the cases of EP occur in breast-fed infants, but rather than developing an allergy to human milk protein, it is felt that the infants are manifesting allergy to antigens ingested by the mother and transferred via the breast milk.

Loose stool, rectal bleeding and increased mucus production, associated with an eosinophil infiltration of the mucosa are the typical symptoms seen in patients who present with EP (45–47). In a well-appearing infant, blood in the stool often begins gradually, initially appearing as small flecks of blood. Usually, increased stool frequency occurs accompanied by water loss or mucus streaks. The development of irritability or straining with stools is also common and can falsely lead to the initial diagnosis of anal fissuring. Atopic symptoms, such as eczema and reactive airway disease may be associated. Continued exposure to the inciting antigen causes increased bleeding and may, on rare occasions, cause anemia or poor weight gain. Despite the progression of symptoms, the infants are gener-

ally well appearing and rarely appear ill. Other manifestations of GI tract inflammation, such as vomiting, abdominal distension or weight loss almost never occur.

EG is a general term that describes a constellation of symptoms attributable to the GI tract, in combination with pathologic infiltration by eosinophils. EG may affect any layer of the GI tract (mucosal, muscular or serosal). While mucosal EG may affect any portion of the GI tract, muscular and serosal EG typically affects the small bowel causing intestinal obstruction with vomiting or ascites, respectively. The exact etiology of EG remains unknown, although it is now recognized to result from both IgE- and non-IgE-mediated sensitivity (48). Specific foods have been implicated as the cause of EG (49). Speculation has also surrounded the role of non-IgE-mediated immune dysfunction, specifically, the interplay between Th2 lymphocyte-produced cytokines and eosinophils.

The most common symptoms of EG include colicky abdominal pain, bloating, diarrhea, weight loss, dysphagia and vomiting (50). In addition, up to 50% have a past or family history of atopy. Other features of severe disease include GI bleeding, iron deficiency anemia, protein losing enteropathy (hypoalbuminemia) and growth failure (51). Approximately, 75% of the affected patients have an elevated blood eosinophilia. Males are more commonly affected than females (52).

Recently, EE has begun to emerge as the most problematic of all GI eosinophilic disorders. EE appears to be caused by an abnormal immunologic response to specific food antigens. In 1995, Kelly published the classic paper on EE (53). Because the suspected etiology was an abnormal immunologic response to specific unidentifiable food antigens, each patient was treated with a strict elimination diet, which included an amino acid-based formula. These findings were later supported by a 10-yr study conducted by Liacouras (54). Spergel (55) later demonstrated that foods that cause EE are often not based on an immediate hypersensitivity reaction. By using a combination of traditional skin testing and a newer technique of 'patch testing', he established that a delayed cellular-mediated allergic response might be responsible for many cases of EE (55). Other investigations suggest that CD8 lymphocytes are the predominant T cells within the squamous epithelium of patients diagnosed with EE (56).

EE is a clinico-pathologic diagnosis which is made by associating typical symptoms with an isolated esophageal eosinophilia unresponsive to

acid blockade (8). It occurs in children and adults. The presentation of EE in children is similar to the symptoms associated with gastro-esophageal reflux. Males develop EE more frequently than females. The typical symptoms include nausea, vomiting, regurgitation, epigastric abdominal pain and poor eating. Young children may demonstrate food refusal while adolescents often experience dysphagia (54). Adults present with similar symptoms; however, dysphagia occurs much more commonly and can be associated with esophageal strictures. Uncommon symptoms include growth failure, hematemesis, globus and water brash. The clinical features of EE may evolve over years. Symptoms such as abdominal pain and heartburn occur regularly; however, patients with vomiting or dysphagia may display these symptoms sporadically complaining only once or twice a month. While the use of acid suppression medication often improves the patient's symptoms, it does not eliminate the symptoms nor change the abnormal esophageal histology. Less common symptoms include growth failure and hematemesis. Approximately 50% of the affected children also exhibit other allergic signs and symptoms including bronchospasm, allergic rhinitis and eczema. Frequently, there is a strong family history of food allergies or other allergic disorders. Treatment consists of determining the dietary antigens responsible for the disease or the use of medications such as systemic or topical corticosteroids.

Identified needs and future perspectives in defining mechanisms and risk factors of food allergy (summarized in Table 1)

Prevention, diagnoses and treatment of food allergies are clearly related to understanding of the mechanisms of food allergy. During the last few years, progress has been made in understanding IgE-mediated food allergies as well as eosinophilic diseases by incorporating data from basic science research. However, black boxes continue to exist with regard to our knowledge of food allergy and mainly in the area of non-IgE-mediated food allergies. It is not yet understood why in a given individual, tolerance might disappear at a given time and why, with some foods (e.g. milk), tolerance can naturally reappear. Future research should encourage translational research in order to gain a better understanding of the cellular and molecular level of tolerance phenomena in relation to the clinical phenomena. To date, most knowledge acquired at this level has been in animal models. Current

Table 1. Research topics identified, directions to address them, and expected outcomes

Research topic	Open questions	How to address it	Expected outcome
Mechanisms of food allergy	Which mechanisms characterize tolerance loss to foods? How do data obtained from animal models correlate to humans? Why do individuals develop a specific pattern of food allergy (e.g. IgE- or non-IgE-mediated, EE)? Which genes predispose to food allergy?	Animal studies Studies with biopsies from patients with food allergy Studies in animal models and with human material	A better understanding of the mechanisms of food allergy promotes a better diagnosis and a potential cure
Genetics High responder genes HLA Predisposition genes Family studies Epidemiology of food allergy		Cross-sectional and/or longitudinal cohort study Family studies	Risk prediction Targeted prevention of food allergy
	What is the distribution of food allergy in Europe? What is the risk of an EE epidemic in Europe? What is the economical implication of IgE- or non-IgE-mediated food allergy? Which tests distinguish food allergy from sensitization in early infancy? Efficient tests are needed for the follow-up of food allergy Which non antibody-related tests (e.g. cellular tests) might be reliable for the diagnosis or follow-up of food allergy? Can allergy tests predict the severity of an allergic reaction to foods?	Addressed by Europrevall Prospective cohort study Cross-sectional or/and longitudinal cohort study	Better prevention of food allergy Preventing a 'new' type of food allergy in Europe Better use of financial resources for health
Diagnostic tools in IgE-mediated food allergy		Birth cohort study Longitudinal cohort study Cross-sectional and/or longitudinal cohort study Cross-sectional and/or longitudinal cohort study	Avoid unnecessary elimination diets in sensitized infants Early detection of food allergy Efficient prediction of tolerance acquisition, less food challenges needed Efficient food allergy diagnosis, less food challenges needed Better prevention of severe anaphylaxis
Validation of food challenge (false negative challenges in non-IgE- eliciting doses for repeated food challenges) Treatment of food allergy	Are food challenges fully reliable for the diagnosis, in particular in non-IgE-mediated food allergy? Can eliciting doses for allergic reaction be safely defined? How can food allergy be best modeled in animals? Which treatment can safely and efficiently prevent and/or cure food allergy by immunotherapy? Which treatment can safely and efficiently prevent and/or cure food allergy by medications?	Design new protocols of food challenge tailored to the specific syndromes of food allergy Cross-sectional or/and longitudinal cohort study	Better diagnosis for the patient suspected with food allergy Safer advice on the risk of an accidental ingestion
		Refine current animal models and define new ones Studies addressing (but not exclusively) OTI, SLIT, α IgE, CpG, re-engineered proteins, peptides, fusion proteins, micro-organisms Studies addressing potential medications such as immunomodulators and herbal medicine	Safe and efficient medications for prevention and/or treatment of food allergy

Ig, immunoglobulin; EE, eosinophilic esophagitis; OTI, oral tolerance induction; SLIT, sub-lingual immunotherapy; CpG, Cytosine Guanine.

animal models are only partly suitable to provide data applicable to humans with regard to food allergies. New animal models are required and a better characterization of current animal models is necessary. It is not yet understood why in a given individual a specific IgE- or non-IgE-mediated food allergy or an eosinophilic disorder might develop. Furthermore, it is not clear if genetic factors are involved and which genes are implicated. In addition to mechanistic disease, genetic studies are strongly needed. Epidemiology of food allergy is largely addressed in the European Commission-funded studies of Euro-Prevall. However, these studies do not specifically address non-IgE-mediated food allergy or eosinophilic diseases. In the light of the epidemic in the United States of eosinophilic diseases, it would be of great importance to have early epidemiological data in Europe in order to prevent a similar European epidemic.

Current diagnostic procedures

Diagnosis – IgE-mediated food allergy

For the identification of patients with clinically relevant food allergy it is important to perform a proper diagnostic evaluation in order to implement an appropriate elimination diet. For this diagnostic work-up, several *in vivo* and *in vitro* tests are available. Every evaluation should start with a thorough patient history, followed by the determination of sensitization by skin prick tests or the measurement of food-specific serum IgE antibodies. The gold standard, however, remains a controlled oral food challenge as it is the sole procedure that can distinguish between sensitization and allergy (2).

Food allergen-specific IgE concentrations in the serum have been correlated both with patient histories and the outcome of oral food challenge tests in order to generate probability curves that depict the likelihood of patients with a particular food allergen-specific IgE level reacting to the food. In this way, diagnostic decision points for several foods have been described (57–61). These diagnostic decision points are meant to reduce the requirement for oral food challenge tests and may also contribute to increased safety when performing the food challenge test. However, it has been observed that the diagnostic decision points varied between the different study populations (62). Importantly, patients with food allergen-specific IgE levels in the undefined range need to undergo oral food challenge test. The measurement of total IgE does not add additional information for the diagnosis of food allergy (63). Similarly, diagnos-

ing cut-off values for skin test mean wheal diameters have been determined for food allergy (64, 65). While helpful, this approach is limited by the lack of standardized allergen extracts. Further information is required about these diagnostic cut-off values in different populations (primary care vs. specialist clinics) and in different age groups, especially in young infants.

Diagnosis – non-IgE-mediated food allergy

The diagnosis of non-IgE-mediated food allergy is generally based on clinical history as well as on recurring symptoms after repeated exposure. It is characterized by negative skin prick tests and absence of detectable food-specific serum IgE antibodies. Positive tests have been described in patients with dietary protein-induced colitis (47) and in patients with enterocolitis who have atypical features (66). In most cases, the diagnosis relies on a suggestive history of repeated similar reactions after exposure to the food (e.g. as in enterocolitis). In other syndromes of non-IgE-mediated food allergy, delayed non-specific reactions might be difficult to attribute to a definite food.

Diagnostic procedures for non-IgE-mediated food allergy highlight three specific aspects. First, the diagnosis of food allergy by typical clinical features of non-IgE-mediated food allergy syndromes (e.g. as in enterocolitis). If diagnostic procedures are needed, they are usually directly related to the mechanisms involved in the disease. In particular, food-induced eosinophilic diseases of the gut need to be diagnosed by endoscopy and biopsy. Normal macroscopic findings are not uncommon, and the diagnosis mostly relies on increased numbers of eosinophils in specific locations such as the intraepithelial, superficial mucosal and intestinal crypt regions (67). Second, the triggering food needs to be identified. Again, the history might be highly suggestive such as in enterocolitis or it may be non-contributory such as in eosinophilic diseases. While elimination diets may be helpful, often patients must be started on an elemental diet followed by food challenges. Food challenges are the cornerstone in the diagnosis of non-IgE-mediated food allergy and are most often conducted following a specific protocol, different from those commonly accepted for IgE-mediated food allergy (2, 68, 69). For example, in enterocolitis, the food can be given in a single dose according to the weight of the child utilizing rescue medications if symptoms appear (epinephrine, intravenous fluids and steroids; 70). Third, food challenges or endoscopy need to be repeated, possibly several times over a period of follow-up that may last many years.

Novel diagnostic procedures

Determination of the time course of food allergy

Many food allergic patients will develop clinical tolerance as they get older. This is especially true for children with cow's milk, hen's egg, wheat and soy allergies. Therefore, these children need to be re-evaluated frequently in order to determine whether tolerance has been developed (71). Recently, a model for predicting the likelihood of developing tolerance in cow's milk or hen's egg allergy based on the decrease in food-specific IgE over time has been developed. These likelihood estimates may be able to aid clinicians in prognosis and in timing subsequent food challenges, thereby decreasing the number of premature and unnecessary food challenges (72). For now, the concept remains as a research tool until it is proven in larger study populations in less specialized settings.

Prediction of the time course of food allergy

Early prediction of the natural course of food allergy would be beneficial to identify children with persistent food allergy. Children who display a potential persistent course are perfect candidates for immunotherapeutic procedures currently under development. For example, the youngest children with persistent cow's milk allergy appear to have IgE antibodies to distinct allergenic epitopes on certain cow's milk allergens that are not recognized by patients who will ultimately become tolerant. Using SPOTs™ membrane technology (Genosys Biotechnologies, TX, USA), it has been shown that IgE-binding epitopes on certain cow's milk proteins are recognized by the majority of patients with persistent cow's milk allergy but not by patients with transient disease (73). In order to confirm this observation in a larger study population, these IgE-binding peptides were coupled to the matrix of a commercial system and screened with a larger study population. Again, milk peptide-specific IgE was found to be significantly higher in patients with persistent cow's milk allergy compared with children who subsequently outgrew their allergy in the first few years of life (74). A similar concept has been shown recently for hen's egg allergy (75). Therefore, measurement of these food-specific IgE antibodies could be used as an early marker of persistent food allergy to help in identifying children for whom specific immunotherapy would be beneficial. This concept must also be confirmed in further study populations.

Component-resolved diagnostics

Commonly, whole food allergen extracts are used for measurement of food-specific IgE. There is growing evidence that the use of purified or recombinant allergen components instead of whole food allergen extracts provide additional information in the diagnosis of food allergy (76). For example, specific serum IgE antibodies against the Brazil nut allergen component Ber e1 or the wheat allergen component ω -5 gliadin have been shown to correlate well with clinically relevant Brazil nut or wheat allergy (77, 78). Therefore, the use of purified or recombinant allergen components, in addition to whole food allergen extracts, might give more accurate results in food allergy diagnostic testing. The identification and characterization of clinically relevant allergen components is necessary for this new methodology. Owing to better technology, the reports on newly identified allergen components have increased dramatically within recent years (76). In addition, novel methods such as peptide microarray technology have been developed recently (79). In this approach, recombinant or purified allergen components are spotted on a chemically modified glass slide in the form of circle-shaped spots by an automated printer. The allergen chips allow the determination of patients' reactivity profiles to hundreds of allergens with minute amounts of serum in single tests. Recently, the microarray technology has been extended for measuring specific IgE to individual peptides representing IgE-binding sites (80).

Identified needs and future perspectives in diagnostic procedures (summarized in Table 1)

The ideal diagnostic tool in food allergy should allow the physician clinicians to clearly distinguish between sensitization and clinical allergy. It should also provide a clear marker of the natural history of food allergy identifying the time when natural tolerance will be reacquired. Furthermore, it should also support or refute a diagnosis in young infants in whom common IgE tests very often gives negative or very low level test results. Current diagnostic tests are only offering part of these ideal requirements in IgE-mediated food allergy. There is also a clear gap in non-IgE-mediated food allergy and in eosinophilic diseases. The various mechanisms of non-IgE-mediated food allergy render the diagnoses of this condition more challenging. Thus, clinicians often have to rely on food challenges. Although food challenges have been standardized over the

last decades, several open questions remain about the design and interpretation of food challenges. Furthermore, it has not yet been decided if challenges can provide safety data for patients, in particular for threshold doses of reactions and their reproducibility over time (81). With regard to non-IgE-mediated food allergies, more accurate food challenge protocols should be designed in association with pediatric gastroenterologists.

Current therapeutic approaches

Currently, no curative treatment for food allergy is available. The only advice that can be given to patients with food allergy is strict avoidance of the allergen that is eliciting the allergic reaction. It is imperative that specific allergens be identified because unsubstantiated elimination diets have been shown to cause nutritional problems and growth failure (82, 83), and have a significant negative effect on the quality-of-life of these patients and their families (84). However, an elimination diet is always difficult to perform. Multi-disciplinary input from specialist pediatric services including dietetics is essential to provide guidance and support for parents, as major lifestyle changes must often be instituted in a household following a diagnosis. This can involve new methods of food preparation and changes in diets of other unaffected family members. Many food allergens such as cow's milk and hen's egg are used frequently in processed food and accidental dietary exposures are not uncommon. In addition, possible contaminations during production might occur. Especially in peanut and tree nut allergies this might lead to severe reactions because contamination is often because of larger particles resulting in severe reactions. Moreover, in infants and young children with cow's milk allergy, a nutritionally complete substitute is necessary to assure proper growth and development. For this purpose, extensively hydrolyzed formulae or amino acid formulae have been used successfully for many years (85).

Fifty percent of infants with non-IgE-mediated cow's milk allergy also react to soy formulae (86), although cross-reactivity is very low in IgE-mediated milk allergy (87). Soy formula is not recommended for prophylaxis of milk allergy and is not recommended for treatment of milk allergy in infants under 6 months of age (88). Goat's milk anaphylaxis has been described in approximately 90% of children allergic to cow's milk (89) and in others who are tolerant to cow's milk (90). The use of other

animal milks is not recommended owing to high cross-reactivity with cow's milk.

In general, the advice that families receive about elimination diet is not adequate; dieticians in this area need greater training and experience. Moreover, many patients with food allergies need an emergency kit including self-injectable epinephrine. It is well known that patients are often not well prepared to deal with accidental ingestions. Therefore, written advice including when and how to use their medication and proper training is crucial. Pragmatic guidelines for prescription of adrenaline autoinjectors are emerging (91, 92).

Natural history and treatment

The prognosis of IgE-mediated food allergy in childhood clearly depends on the age of diagnosis, type of symptoms, concentration of food-specific IgE in the serum and most importantly of the food involved. Food allergies that are often 'outgrown' include among others milk, soy, wheat and egg. A prospective study on cow's milk allergy has well shown that after a follow-up of 5 yr, more than 90% of the patients had outgrown their milk allergy (93). In contrast, a fish allergy is rarely lost over time and peanut allergy is outgrown in up to 50% of young children with a peanut-specific IgE level of less than 5 kU/l (94). Regular follow-up including food challenges are important in most patients with IgE-mediated food allergy.

FPIES is a diagnosis that is generally made clinically; and an approach to the diet must take into consideration the reaction history, age of the child, number of foods involved, results of tests for IgE antibody and results of oral food challenges. Data are limited, and on the basis of a few case series and reports, it may not be possible to suggest a specific course of action applicable to all situations.

The clinician must determine a practical sequence, timing and modality of administration from various options such as an oral food challenge with or without intravenous access in place or routine addition to the diet at home. For infants, an extensively hydrolyzed casein formula is usually tolerated, but if not, an amino acid-based formula should be tolerated (95). For infants with milk-induced FPIES, soy formula is not a good option as up to 50% of these infants will react to soy (37). Dietary avoidance must be reviewed in detail, including careful label reading and concern for cross-contact of the allergen during food preparation. Excellent resources on this subject are available from the Food Allergy

and Anaphylaxis Network (<http://www.foodallergy.org>).

The true natural history of FPIES is unknown. A recent publication calculated the resolution by 3 yr of age for various foods: milk, 63%; soy, 25%; oat, 66%; rice, 40%; barley, 100% and poultry, 100% (35). At least yearly evaluation is needed to determine if the child is still allergic to the foods in question. Whether a food challenge is conducted and where it is to be performed are dependent on the clinical history of that child within the past 12 months.

Reactions to accidental exposures can be severe, so instructions on emergency management should be given. If an accidental ingestion is known to have occurred, the patient should be instructed to seek medical attention for observation and treatment, which may differ between FPIES and severe IgE-mediated reactions. Intravenous fluid resuscitation may be needed. For patients with FPIES with a history of severe reactions and onset of any symptoms, consideration should be given for administration of corticosteroids to suppress a presumed T-cell-mediated reaction. This treatment could be considered for any patient with more than minimal symptoms. The reaction can include symptoms of shock that may respond to epinephrine but intravenous hydration and steroids are the only medications typically required (66). Theoretically, fluid loss from the GI symptoms is partly responsible for the hypotension, so epinephrine without intravenous hydration may be less efficacious. The role for and efficacy of antihistamines are unknown.

Novel therapeutic options

An effective therapy for food allergy is still missing. Dietary failures in food allergic patients are not uncommon often resulting in severe reactions (3). Therefore, new therapeutic approaches especially for patients with persistent food allergy are currently under development.

Biologic therapy in food allergy

Using TNX-901, a humanized IgG1 monoclonal antibody against IgE, a double-blind, randomized, dose-ranging trial was conducted in patients with peanut allergy. In this study, it has been shown that a 450-mg dose of TNX-901 significantly and substantially increased the threshold of sensitivity to peanut on oral food challenge from a level equal to approximately half a peanut to one equal to almost nine peanuts, an effect that should translate into protection against most

unintended ingestions (96). However, the humanized monoclonal anti-IgE antibody, omalizumab [Xolair®; Genentec/Novartis] that is currently on the market for the treatment of patients with bronchial asthma has not been studied in food allergy. Unfortunately, a phase II multicenter clinical trial in peanut allergy was recently discontinued because of concerns with the safety of peanut challenge protocols (97). With regard to the eosinophilic disorders, future research is being conducted involving biologic therapy targeting specific cytokines that may affect the function of peripheral and tissue eosinophils. In particular, anti-IL5 has not only been shown to significantly decrease circulating and tissue eosinophils in animal models (mouse) but also has been shown to be effective in a few case-controlled trials. Other possible monoclonal antibodies that have a potential therapeutic role include anti-IL-13 and anti-eotaxin (98).

Oral immunotherapy in food allergy

Food allergy occurs if oral tolerance fails to develop or breaks down. The reintroduction of oral tolerance induced by oral exposure to increasing doses of the specific food allergen seems to be a promising therapeutic approach for IgE-mediated food allergy (99). Several uncontrolled trials using this approach in food allergy showed efficacy rates of 75–86% (100–103). In at least a subset of these patients, regular intake of the allergenic food seems to be necessary (104). It is therefore unclear whether this approach induces a temporary shift in threshold reactivity to allergen as opposed to inducing long-lived clinical and immunological tolerance. However, certain scepticism towards this approach remains, owing to the risks of side-effects and the lack of sufficiently large controlled studies. Moreover, it is still questionable whether the natural course of food allergy can be changed or if oral tolerance is only acquired earlier through this approach (105). Future studies need to investigate whether this approach is also suitable for children with persistent food allergy and those with high risk of anaphylactic reactions.

Specific immunotherapy for food allergy with mutated proteins

Specific immunotherapy is commonly used for the treatment of inhalant allergies. In food allergy, however, it has been shown that the rate of side effects is much higher (106). Therefore, several novel approaches are being explored to increase the safety of specific immunotherapy in food allergy in order to develop a causal therapy

(107, 108). One of the most promising approaches is immunotherapy with mutated proteins. The idea behind it is that alteration of the amino acid sequences at the IgE-binding sites reduces the IgE antibody binding to the protein.

Many food allergens are well characterized including the characterization of IgE-binding sites. For example in cow's milk allergy, the IgE-binding sites for casein and whey proteins and the amino acids necessary for IgE binding have been delineated (109–112). Importantly, mutations of the IgE-binding sites appear to leave the T-cell response unaffected (113). Using these mutated hypoallergenic proteins in animal studies appears to be very promising. However, heterogeneity in IgE-binding sites and their amino acids critical for IgE-binding have been observed (114). Therefore, future studies in humans are necessary to prove the effectiveness of this approach..

Identified needs and future perspectives in therapeutic options (summarized in Table 1)

The goal of the treatment of food allergies is to provide an effective and safe cure. Currently explored options include oral tolerance induction protocols as well as sublingual immunotherapy or systemic immunotherapy. They also include anti-IgE treatments. It remains unclear to date which one of these options is the safest and the most effective. Treatment options will probably need to be tailored to specific patient populations. In addition, better adjuvants for immunotherapy including microbial triggers or triggers of innate immunity are strongly needed. All these options initially need to be tested in animal models. The current mouse model of food allergy seems to be fairly similar to human food allergy; however, translation of mice data to humans is not yet warranted. Although IgE-mediated food allergy is the most severe form of food allergy, non-IgE-mediated food allergy and eosinophilic disease provides an important burden to the patients. Studies on the treatment of these forms of food allergy are far less advanced and need strong support in the near future.

Conclusions

Food allergy is a prototypic disease of childhood allergy. It often appears early in life and can be considered as an early marker of the ongoing allergic marathon in a given child. Addressing the needs of these children, with regards to the risk of developing food allergy and improvement of the care of children diagnosed with food allergy will

provide a clear benefit to them. It must be stressed that to date, IgE-mediated food allergies are the most well understood. It is of major importance to strongly encourage research of non-IgE-mediated food allergy as well as eosinophilic diseases, as epidemiology of food allergy might change over the next decades and shift towards these diseases. When addressing food allergy, a disease with a high morbidity in this age population, it also has an impact on children with a significant risk of mortality. Indeed, reducing the overall burden of severe IgE-mediated food allergy will largely benefit general health care in children.

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