Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

REVIEW ARTICLE

Update on food allergy

A. Carrard[1], D. Rizzuti[2] & C. Sokollik[2]

[1]Division of Pediatric Pulmonology and Allergology, University Children's Hospital, Inselspital, University of Bern; [2]Division of Pediatric Gastroenterology, Hepatology and Nutrition, University Children's Hospital, Inselspital, University of Bern, Bern, Switzerland

To cite this article: Carrard A, Rizzuti D, Sokollik C. Update on food allergy. *Allergy* 2015; **70**: 1511–1520

Keywords
component-resolved diagnostics; cow's milk protein allergy; eosinophilic esophagitis; food allergy; peanut allergy.

Correspondence
Christiane Sokollik, MD, Division of Pediatric Gastroenterology, Hepatology and Nutrition, University Children's Hospital, Inselspital, University of Bern; Freiburgstrasse, 3010 Bern, Switzerland.
Tel.: +41-31-632-9482
Fax: +41-31-632-9837
E-mail: christiane.sokollik@insel.ch

Accepted for publication 1 October 2015

DOI:10.1111/all.12780

Edited by: Hans-Uwe Simon

Abstract

Food allergies are a global health issue with increasing prevalence. Allergic reactions can range from mild local symptoms to severe anaphylactic reactions. Significant progress has been made in diagnostic tools such as component-resolved diagnostics and its impact on risk stratification as well as in therapeutic approaches including biologicals. However, a cure for food allergy has not yet been achieved and patients and their families are forced to alter eating habits and social engagements, impacting their quality of life. New technologies and improved *in vitro* and *in vivo* models will advance our knowledge of the pathogenesis of food allergies and multicenter-multinational cohort studies will elucidate interactions between genetic background, lifestyle, and environmental factors. This review focuses on new insights and developments in the field of food allergy and summarizes recently published articles.

Food allergy is an adverse, reproducible immune-mediated reaction to a given food. The most common allergens affecting infants are milk and egg. Peanuts, tree nuts, seafood, eggs, and milk commonly trigger allergic reactions in older children. In adults, pollen allergy often leads to cross-reactive food allergies. Allergic reactions can range from mild local symptoms, for example, in oral allergy syndrome (OAS), to severe life-threatening anaphylaxis. These reactions are absent during avoidance of the specific trigger. The underlying immune responses can be classified as IgE-mediated, non-IgE-mediated, or a mixture of both (Fig. 1). However, the pathogenesis of food allergy is still not completely understood. Importantly, the prevalence of food allergies is rising in both developed and developing countries, especially over the last 10–15 years (1), which increases the personal as well as global health burden. New diagnostic tools allow for better risk stratification of allergic reactions, but therapeutic options are still limited.

In this review, we will examine recent publications and their impact on our knowledge of the epidemiology, pathogenesis, diagnosis, and management of food allergy. The primary aim is to summarize novelties and put them into perspective rather than providing a comprehensive review.

Abbreviations
AAI, adrenaline auto-injector; AIT, allergen-specific immunotherapy; BAT, basophil activation test; CMPA, cow's milk protein allergy; CRD, component-resolved diagnostics; EoE, eosinophilic esophagitis; FPE, food protein enteropathy; FPIAP, food protein-induced allergic proctocolitis; FPIES, food protein-induced enterocolitis syndrome; HRQL, health-related quality of life; HWP, hydrolyzed wheat protein; IL, interleukin; nsLTP, nonspecific lipid-transfer protein; OAS, oral allergy syndrome; OFC, oral food challenge; OIT, oral immunotherapy; PA, peanut allergy; sBT, serum basal tryptase; sIgE, specific IgE; SPT, skin prick test; UA, uric acid; α-Gal, galactose-α-1,3-galactose.

Epidemiology

The prevalence of food allergy is not well established; it varies widely according to the methodology used to diagnose a food allergy. In a systematic review and meta-analysis of European studies, the self-reported lifetime prevalence of allergy to cow's milk was 6.0% but only 0.6% for positive food challenge (2). The EuroPrevall project has set up three complementary studies: a birth cohort study (3), a

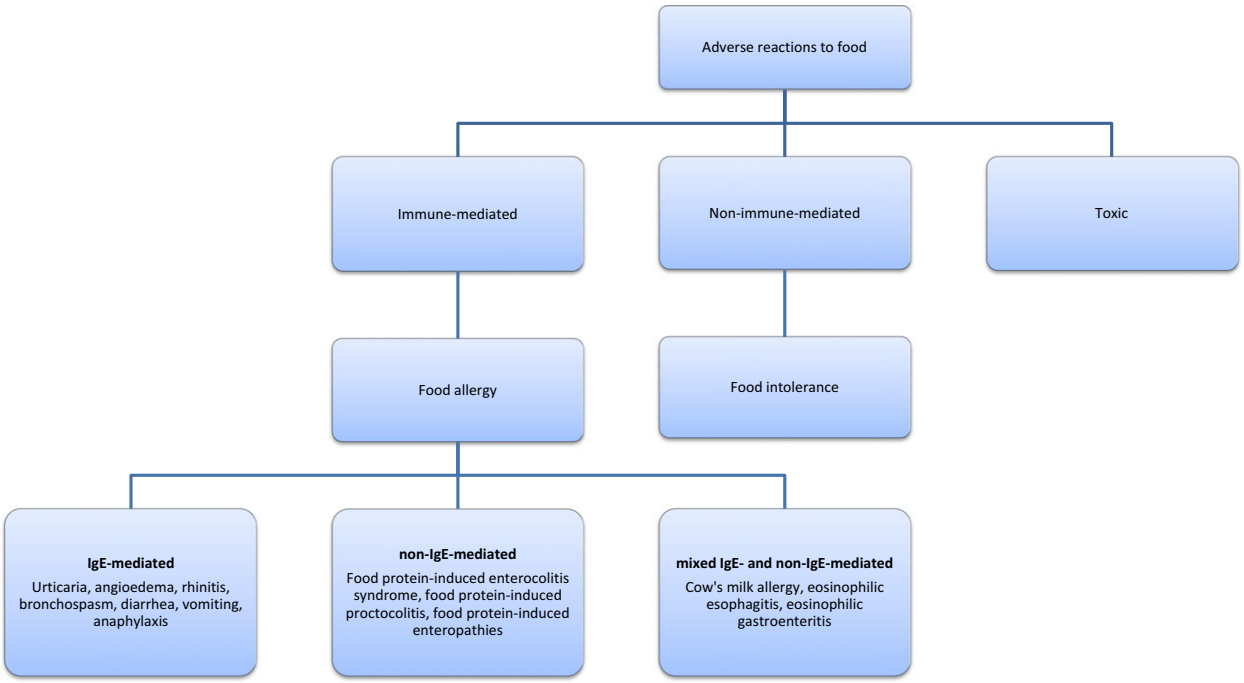

Figure 1 Classification of food allergy.

general population survey (4), and a cross-sectional study in specialized allergy outpatient clinics (5) to better answer arising epidemiological questions. Using the EuroPrevall allergen library (6), the prevalence of IgE sensitization in adults ranged from 6.6% in Iceland to 23.6% in Switzerland (7). Importantly, the relative prevalence of sensitization against the different foods between each country was well preserved suggesting a true difference between populations. In children from the EuroPrevall birth cohort, the incidence of challenge-proven cow's milk protein allergy (CMPA) was 0.54%, with national incidences ranging from <0.3% to 1% (8).

Allergens

Food allergens can be classified as plant food allergens with pollen allergen cross-reactive responses, plant food allergens without pollen allergen cross-reactivity, or animal-derived food allergens.

Profilin, a pan-allergen found in high concentrations in grass pollen and melon, is considered to be a minor respiratory allergen which causes only mild food allergies. However, it has been shown that patients exposed to high levels of grass pollen can have severe food reactions even to low doses of profilin (9). Geographical differences in exposure to pollen allergens thus may explain and influence the grades of reactions to certain food allergens.

Nonspecific lipid-transfer proteins (nsLTP) are one of the main causes of systemic allergic reactions, particularly in the Mediterranean area. These nsLTP are found in higher plants, such as fruits and nuts/peanuts, and are involved in plant defenses against fungi and bacteria. Due to their compact secondary structure, they exhibit extreme resistance to gastrointestinal proteolysis, pH changes, and thermal processing. In a large Italian cohort, it has been shown that severe reactions occur more often in patients with reactivity to multiple (>5) nsLTP (10). Furthermore, the authors found that co-sensitization to PR-10 and/or profilins was associated with milder symptoms (10). Therefore, testing patients for sensitization profiles may enable risk stratification and prediction of reaction patterns.

While most food-allergic reactions occur rapidly after ingestion, allergy to red meat can present with severe reactions several hours after intake. Interestingly, in meat allergy the reactions are not only directed against proteins but also against the carbohydrate galactose-α-1,3-galactose (α-Gal). One potential hypothesis to explain this delay in symptom onset is that digestion and metabolism of lipids delays the appearance of the allergen α-Gal in the circulation (11). A recent study also demonstrated that several α-Gal-containing beef allergens are heat-stable, explaining the preservation of meat allergenicity after heat treatment such as cooking (12).

Sensitization to food allergens can also occur via repeated transdermal exposure. Data from a study performed in mice suggest that transdermal administration of hydrolyzed wheat protein (HWP) through skin patches results in production of specific IgE (sIgE) and induction of a type 2 cytokine response (13). Further evidence for transdermal sensitization has been shown in a recent epidemiological study, where Japanese women who used a facial soap containing HWP were more likely to suffer from wheat protein allergy than women who had never used this skin care product (14).

Cross-reactivity and co-sensitization

The occurrence of cross-reactivity to different allergens in a single patient is well known. One well-characterized mechanism is IgE cross-reactivity to structurally similar epitopes, known as OAS, which can occur in birch pollen-sensitized patients, among others. Additionally, T-cell cross-reactivity can occur independently of IgE cross-reactivity. Cross-reactivity between Bet v 1 (birch) and the related food allergens Mal d 1 (apple) and Api g 1 (celery) was demonstrated in a T-cell-mediated reaction even when IgE reactivity was eliminated by pepsin digestion of allergens (15). Furthermore, mice who were sensitized to cashew allergen and then exposed to a homologous walnut allergen developed an allergic reaction to the latter, suggesting the activation of cashew-specific type 2 T helper (T_h2) cells by walnut which led to walnut sIgE production (16). Additionally, in an oral challenge study, children diagnosed with tree nut allergy reacted to peanuts and/or other tree nuts despite a negative skin prick test, which detects IgE sensitizations, for the challenged nut (17).

Combined sensitization to tree nuts and peanuts is very common; however the underlying mechanisms are not well understood. sIgE inhibition experiments demonstrated no cross-reactivity between the major allergens for hazelnut (Cor a 14) and peanut (Ara h 2), implying that primary sensitization rather than cross-reactivity is the underlying cause of co-sensitization (18). Alternatively, the Kiwi fruit allergens Act d 12 and Act d 13 have been demonstrated to be highly cross-reactive with homologous counterparts from peanut and tree nuts (19).

Pathogenesis and pathophysiology

IgE-mediated food allergy occurs when food allergen-specific IgE antibodies are developed after an initial contact with an allergen. Antigen-presenting cells phagocytose food proteins, process them, and present them to T helper cells. These in turn release pro-inflammatory cytokines (IL-5, IL-13 and IL-14) in a predominantly T_h2 response. This results in the activation of B cells, which produce sIgE. A second exposure to the same allergen results in IgE binding and activation of eosinophils, basophils, and mast cells, which release mediators such as histamine to cause typical symptoms, including urticaria, rhinitis, angioedema, bronchospasm, laryngospasm, or anaphylaxis (Fig. 2). Interestingly, a T_h2 response in

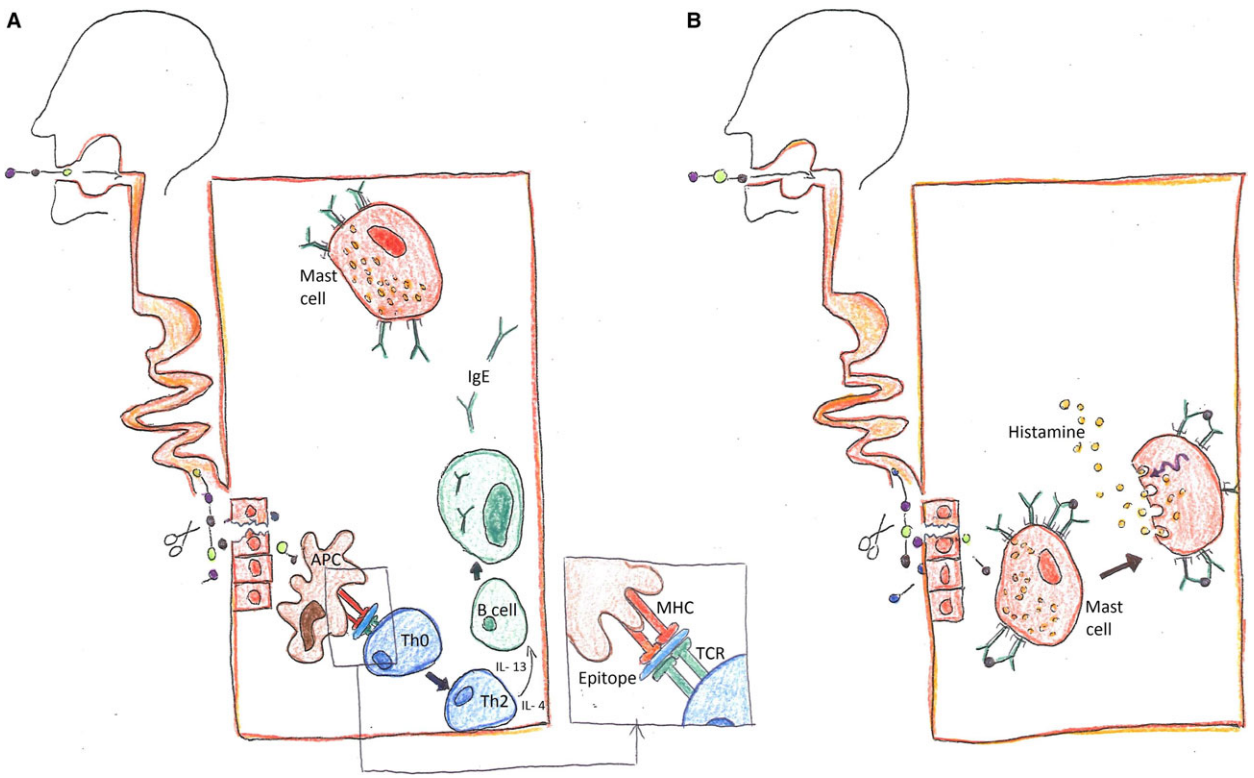

Figure 2 Pathomechanism of IgE-mediated food allergy. (A) Sensitization to specific allergens in genetically predisposed individuals occurs via microlesions in the gastrointestinal tract, the respiratory tract, or the skin. Dendritic cells acquire allergens which have crossed these barriers and present them to T helper cells which differentiate into T_h2 cells. The resulting release of inflammatory cytokines such as IL-4, IL-5, and IL-13 subsequently stimulates B cells to produce sIgE. (B) A second contact with the same allergen leads to sIgE binding and cross-linking with activation of mast cells, eosinophils, and basophils. Mediators such as histamine are released in turn causing allergic reactions with symptoms including urticaria, angioedema, rhinitis, diarrhea, vomiting, bronchospasm, laryngospasm, or anaphylaxis. IL, interleukin; MHC, major histocompatibility complex; TCR, T-cell receptor; and T_h2 cell, type 2 T helper cell.

children at 3 years of age was demonstrated prior to the detection of sIgE immunoglobulin (20). This indicates that allergen-specific T_h2 responses are primed in early life.

Metabolomic analysis revealed an increase in the alarmin uric acid (UA) in sensitized mice and peanut-allergic children. Depletion of UA led to a reduction in sIgE and protection from anaphylaxis in sensitized mice (21). From this study, it can be hypothesized that UA, which is released during local tissue damage and can activate dendritic cells, is a critical mediator in peanut allergy development (21).

While the pathogenesis of non-IgE-mediated food allergy is significantly less well-described, a T cell-mediated process is hypothesized. Children with non-IgE-mediated eosinophilic gastrointestinal disorders such as food protein-induced enterocolitis syndrome (FPIES), food protein-induced proctocolitis (FPIP), and food protein-induced enteropathy showed a T_h2 cytokine profile of their *in vitro*-stimulated peripheral blood mononuclear cells with increased levels of IL-3, IL-5, and IL-13 (22). Eosinophils are recruited by these cytokines which leads to an eosinophilic inflammation of the gastrointestinal tract.

Eosinophilic esophagitis (EoE) is a chronic T_h2 type inflammatory disease limited to the esophagus with complex interactions between innate and adaptive immune cells (Fig. 3) (23). Interplay between IgE- and non-IgE-mediated allergic reactions is hypothesized as an underlying mechanism in this chronic disease. Initial events involve a disrupted esophageal epithelial barrier which may increase epithelial permeability to allergens. A reduction in the desmosomal cadherin desmoglein-1 (DSG1), an intercellular adhesion molecule, has been found in patients with active EoE (24). This loss of DSG1 also induces the release of pro-inflammatory mediators, increasing the inflammation in active EoE. A recent study found that recruited eosinophils form eosinophil extracellular traps and the production of antimicrobial peptides is increased in active EoE (25). Despite the activation of these antimicrobial reactions, the precise role of microbes in the pathogenesis of EoE has yet to be elucidated. In one study, 43% of patients with EoE had sIgE against *Candida albicans* (26). However, all these patients were previously treated with topical steroids, which predisposes them to *C. albicans* infections (26). Studies examining the local microbiome of the esophagus in EoE may help clarify the influence of microbes in the development of this inflammatory disease. The first of such studies has already shown a significant increase in *Haemophilus* species present in patients with untreated EoE (27).

A positive family history is a strong risk factor for development of food allergy suggesting a central role of genetic factors in food allergy. Loss-of-function mutations of the filaggrin gene are relatively common and associated with ichthyosis vulgaris, atopic eczema, and dermatitis. Filaggrin is a protein involved in the maintenance of an effective skin barrier and the regulation of skin hydration (28). It has been shown to regulate the permeability of the skin to diverse substances, including allergens (28). Importantly, filaggrin appears to play a role in food allergy, as it was shown that children with loss-of-function filaggrin genetic variants were

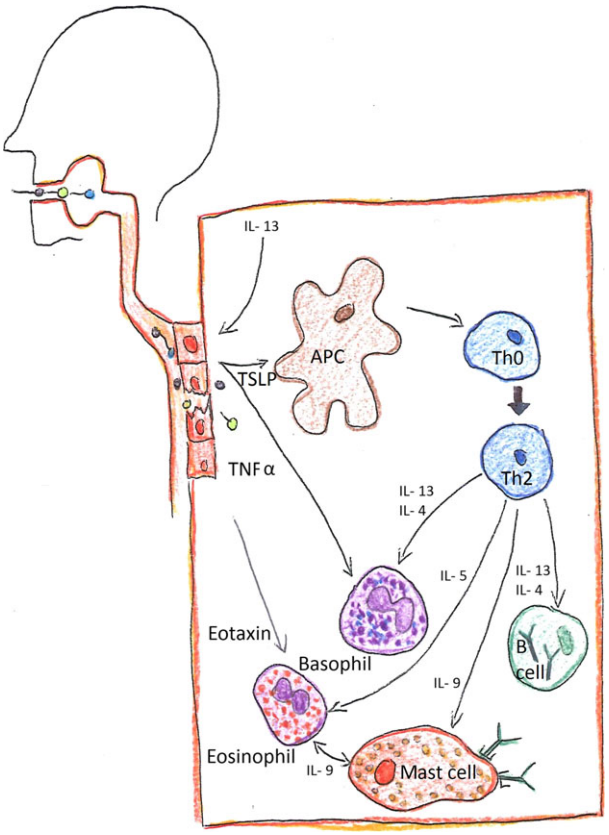

Figure 3 Pathomechanism of eosinophilic esophagitis (EoE). Esophageal epithelial barrier function is disrupted in EoE allowing allergen crossing of the epithelial barrier. Epithelial cells release cytokines (TSLP, eotaxin) and thereby recruit and activate antigen-presenting cells and other immune cells. The vicious cycle is expanded by differentiation of T helper cells into T_h2 cells and the release of further cytokines (IL-4, IL-5, IL-9, and IL-13) amplifying the inflammatory response. APC, antigen-presenting cell; IL, interleukin; T_h2 cell, type 2 T helper cell; TNFα, tumor necrosis factor α; TSLP, thymic stromal lymphopoietin.

1.5 times more likely to react during food challenge to at least one food as compared to carriers of the wild-type alleles (29).

The use of several emerging research technologies, combined with already-established techniques, will advance and expand the study of food allergy. Immortalization of murine bone marrow-derived immune cells, inducible single cell type ablation in mouse models and humanized mice will help to elucidate and to better understand the underlying pathophysiological mechanisms of allergic diseases (30). Ongoing research using these techniques currently focuses on mast cells, basophils, and regulatory B cells and their role in promoting allergic reaction and alternatively inducing allergen tolerance (31, 32).

Transcriptomic and proteomic methods can be used to identify undescribed epitopes for further reactivity analysis. These approaches enabled the identification of several new Timothy grass antigens which are targeted by T cells and not

by sIgE (33). They also permitted the evaluation of the T cell-activating potential of these Timothy grass antigens (33). These methodologies may facilitate the development of specific T cell-targeted immunotherapies in the future.

Additionally component-resolved diagnostics (CRD) which use automated microarrays with highly pure, standardized recombinant allergens will improve the characterization of the type of allergic reaction by enabling the discernment between multiple sensitizations and cross-reactivity (34). Determination of the crystal structure of allergens and their changes by mutations will further the understanding of consequences of IgE recognition and cross-reactivity (35).

Diagnosis

The diagnosis of food allergy is based on clinical symptoms. An in-depth clinical history is important to identify the triggering food allergen (36), while a full dietary history is a prerequisite for further diagnostic tests (37). Based on this specific IgE (sIgE) measurements and skin prick test (SPT) may identify a sensitization to a specific allergen. However, positive results in these assays do not necessarily predict the existence of a clinically significant food allergy. It may be tempting to use large test batteries, but these may lack specificity and return many false-positive results. Therefore, the EAACI food allergy and anaphylaxis guidelines recommends at present testing for specific food and aeroallergens related to the clinical presentation, age, geographic location, and ethnic dietary habits of the patient (38). An emerging method to improve and standardize immunoassays is the use of monoclonal allergen sIgE as controls, which can be produced by hybridomas (39).

Importantly, a skin prick test should preferably utilize fresh foods, especially fruits and vegetables, instead of a commercial extracts. Production of these commercial extracts via thermal processing may destroy heat-labile proteins which contribute to the allergenicity of the foods, thereby producing false-negative results (40).

While both SPT and sIgE are utilized in the diagnosis of allergic sensitization, recent studies suggest that these two assays are not interchangeable tests as they show only a moderate agreement in young children. One study also suggests SPT results are more closely related to clinical symptoms than sIgE in children under the age of 5 (41). Furthermore in adult patients with birch pollen-associated plant food allergy, also termed OAS, the level of IgE, IgG4, or IgA specific to most Bet v 1-related allergens did not correlate with clinical allergy (42). However, all peach- and soy-allergic patients had a positive basophil activation test (BAT) (42). The BAT can be considered as an *ex vivo* provocation test, where basophils respond with degranulation to different allergens (43). Thus, different allergy tests complement each other and their results need to be analyzed conjunctively in order to properly diagnose allergies and identify their contributing allergens.

The prediction of the severity of an allergic reaction is of utmost clinical importance after diagnosis of an allergy and identification of the triggering allergen. A reliable marker to predict the risk of anaphylaxis in children with hymenoptera venom allergy is serum basal tryptase (sBT), a marker for mast cell activity. Anaphylactic reaction in food allergy is most often associated with tree nut/peanut allergy as compared to allergies to other food types. Interestingly, children with nut/peanut allergies had significantly higher sBT levels than those with milk or egg allergies, suggesting that sBT levels may be useful as a predictive marker of anaphylaxis in children with food allergies (44).

The gold standard for food allergy diagnosis is an oral food challenge (OFC) which provides direct proof of the clinical relevance of an allergen. Importantly, risk stratification for an anaphylactic reaction prior to performing an OFC is advisable (45). The protective effect of a high total IgE level in patients with hymenoptera venom allergy has been well documented (46). Similarly, a low level of IgE leaves patients prone to more severe reactions (46). Saturation of IgE receptors by nonspecific IgE immunoglobulin impeding the binding of sIgE and secondary basophil degranulation is the hypothesized mechanism for these effects. Recent studies support the use of IgE levels in predicting allergic reactivity, and thus stratifying risk, as total IgE levels were also inversely correlated with responsiveness in OFCs in patients with hen's egg and CMPA allergies (47). Another method to predict reaction in OFC involves testing for single components using CRD. For example, in hazelnut- and peanut-allergic patients the component sIgE Cor a 14 and Ara h 2 discriminated better between tolerant and allergic patients than hazelnut or peanut sIgE (48). In children with CMPA who were egg-sensitized but had never ingested egg, the probability of a positive OFC was determined to be 94% when the wheal size was $\geq$ 8 mm in the egg white SPT and/or egg white sIgE was $\geq$ 8.36kU/l (49). Thus, in some patients OFC may be unnecessary or postponed depending on their IgE repertoire composed of total IgE, sIgE, and component sIgE.

A recent study suggests quantification of casein-specific IL-4- and IL-13-secreting T_h2 cells in children with suspected CMPA could provide diagnostic guidance for this food allergy (50). This study found that the number of these casein-specific T_h2 cells in children with confirmed CMPA was significantly higher compared with children without CMPA (50). Furthermore, the number of casein-specific IL-4- and IL-13-secreting T_h2 cells was inversely correlated with the cumulative dose of tolerated cow's milk (50). Confirmation of these findings in larger studies will provide further evidence that this functional assay can help improve diagnosis, stratify risk, and potentially eliminate the need for OFCs in certain CMPA cases.

Allergen-specific immunotherapy (AIT) targets CD4 + T cells resulting in suppression of type 1 (T_h1) and type 2 (T_h2) helper T cells and generation of regulatory T cells. As the frequency of allergen-specific CD4 + T cells is low, a promising tool to monitor allergen-specific CD4 + T cells during AIT could be detection via MHC class II/peptide tetramer complexes. Unfortunately, a recent study showed that while specificity of this detection was very high, the sensitivity was quite low with only 12 of 27 allergen-specific T-cell clones (44%) detected (51). Therefore, quantification and

tracking of allergen-specific CD4+ T cells responses utilizing currently available techniques must be interpreted with caution.

Symptoms

Oral allergy syndrome is a localized immediate IgE-mediated food allergy to fruits and vegetables which occurs mainly in patients with sensitization to the major birch pollen allergen Bet v 1 due to cross-reactivity with plant food-derived allergens (Mal d 1—apple, Pru av 1—cherry, Cor a 1—hazelnut, Ara h 8—peanut). Oral allergy syndrome presents with itching and swelling of the lips, tongue, and pharynx. Digestion by the gastrointestinal tract, heating, and processing reduces the IgE-mediated allergenicity of these allergens; therefore OAS reactions occur only after ingestion of raw food and systemic reactions do not usually occur (40). Unfortunately, successful AIT targeting birch pollen does not influence the occurrence of OAS, possibly due to some unique structural characteristics of Bet v 1 which are not present in PR-10-related foods such as hazelnut or apple (52).

Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction. Typical organ manifestations are listed in Table 1. Epidemiological studies suggest that in up to 30% of cases cofactors such as physical exercise, alcohol consumption, co-administration of nonsteroidal anti-inflammatory drugs, or concomitant infections trigger a severe anaphylactic reaction (53). These cofactors, also known as augmenting factors, may lower the threshold for a reaction, increase the severity, or reverse a previously acquired clinical tolerance (54). Advice for patients should therefore always include possible risk factors and appropriate preventive measures for an anaphylactic reaction. The sensitization profile of children with food allergy should also be taken into consideration when counseling. Children with history of anaphylaxis were more likely to have high IgE to raw peanut and multiple positivity to Ara h 1, Ara h 2, and Ara h 3 (55).

Management

The two main components of the management of food allergy are avoidance of the triggering food and preparation for accidental exposure. The extent of responsibility assigned to the general public via introduction of public health policies is a highly debated subject in the field of food allergy (56). One important step is correct labeling of food ingredients and appropriate training of staff in the food industry. Mislabeling is a particular concern as it is still common, especially in non-pre-packaged food with voluntary allergen labeling, such as bakery products (57).

Table 1 Organ manifestations of anaphylactic reactions

Ear, nose, throat	Swelling of lips/tongue, itching of lips/tongue, rhinorrhea, nasal obstruction
Skin	Urticaria, flush, rash, angioedema, exacerbation of eczema
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal pain
Respiratory	Cough, dyspnoea, wheeze
Systemic	Hypotension, shock

Despite increased awareness, annual incidence rates of accidental exposure to peanut remains stable around 12–14% in peanut-allergic children over the last 10 years (58, 59). First-line emergency medication in anaphylaxis consists of intramuscular adrenaline delivery via an auto-injector; antihistamines and corticosteroids are not recommended as front-line treatment (60). Despite these indications, adrenaline auto-injectors (AAI) remain underused. Therefore, it is essential to educate patients, their caregivers, and doctors on proper assessment of the risks of accidental allergic reactions and management of emergency situations (56).

New promising therapies for IgE-mediated food allergy are currently being evaluated. Allergen-specific immunotherapy, including both sublingual and oral (OIT) administration, is deployed to induce tolerance to specific allergens. However, not all studies examining AIT have shown a benefit and the risk of adverse reactions such as anaphylaxis requires consideration (61, 62). Furthermore, tolerance may be only transient as after discontinuation of a maintenance dose of the allergen some patients lose their tolerance (63). This clinical observation of tolerance loss occurred in concordance with an observed lack of immunologic change in skin prick tests as well as *in vitro* assays. In children with CMPA, determination of component sIgE prior to OIT was shown to be a useful predictor for OIT success (64). In this study, high levels of α-lactalbumin, β-lactoglobulin, and casein sIgE were associated with tolerance of a lower dose of cow's milk, while a larger increase in IgG_4 concentration was associated with better tolerance.

Biological agents, also termed biologicals, are relatively newer therapeutics that are synthesized by living organisms. These molecules target specific mediators of an allergic reaction such as cytokines, antibodies, or receptors (65). One such biological is omalizumab, a monoclonal anti-IgE antibody, which is already approved for asthma therapy. When omalizumab is administered parallel to OIT, the efficacy of OIT can be improved and a reduction in systemic reactions can occur (66). Therefore, in highly reactive patients, biologicals may become an important adjuvant therapeutic tool. However, in a prospective study in EoE patients, omalizumab failed to improve symptoms or reduce the eosinophilic count in esophageal tissue (67). Further targets including IL-5 and IL-9 are already under investigation (65), and increased understanding of the pathogenesis of the different food allergy subtypes will result in the emergence of new targets.

Different preventative measures aimed at food allergies are highly debated. For example, studies show that in infants at high risk for developing an allergic disease the use of extensively or partially hydrolyzed formula and avoidance of standard cow's milk-based formula for the first 4 months is beneficial if breastfeeding is not possible (68, 69). However, many of these studies which examine preventative measures lack well-defined outcome parameters and are underpowered (70).

Quality of life

Constant vigilance in the avoidance of specific foods to prevent an allergic reaction as well as the management of an acute reaction (including application of adrenaline) often exerts immense pressure on patients and their caregivers. Validated health-related quality of life (HRQL) instruments are available for children, adolescents, and adults with food allergies and for their parents or caregivers (71). Interestingly, one study on HRQL showed that experience of anaphylaxis had limited impact on HRQL; it also found that allergies to fish and milk in adults and peanuts and soy in children caused greater HRQL impairment as compared to other foods (72). A prospective cohort study examining food allergy-associated quality of life found that performing a food challenge improved the quality of life irrespective of the outcome of the challenge (73). This improvement was sustained for tolerant patients, whereas it waned after 6 months in allergic patients. The utilization of HRQL instruments may allow physicians to derive unexpected insights into factors impairing the health-related quality of life in patients. Ultimately, this information will help to improve the management of food-allergic patients.

Cow's milk protein allergy and peanut allergy

Both CMPA and peanut allergy (PA) are relatively common allergies with some specific clinical features and new findings. A recent study demonstrated that two-thirds of children with CMPA will outgrow their allergy within the first year of life (8). However, children with specific IgEs at initial diagnosis are less likely to tolerate cow's milk during rechallenge at 1 year of age than children with non-IgE associated CMPA (8). In contrast to CMPA, in which the majority of patients outgrow their allergy, only 22% of children who were diagnosed with PA at 1 year of age developed tolerance at 4 years of age (74).

Interestingly, a microarray analysis demonstrated that multiple allergens can be detected in human breast milk, including cow's milk allergens (75). This may help explain why CMPA can develop in breastfed children in the absence of cow's milk ingestion. Similar to cow's milk protein allergens, peanut allergens such as Ara h 2 and Ara h 6 are transferred in human breast milk and are immunologically active (76). However, administration of human breast milk containing peanut allergens appeared to invoke tolerance in mice subjected to an oral peanut sensitization procedure (76). A recent intervention study in infants at high risk for atopic disease has shown that early introduction of peanut into the diet in comparison with avoidance of peanut resulted in a dramatic reduction in PA frequency at 60 months of age (77). These findings will invoke questions addressing optimal timing and appropriate protective measures for the introduction of different allergens into the diet of infants.

Peanut allergy has a prevalence of approximately 1–2% in children in the Western Hemisphere, whereas in Asian countries it is very rare. Interestingly, Australian infants with Asian-born parents are over-represented among children with PA in Australia. It is hypothesized that genetic-environmental interactions may explain these findings, including differences in climate, microbial exposures, and dietary habits (78). Specific IgE to either Ara h 2 or Ara h 6 can be used to confirm PA in children and adults with high specificity (79). However, a relatively low sensitivity of 70% in adults means that a negative test result does not necessarily exclude PA. In a study examining age-dependent IgE recognition patterns in PA, Ara h 1, Ara h 2, and Ara h 3 were only positive in patients who experienced allergy onset in childhood prior to the age of 14 (80). Patients with late-onset PA were mainly sensitized to peanut components that were cross-reactive to pollen (Ara h 8) or plant-derived food (Ara h 9). The exact mechanism underlying these different recognition patterns is not currently known. It is speculated that the observed impaired intestinal barrier in children with a genetic predisposition for allergic diseases leads to an increased intestinal permeability and allows sensitization to storage proteins.

Geographical differences in sensitizations patterns have also been demonstrated for PA. In the Mediterranean population, the prevalence of sensitization to Ara h 2 is lower and to Ara h 9 higher as compared with northern European countries. Interestingly, in a Spanish study, the BAT to Ara h 2 showed a high sensitivity for PA, but the correlation with sIgE for Ara h 2 was poor (81). These results indicate that different tests require evaluation in different populations.

Another clinically relevant finding using component sIgE is the high predictive value of Ara h 2 for systemic reactions to peanut including anaphylaxis. In two different cohorts including children and adults the level of sIgE to Ara h 2 highly correlated with the probability for a systemic reaction (48, 80).

Conclusion

In conclusion, food allergy is an evolving field with many questions that remain to be answered. Cohort studies such as EuroPrevall will enable the standardization of diagnostic and therapeutic approaches as well as the collection of data and biological material for translational and clinical research. Future basic and clinical studies are needed to further elucidate the pathomechanism of food allergy and to improve preventive strategies, diagnostic tools, and therapeutic options.

Acknowledgement

The authors thank Daniela Hofmann for drawing the figures.

Author contributions

AC, DR, and CS participated in conception and design of the review, analysis and interpretation of published manuscripts, drafting and revising the of the review, and final approval of the version to be published.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn J, Fiocchi A et al. A global survey of changing patterns of food allergy burden in children. *World Allergy Organ J* 2013;**6**:21.
2. 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.
3. Keil T, McBride D, Grimshaw K, Niggemann B, Xepapadaki P, Zannikos K et al. The multinational birth cohort of EuroPrevall: background, aims and methods. *Allergy* 2010;**65**:482–490.
4. Kummeling I, Mills EN, Clausen M, Dubakiene R, Perez CF, Fernandez-Rivas M et al. The EuroPrevall surveys on the prevalence of food allergies in children and adults: background and study methodology. *Allergy* 2009;**64**:1493–1497.
5. Fernandez-Rivas M, Barreales L, Mackie AR, Fritsche P, Vazquez-Cortes S, Jedrzejczak-Czechowicz M et al. The EuroPrevall outpatient clinic study on food allergy: background and methodology. *Allergy* 2015;**70**:576–584.
6. Hoffmann-Sommergruber K, Mills EN, Vieths S. Coordinated and standardized production, purification and characterization of natural and recombinant food allergens to establish a food allergen library. *Mol Nutr Food Res* 2008;**52**(Suppl. 2):S159–S165.
7. Burney PG, Potts J, Kummeling I, Mills EN, Clausen M, Dubakiene R et al. The prevalence and distribution of food sensitization in European adults. *Allergy* 2014;**69**:365–371.
8. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L et al. Incidence and natural history of challenge-proven cow's milk allergy in European children - EuroPrevall birth cohort. *Allergy* 2015;**70**:963–972.
9. Alvarado MI, Jimeno L, De La Torre F, Boissy P, Rivas B, Lazaro MJ et al. Profilin as a severe food allergen in allergic patients overexposed to grass pollen. *Allergy* 2014;**69**:1610–1616.
10. Scala E, Till SJ, Asero R, Abeni D, Guerra EC, Pirrotta L et al. Lipid transfer protein sensitization: reactivity profiles and clinical risk assessment in an Italian cohort. *Allergy* 2015;**70**:933–943.
11. Steinke JW, Platts-Mills TA, Commins SP. The alpha-gal story: lessons learned from connecting the dots. *J Allergy Clin Immunol* 2015;**135**:589–596.
12. Apostolovic D, Tran TA, Hamsten C, Starkhammar M, Cirkovic Velickovic T, van Hage M. Immunoproteomics of processed beef proteins reveal novel galactose-alpha-1,3-galactose-containing allergens. *Allergy* 2014;**69**:1308–1315.
13. Adachi R, Nakamura R, Sakai S, Fukutomi Y, Teshima R. Sensitization to acid-hydrolyzed wheat protein by transdermal administration to BALB/c mice, and comparison with gluten. *Allergy* 2012;**67**:1392–1399.
14. Fukutomi Y, Taniguchi M, Nakamura H, Akiyama K. Epidemiological link between wheat allergy and exposure to hydrolyzed wheat protein in facial soap. *Allergy* 2014;**69**:1405–1411.
15. Bohle B. The impact of pollen-related food allergens on pollen allergy. *Allergy* 2007;**62**:3–10.
16. Kulis M, Burks AW. Effects of a pre-existing food allergy on the oral introduction of food proteins: findings from a murine model. *Allergy* 2015;**70**:120–123.
17. Ball H, Luyt D, Bravin K, Kirk K. Single nut or total nut avoidance in nut allergic children: outcome of nut challenges to guide exclusion diets. *Pediatr Allergy Immunol* 2011;**22**:808–812.
18. Masthoff LJ, van Hoffen E, Mattsson L, Lidholm J, Andersson K, Zuidmeer-Jongejan L et al. Peanut allergy is common among hazelnut-sensitized subjects but is not primarily the result of IgE cross-reactivity. *Allergy* 2015;**70**:265–274.
19. Sirvent S, Canto B, Gomez F, Blanca N, Cuesta-Herranz J, Canto G et al. Detailed characterization of Act d 12 and Act d 13 from kiwi seeds: implication in IgE cross-reactivity with peanut and tree nuts. *Allergy* 2014;**69**:1481–1488.
20. Reubsaet LL, Meerding J, Scholman R, Arets B, Prakken BJ, van Wijk F et al. Allergen-specific Th2 responses in young children precede sensitization later in life. *Allergy* 2014;**69**:406–410.
21. Kong J, Chalcraft K, Mandur TS, Jimenez-Saiz R, Walker TD, Goncharova S et al. Comprehensive metabolomics identifies the alarmin uric acid as a critical signal for the induction of peanut allergy. *Allergy* 2015;**70**:495–505.
22. Morita H, Nomura I, Orihara K, Yoshida K, Akasawa A, Tachimoto H et al. Antigen-specific T-cell responses in patients with non-IgE-mediated gastrointestinal food allergy are predominantly skewed to T(H)2. *J Allergy Clin Immunol* 2013;**131**:590–592.
23. Straumann A, Aceves SS, Blanchard C, Collins MH, Furuta GT, Hirano I et al. Pediatric and adult eosinophilic esophagitis: similarities and differences. *Allergy* 2012;**67**:477–490.
24. Sherrill JD, Kc K, Wu D, Djukic Z, Caldwell JM, Stucke EM et al. Desmoglein-1 regulates esophageal epithelial barrier function and immune responses in eosinophilic esophagitis. *Mucosal Immunol* 2014;**7**:718–729.
25. Simon D, Radonjic-Hosli S, Straumann A, Yousefi S, Simon HU. Active eosinophilic esophagitis is characterized by epithelial barrier defects and eosinophil extracellular trap formation. *Allergy* 2015;**70**:443–452.
26. Simon D, Straumann A, Dahinden C, Simon HU. Frequent sensitization to *Candida albicans* and profilins in adult eosinophilic esophagitis. *Allergy* 2013;**68**:945–948.
27. Harris JK, Fang R, Wagner BD, Choe HN, Kelly CJ, Schroeder S et al. Esophageal microbiome in eosinophilic esophagitis. *PLoS ONE* 2015;**10**:e0128346.
28. Sandilands A, Sutherland C, Irvine AD, McLean WH. Filaggrin in the frontline: role in skin barrier function and disease. *J Cell Sci* 2009;**122**:1285–1294.
29. van Ginkel CD, Flokstra-de Blok BM, Kollen BJ, Kukler J, Koppelman GH, Dubois AE. Loss-of-function variants of the filaggrin gene are associated with clinical reactivity to foods. *Allergy* 2015;**70**:461–464.
30. Siebenhaar F, Falcone FH, Tiligada E, Hammel I, Maurer M, Sagi-Eisenberg R et al. The search for mast cell and basophil models – are we getting closer to pathophysiological relevance? *Allergy* 2015;**70**:1–5.
31. Braza F, Chesne J, Castagnet S, Magnan A, Brouard S. Regulatory functions of B cells in allergic diseases. *Allergy* 2014;**69**:1454–1463.
32. Liu ZQ, Wu Y, Song JP, Liu X, Liu Z, Zheng PY et al. Tolerogenic CX3CR1 + B cells suppress food allergy-induced intestinal inflammation in mice. *Allergy* 2013;**68**:1241–1248.
33. Schulten V, Greenbaum JA, Hauser M, McKinney DM, Sidney J, Kolla R et al. Previously undescribed grass pollen antigens are the major inducers of T helper 2 cytokine-producing T cells in allergic individuals. *Proc Natl Acad Sci U S A* 2013;**110**:3459–3464.
34. Palomares O, Crameri R, Rhyner C. The contribution of biotechnology toward progress in diagnosis, management, and treatment of allergic diseases. *Allergy* 2014;**69**:1588–1601.
35. Devanaboyina SC, Cornelius C, Lupinek C, Fauland K, Dall'Antonia F, Nandy A et al. High-resolution crystal structure and IgE recognition of the major grass pollen allergen Phl p 3. *Allergy* 2014;**69**:1617–1628.
36. Turnbull JL, Adams HN, Gorard DA. Review article: the diagnosis and management of food allergy and food intolerances. *Aliment Pharmacol Ther* 2015;**41**:3–25.
37. Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K et al. The diagnosis of food

allergy: a systematic review and meta-analysis. *Allergy* 2014;**69**:76–86.
38. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014;**69**:1008–1025.
39. Lu CS, Hung AF, Lin CJ, Chen JB, Chen C, Shiung YY et al. Generating allergen-specific human IgEs for immunoassays by employing human epsilon gene knockin mice. *Allergy* 2015;**70**:384–390.
40. Masthoff LJ, Hoff R, Verhoeckx KC, van Os-Medendorp H, Michelsen-Huisman A, Baumert JL et al. A systematic review of the effect of thermal processing on the allergenicity of tree nuts. *Allergy* 2013;**68**:983–993.
41. Schoos AM, Chawes BL, Folsgaard NV, Samandari N, Bonnelykke K, Bisgaard H. Disagreement between skin prick test and specific IgE in young children. *Allergy* 2015;**70**:41–48.
42. Guhsl EE, Hofstetter G, Lengger N, Hemmer W, Ebner C, Froschl R et al. IgE, IgG4 and IgA specific to Bet v 1-related food allergens do not predict oral allergy syndrome. *Allergy* 2015;**70**:59–66.
43. Hoffmann HJ, Santos AF, Mayorga C, Nopp A, Eberlein B, Ferrer M et al. The clinical utility of basophil activation testing in diagnosis and monitoring of allergic disease. *Allergy* 2015;**70**:1393–1405.
44. Sahiner UM, Yavuz ST, Buyuktiryaki B, Cavkaytar O, Yilmaz EA, Tuncer A et al. Serum basal tryptase may be a good marker for predicting the risk of anaphylaxis in children with food allergy. *Allergy* 2014;**69**:265–268.
45. Agache I, Bilo M, Braunstahl GJ, Delgado L, Demoly P, Eigenmann P et al. *In vivo* diagnosis of allergic diseases–allergen provocation tests. *Allergy* 2015;**70**:355–365.
46. Sturm GJ, Heinemann A, Schuster C, Wiednig M, Groselj-Strele A, Sturm EM et al. Influence of total IgE levels on the severity of sting reactions in Hymenoptera venom allergy. *Allergy* 2007;**62**:884–889.
47. Horimukai K, Hayashi K, Tsumura Y, Nomura I, Narita M, Ohya Y et al. Total serum IgE level influences oral food challenge tests for IgE-mediated food allergies. *Allergy* 2015;**70**:334–337.
48. Beyer K, Grabenhenrich L, Hartl M, Beder A, Kalb B, Ziegert M et al. Predictive values of component-specific IgE for the outcome of peanut and hazelnut food challenges in children. *Allergy* 2015;**70**:90–98.
49. Alvaro M, Garcia-Paba MB, Giner MT, Piquer M, Dominguez O, Lozano J et al. Tolerance to egg proteins in egg-sensitized infants without previous consumption. *Allergy* 2014;**69**:1350–1356.
50. Michaud B, Aroulandom J, Baiz N, Amat F, Gouvis-Echraghi R, Candon S et al. Casein-specific IL-4- and IL-13-secreting T cells: a tool to implement diagnosis of cow's milk allergy. *Allergy* 2014;**69**:1473–1480.
51. Van Hemelen D, Mahler V, Fischer G, Fae I, Reichl-Leb V, Pickl W et al. HLA class II peptide tetramers vs allergen-induced proliferation for identification of allergen-specific CD4 T cells. *Allergy* 2015;**70**:49–58.
52. Roulias A, Pichler U, Hauser M, Himly M, Hofer H, Lackner P et al. Differences in the intrinsic immunogenicity and allergenicity of Bet v 1 and related food allergens revealed by site-directed mutagenesis. *Allergy* 2014;**69**:208–215.
53. Wolbing F, Fischer J, Koberle M, Kaesler S, Biedermann T. About the role and underlying mechanisms of cofactors in anaphylaxis. *Allergy* 2013;**68**:1085–1092.
54. Niggemann B, Beyer K. Factors augmenting allergic reactions. *Allergy* 2014;**69**:1582–1587.
55. Ciprandi G, Pistorio A, Silvestri M, Rossi GA, Tosca MA. Peanut anaphylaxis: the usefulness of molecular-based allergy diagnostics. *Allergy* 2015;**70**:129–130.
56. Muraro A, Agache I, Clark A, Sheikh A, Roberts G, Akdis CA et al. EAACI food allergy and anaphylaxis guidelines: managing patients with food allergy in the community. *Allergy* 2014;**69**:1046–1057.
57. Trendelenburg V, Enzian N, Bellach J, Schnadt S, Niggemann B, Beyer K. Detection of relevant amounts of cow's milk protein in non-pre-packed bakery products sold as cow's milk-free. *Allergy* 2015;**70**:591–597.
58. Yu JW, Kagan R, Verreault N, Nicolas N, Joseph L, St Pierre Y et al. Accidental ingestions in children with peanut allergy. *J Allergy Clin Immunol* 2006;**118**:466–472.
59. Cherkaoui S, Ben-Shoshan M, Alizadehfar R, Asai Y, Chan E, Cheuk S et al. Accidental exposures to peanut in a large cohort of Canadian children with peanut allergy. *Clin Transl Allergy* 2015;**5**:16.
60. Song TT, Worm M, Lieberman P. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. *Allergy* 2014;**69**:983–991.
61. de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K et al. Acute and long-term management of food allergy: systematic review. *Allergy* 2014;**69**:159–167.
62. Romantsik O, Bruschettini M, Tosca MA, Zappettini S, Della Casa Alberighi O, Calevo MG. Oral and sublingual immunotherapy for egg allergy. *Cochrane Database Syst Rev* 2014;**11**:CD010638.
63. Kopac P, Rudin M, Gentinetta T, Gerber R, Pichler C, Hausmann O et al. Continuous apple consumption induces oral tolerance in birch-pollen-associated apple allergy. *Allergy* 2012;**67**:280–285.
64. Kuitunen M, Englund H, Remes S, Moverare R, Pelkonen A, Borres MP et al. High IgE levels to alpha-lactalbumin, beta-lactoglobulin and casein predict less successful cow's milk oral immunotherapy. *Allergy* 2015;**70**:955–962.
65. Boyman O, Kaegi C, Akdis M, Bavbek S, Bossios A, Chatzipetrou A et al. EAACI IG Biologicals task force paper on the use of biologic agents in allergic disorders. *Allergy* 2015;**70**:727–754.
66. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;**132**:1368–1374.
67. Clayton F, Fang JC, Gleich GJ, Lucendo AJ, Olalla JM, Vinson LA et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology* 2014;**147**:602–609.
68. de Silva D, Geromi M, Halken S, Host A, Panesar SS, Muraro A et al. Primary prevention of food allergy in children and adults: systematic review. *Allergy* 2014;**69**:581–589.
69. Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy* 2014;**69**:590–601.
70. Lodge CJ, Lowe AJ, Allen KJ. Primary prevention of food allergy in children and adults. *Allergy* 2014;**69**:971–972.
71. Salvilla SA, Dubois AE, Flokstra-de Blok BM, Panesar SS, Worth A, Patel S et al. Disease-specific health-related quality of life instruments for IgE-mediated food allergy. *Allergy* 2014;**69**:834–844.
72. Saleh-Langenberg J, Goossens NJ, Flokstra-de Blok BM, Kollen BJ, van der Meulen GN, Le TM et al. Predictors of health-related quality of life of European food-allergic patients. *Allergy* 2015;**70**:616–624.
73. Soller L, Hourihane J, DunnGalvin A. The impact of oral food challenge tests on food allergy health-related quality of life. *Allergy* 2014;**69**:1255–1257.
74. Peters RL, Allen KJ, Dharmage SC, Koplin JJ, Dang T, Tilbrook KP et al. Natural history of peanut allergy and predictors of resolution in the first 4 years of life: a population-based assessment. *J Allergy Clin Immunol* 2015;**135**:1257–1266.
75. Pastor-Vargas C, Maroto AS, Diaz-Perales A, Villaba M, Casillas Diaz N, Vivanco F et al. Sensitive detection of major food allergens in breast milk: first gateway for allergenic contact during breastfeeding. *Allergy* 2015;**70**:1024–1027.
76. Bernard H, Ah-Leung S, Drumare MF, Feraudet-Tarisse C, Verhasselt V, Wal JM et al.

Peanut allergens are rapidly transferred in human breast milk and can prevent sensitization in mice. *Allergy* 2014;**69**:888–897.
77. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;**372**:803–813.
78. Koplin JJ, Peters RL, Ponsonby AL, Gurrin LC, Hill D, Tang ML et al. Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents. *Allergy* 2014;**69**:1639–1647.
79. Klemans RJ, Knol EF, Bruijnzeel-Koomen CA, Knulst AC. The diagnostic accuracy of specific IgE to Ara h 6 in adults is as good as Ara h 2. *Allergy* 2014;**69**:1112–1114.
80. Ballmer-Weber BK, Lidholm J, Fernandez-Rivas M, Seneviratne S, Hanschmann KM, Vogel L et al. IgE recognition patterns in peanut allergy are age dependent: perspectives of the EuroPrevall study. *Allergy* 2015;**70**:391–407.
81. Mayorga C, Gomez F, Aranda A, Koppelman SJ, Diaz-Perales A, Blanca-Lopez N et al. Basophil response to peanut allergens in Mediterranean peanut-allergic patients. *Allergy* 2014;**69**:964–968.