

Food allergy: definitions, prevalence, diagnosis and therapy

Ronald van Ree, Lars K. Poulsen, Gary WK Wong, Barbara K. Ballmer-Weber, Gao Zhongshan, Jia Xudong

ABSTRACT

Food allergy is phenotypically an extremely heterogeneous group of diseases affecting multiple organs, sometimes in an isolated way, sometimes simultaneously, with the severity of reactions ranging from mild and local to full-blown anaphylaxis. Mechanistically, it is defined as a Th2-driven immune disorder in which food-specific IgE antibodies are at the basis of immediate-type adverse reactions. The sites of sensitization and symptoms do not necessarily overlap. Food allergy, which is the theme of this paper, is often confused with other adverse reactions to food of both an immune (e.g., celiac disease) and non-immune (e.g., lactose intolerance) nature. To reliably diagnose food allergy, a careful history (immediate-type reactions) needs to be complemented with demonstration of specific IgE (immune mechanism) and confirmed by an oral challenge. Co-factors such as exercise, medication, and alcohol may help trigger food allergy and further complicate accurate diagnosis. Where food extract-based diagnostic tests are poorly correlated to symptom severity, new generation molecular diagnostics that measure IgE against individual food allergens provide clinicians and patients with more reliable symptom severity risk profiles. Molecular diagnostics also support establishing

Departments of Experimental Immunology and Otorhinolaryngology, Academic Medical Center, University of Amsterdam, The Netherlands(Ronald van Ree); Allergy Clinic, Copenhagen University Hospital at Gentofte, Denmark(Lars K. Poulsen); Department of Paediatrics and School of Public Health, Chinese University of Hong Kong, China(Gary WK Wong); Allergy Unit, Department of Dermatology, University Hospital Zürich, Switzerland(Barbara K. Ballmer-Weber); Allergy Research Center, Zhejiang University, China(Gao Zhongshan); Key Laboratory of Food Safety Risk Assessment of Ministry of Health, China National Centre for Food Safety Risk Assessment, China (Jia Xudong);

Corresponding Author: Jia Xudong, Email: jiaxudong2004@163.com

NOTE: [*Should there be any inconsistency between the Chinese version and the English version, the Chinese version shall prevail*](#)

whether food sensitization originates directly from exposure to food or indirectly (cross-reactivity) from pollen sensitization. Epidemiological surveys have indicated that allergy to peach primarily originates from peach consumption in Europe, whereas in China it is the result of primary sensitization to mugwort pollen, in both cases mediated by an allergen molecule from the same family. Epidemiological surveys give insight into the etiology of food allergy, the size of the problem (prevalence), and the risk factors involved, which together support evidence-based strategies for prevention. Over the past decade, food allergy has increased in the affluent world. Economic growth and urbanization in upcoming economies are likewise expected to lead to increased prevalence of food allergies, sometimes to different foods due to dietary habits. Molecular allergology and biotechnology now offer the possibility to combat the increasing burden of food allergy by developing safe immunotherapies for food allergy, using hypoallergenic mutant recombinant molecules. The first clinical trials to evaluate such approaches are underway. Last but not least, the identification and clinical risk characterization of a more and more complete list of food allergens additionally provides the allergenicity risk assessment of genetically modified foods a firmer basis.

[Key words] Food hypersensitivity; Epidemiology; Diagnosis; Immunotherapy

The symptomatology of food allergy is quite variable, and often symptoms originate from more than a single organ, including the oral cavity (oral allergy syndrome), the skin (urticaria and exacerbation of atopic eczema), the respiratory system (rhinitis and asthma), the gastrointestinal system (nausea, vomiting, abdominal pain, diarrhea), and additional symptoms such as conjunctivitis, angioedema, and generalized anaphylaxis. It is generally believed that whole food allergen proteins either act on the mucosa in the intestinal tract or may be absorbed systemically in a bioactive form.

The fact that most people ingest large amounts and perhaps even high numbers of foods every day makes the diagnostic process complicated. Depending on the affected organs and the symptoms, many inflammatory and other disease states may have to be excluded before the food allergy diagnosis is considered. If the anamnesis

suggests a link between food or drink intake and symptoms, it may be helpful to consider that food allergy is but a subgroup of adverse reactions to foods (Figure 1).

Figure 1. Food allergy is a subgroup of adverse reactions to foods.

First, it is important to exclude food poisonings or infections, i.e., if more than a single person has reacted to the same exposure to food, it is likely to be a mechanism other than allergy. In this respect, it is important to remember, that allergy-like symptoms may also be a part of the pattern of a food-borne poisoning such as for scombroid poisoning, a dramatic example of an outbreak (Demoncheaux et al., 2012)^[1], where the active substance is histamine stemming from decarboxylation of the amino acid histidine in, for example, fish during putrefaction.

Another differential diagnosis comprises genetic or acquired deficiencies in metabolism, of which lactase deficiency (Jarvela et al., 2009)^[2] is probably the most common. In adult and adolescent patients, alcohol intolerance may be another important diagnosis in this respect, but alcohol could also be a co-factor in eliciting food allergy by reducing the threshold dose to which the patient reacts.

Physiological and pathophysiological reactions may be mediated via taste (Negri et al., 2011)^[3], and this may lead to conditional behavior, such as aversion, where stimulation of taste receptors initiates a central nervous reflex (Spector and Glendinning, 2009)^[4] that may ultimately lead to reactions that could be misinterpreted as food allergy. This, in combination with a patient's potential psychological fear of ingesting a food believed to previously cause a severe reaction, is the main reason for employing double blind placebo controlled challenges in the diagnosis of food allergy.

If the considerations and exclusions of the above-mentioned differential diagnoses lead to the tentative conclusion that the patient reacts to amounts of food that would be tolerated by most individuals in the

population, the diagnosis of food hypersensitivity may be reached. Such a diagnosis can be strongly supported by a positive challenge with the offending food, but it is important to emphasize that the positive challenge rarely in itself can suggest the disease mechanism. By definition, food allergy is a food hypersensitivity that has an immunological background, whereas non-immunological food hypersensitivity (formerly described as food intolerance) depends on other, not necessarily known, mechanisms. Because the latter disease states are not well described in terms of pathophysiology, it is mandatory to establish a clinically proven diagnosis of food hypersensitivity and not rely only on laboratory or other paraclinical tests (Ortolani et al., 1999; Bindslev-Jensen et al., 1994)^[5-6].

This definition of food allergy^[7] [see Burks et al. (2012)^[8] for discussion and reference to further guidelines for classification] leads to inclusion of diseases, such as celiac disease or rare conditions such as food-induced nickel allergy (systemic contact dermatitis) (Menne et al., 1994)^[9] in addition to IgE-mediated food allergy. A number of conditions, such as eosinophilic esophagitis or gastroenteritis IgE-mediated food allergy, may play a role in worsening of symptoms, as well as driving the pathology. The reader is referred to the specialty literature, but in terms of diagnosis, it is important to establish whether a specific food actually plays a role in patients with these diseases.

While total-IgE may be an indicator of general atopy, it is rarely if ever helpful in discriminating persons with or without food allergy (Boyce et al., 2010)^[10]. Likewise, acute measurements during challenge such as plasma-histamine or tryptase have not been documented to be of large clinical value (Sampson et al., 2012)^[11]. Thus, the most important single factor in food allergy is specific IgE directed against the food allergens. IgE is situated on mast cells and, by allergen cross-linking, mediators are released. This forms the basis of the acute symptoms mentioned above. IgE and mast cells in skin also form the basis of diagnosis made by the skin prick test which is the major diagnostic tool in addition to blood samples.

The production of IgE by B-lymphocytes that have undergone an isotype switch to IgE-producing plasma cells (Poulsen and Hummelshøj, 2007)^[12] is believed to be governed by the dominating CD4+ T-cell in allergy, i.e.,

the Th2-cell which expresses the cytokines IL-4, IL-5, IL-13, and likely also IL-9 and IL-22. However, the migratory patterns of T-cells in allergy and in particular food allergy are much less clear. Depending on the manifestation of clinical symptoms in different organs such as the gut, the skin, or the airways, T-cells may often be found in each of these inflammatory foci with different characteristics. Whether these cells are the primary drivers of the disease or secondary to the primary sensitization is not known, but the generalized IgE-immune response most often seen in food allergies could suggest that the initiation of the food allergic immune reaction is not always related to the organ in which elicitation takes place. In this respect, it is interesting that recent studies of food allergy applying the tetramer technique for enumerating allergen specific T-cells have found relatively few gut-specific ($\alpha 4\beta 7+$) T-cells compared to a higher frequency of skin-specific (CLA+) T-cells (Chan et al., 2012)^[13], although varying results have been found by others (DeLong et al., 2011)^[14]. Future studies will have to further address the role of the allergen-specific CD4+ T-cells and their localization. It is likely that such studies will help to increase our understanding of the sensitization process, which may ultimately lead to a better primary prevention of food allergy.

GLOBAL PREVALENCE OF FOOD ALLERGY

Allergic disorders, including asthma, allergic rhinitis, atopic dermatitis, and food allergies, are very common in westernized societies. In the developed world, about one-third of children are suffering from at least one or more of these allergic conditions. The exact causes of food allergies are unknown and the only preventive treatment for this potentially fatal disorder is avoidance of the offending food. Epidemiology studies are important to define the scope of the problem and may reveal possible clues for the possible etiologies of food allergies.

Followed by the increase in the prevalence of asthma and allergic rhinitis, the rise in food allergy appears to be more apparent in the past decade (Prescott and Allen, 2011)^[15]. Food allergy is often the first manifestation of the “atopic march.” From prospective birth cohort studies, early sensitization to food allergens has been found to be an important factor predicting subsequent development of other forms of allergies (Illi et al., 2006; Guilbert et al., 2004)^[16-17]. In the last few decades, the prevalence of asthma has been increasing steadily, and

recent studies have found that the prevalence has reached a plateau in countries where prevalence rates are high. The increase in food allergies appears to be a recent event, and has been described as a “second wave” following the increase of asthma (Prescott and Allen, 2011)^[15]. Both population-based and hospital surveys have shown that food allergies and food-induced anaphylaxis are on the rise in the last decade. However, there were wide variations in the methodologies used in food allergy studies across the world, making comparison of the available data difficult. Furthermore, many studies use questionnaires alone and did not include any objective measures or validation by food challenges. Subjects and parents were likely to over-report the possibility of adverse food reactions, and some of these reactions may not be related to true food allergies. A recent meta-analysis has clearly shown that the use of objective measurement and food challenge to confirm the diagnosis of food allergies would result in a much lower prevalence of food allergies (Rona et al., 2007)^[18]. This is why the EuroPrevall research consortium was developed and funded by the European Union. The consortium used standardized instruments to evaluate the epidemiology of food allergies in many European and several other non-European countries (Kummeling et al., 2009; Wong et al., 2010)^[19-20].

Because dietary patterns vary in different parts of the world, it is not surprising that there are marked variations in the prevalence, as well as the patterns, of food allergies. Globally, egg, milk, peanut, and tree nuts and fruits are the most common allergens, followed at a distance by shrimp and fish (Burney et al., 2010, 2014)^[21]. In the US alone, there are more than 30,000 episodes of food-induced anaphylaxis, resulting in more than 150 deaths every year (Sampson, 2003)^[22]. In a recent study based on hospitalization data from Australia, food-induced anaphylaxis resulting in hospital admission increased by almost four-fold from 1994 to 2005 in children under four years of age (Poulos et al., 2007)^[23]. Furthermore, the prevalence of food allergies confirmed by food challenge has been found to be as high as 10% in Australian infants (Osborne et al., 2011)^[24]. Three telephone surveys using the same methodology conducted in the US over the past 12 years has also documented increases in peanut allergy by three-fold in children less than 18 years of age^[25]. Research into the exact reasons for such a dramatic rise is urgently needed. Furthermore, there is evidence that the natural history of food allergy has changed. In the past, most children with milk allergy would be able to

tolerate milk intake by the time they reached school age. A study from the US suggested that cow's milk allergy is more likely to persist into adolescents^[26].

In Asia, food allergies are relatively uncommon with the exception of highly developed places like Japan, Singapore, and Hong Kong. As dietary intake varies widely among Asian countries, it is not surprising that the patterns of food allergies are different among different ethnic groups. Shrimp allergy has been reported to be rather common in Singapore, Thailand, and Hong Kong^[27]. One intriguing finding is that peanut allergy is very uncommon in Chinese populations despite widespread consumption of peanuts in China. Furthermore, Chinese children from Hong Kong have significantly higher prevalence of sensitization and reported food allergies when compared with children from mainland China. It is highly likely that some of the protective factors are lost along with the process of urbanization. Identification of these factors and understanding of the underlying mechanisms are important for future development of possible primary preventive strategies against this 'epidemic' of food allergies.

DIAGNOSIS OF FOOD ALLERGY

In unstructured interviews, up to 30% of the general population reports suffering from a food allergy. These figures clearly summarize the difficulties clinicians confront when diagnosing food allergy.

Diagnosis of food allergy includes the establishment of a reliable link between the clinical history of an adverse reaction to one or several foods as reported by the patient and the immunological basis of this reaction. The first step in assessment of patients with adverse reactions to foods is a careful case history. The case history is not reliable as a sole criterion to establish the diagnosis of food allergy, but it might provide the clinician with an estimation of the severity of the allergic response. The most frequent symptom of food allergy is oral contact urticaria (i.e., a swelling and itching of the oral mucosa immediately after contact with the allergenic food), which is a mild reaction. Systemic reactions may involve one or more target organs, including the skin, the gastrointestinal and upper/lower respiratory tracts, and the cardiovascular system. Anaphylaxis is the most severe manifestation of food allergy and a medical emergency. It is defined as a

generalized, potentially lethal allergic reaction. A detailed definition establishing diagnostic criteria for anaphylaxis has been published by Sampson et al^[28]. (2006).

As a next step, specific IgE antibodies to the suspected foods are measured by in vitro or skin testing to link the clinical reaction with the IgE-mediated pathophysiology. These diagnostic tests, however, only indicate the presence of food-specific IgE antibodies; they do not establish the diagnosis of food allergy. To finally prove the clinical relevance of the reported history and the detected food-specific IgE, a positive food challenge is often needed. In case of an anaphylactic reaction (if fulfilling the diagnostic criteria), clinicians try to omit confirmatory food challenges.

The quality of extract-based diagnostic testing is, among other factors, dependent on the pathogenesis of the food allergy^[29]. In infancy, food allergy is most frequently the result of primary sensitization to food allergens over the gastrointestinal tract and directed to digestion-resistant food allergens. A hallmark of adult food allergy is the high prevalence of secondary food allergy, where the primary sensitization is directed to an inhalant allergen (i.e., pollen). The food allergen is recognized by these inhalant allergen-specific IgEs due to a high structural homology between the food and the inhalant allergen on the basis of cross-reaction. Usually, the sensitivity of food extract-based diagnostic testing is higher in primary than in cross-reactive food allergy. In primary food allergy, it has been observed, at least for a limited number of foods, that higher levels of allergen-specific IgE are associated with an increased likelihood of allergic reactions under provocation (so-called 95% positive predictive values). This procedure, however, is not precise and, most importantly, does not predict the severity of the allergic response to foods (Wang and Sampson, 2011)^[30].

Assessment of a food allergic patient also includes factors which might have influenced the severity of the allergic response. Factors which might enhance the allergic reactions to foods are physical exercise, concomitant intake of nonsteroidal anti-inflammatory drugs, beta-blocking agents, and alcohol. Another important factor which influences the allergic response is the dose or amount of the ingested allergenic food. Titrated, double-blind, placebo-controlled food challenge studies have provided important knowledge on the

effect of dose on the development of allergic symptoms in tested individual patients. Very low doses of the investigated food that do not lead to allergic symptoms indicate that there is a NOAEL (no observed adverse effect level), i.e., an amount of the allergenic food that is safe for the individual patient (Taylor et al., 2002)^[31]. With increasing doses, patients often develop subjective or mild symptoms as the first manifestation of the food allergic response, whereas more severe and systemic symptoms usually occur at higher doses (Ballmer-Weber et al., 2007; Mackie et al., 2012)^[32-33].

As observed in many recent studies, allergy to a particular food may give rise to differentially severe symptoms depending on which precise allergen component(s) to which the individual is sensitized (Lidholm et al., 2006, Ballmer-Weber and Hoffmann-Sommergruber, 2011)^[34-35]. The increasing knowledge and availability of allergen components from various foods enables a detailed analysis of sensitization profiles in individual patients and a comparison of such sensitization patterns with the clinical presentation. This concept has been defined as “Component Resolved Diagnostics” (CRD). For example, the predominant sensitization to lipid transfer proteins (LTPs) in Rosaceae fruit or hazelnut allergic individuals in the Mediterranean area is often accompanied by a history of systemic food reactions. This is rarely the case in northern European populations where the sensitization to Rosaceae fruits or hazelnut is characteristically directed to Bet v 1-related food allergens (Ballmer-Weber et al., 2002; Fernández-Rivas et al., 2006; Hansen et al., 2009)^[36-38].

Of the major peanut seed storage proteins, the 2S albumin Ara h 2 appears to be a particularly important marker of primary peanut sensitization (Nicolaou et al., 2010)^[39]. Other allergen components that hold promise as risk markers for potentially severe allergic reactions include omega-5 gliadin (Tri a 19), showing association to wheat-dependent exercise-induced anaphylaxis, and actinide (Act d 1) in kiwi allergy or Gly m 5 (beta-conglycinin) and Gly m 6 (glycinin) in soy allergy (Takahashi et al., 2012; Le et al., 2013; Holzhauser et al., 2009)^[40-42].

Peach is one of the most frequently reported fruits causing allergy in China, and cross-reactivity among Rosaceae fruits is also observed. Mugwort pollen allergy is dominantly prevalent in most parts of China except

for south and east coastal regions where mugwort pollen exposure load is very low. A number of foods (peach, beans, peanut, sunflower seed) have been reported to produce cross-reactive allergic reactions when consumed by Chinese mugwort allergic patients (Gao et al., 2013; Wen and Ye, 2002)^[43-44]. In Europe, at least four and six allergenic proteins have been identified for peach fruit and mugwort pollen, respectively (Chen et al., 2008; Wopfner et al., 2005)^[45-46], and a few component ImmunoCAPs are commercially available. To identify the main allergens of peach and mugwort pollen in China, both extract and single components of ImmunoCAPs were used to test 70 sera from peach and/or mugwort allergy patients (Gao et al., 2013)^[43]. They found that LTP Pru p 3 is a major allergen, with the mean IgE response to Pru p 3 being very similar to that of peach, indicating the relative importance of peach LTP. It seems to be a primary sensitizer in a smaller group in south China, which is similar to “typical Mediterranean” peach allergic patients (Fernández-Rivas et al., 2003; Zuidmeerand van Ree, 2007)^[47-48]. The virtual absence of birch pollen in China is reflected by the very low frequency of recognized Pru p 1. The results also suggest that high exposure to mugwort pollen in north China results in strong IgE responses to Art v 3 that cross-react with Pru p 3, thereby causing peach allergy. ImmunoCAP inhibition experiments with Art v 3 and Pru p 3 recombinant allergens clearly support the dichotomy of the population of Chinese peach allergic patients, i.e., a larger group of peach allergic patients with primary sensitization to mugwort LTP and a smaller group of patients with primary sensitization to peach LTP. With CAP inhibition experiments, there was complete inhibition of IgE binding to Pru p 3 by Art v 3 in the former group, and the absence of significant reverse inhibition. In the latter group, the results of the inhibition experiments were close to a mirror image. In conclusion, significant exposure to mugwort pollen gives rise to a peach allergy phenotype that is LTP-associated pollen-sensitization driven allergy. It may also imply that LTP from other foods such as beans and peanut are potential relevant allergens. There is a great need to identify food allergen molecules using modern techniques.

INNOVATIVE APPROACHES FOR IMMUNOTHERAPY OF FOOD ALLERGY

The FAST project (Food Allergy Specific ImmunoTherapy) is a seven-year project funded under the 7th Framework Programme of the European Union, aiming at the development of a safe and effective treatment of food allergies (Zuidmeer-Jongejan et al., 2012)^[49]. It targets persistent and severe allergy to fish and fruit.

Besides persistence and severity, this choice is based on prevalence and the importance of these foods for a healthy diet. Classical allergen-specific immunotherapy (SIT) for treatment of food allergy using subcutaneous injections with food extracts has proven to be effective but too dangerous due to anaphylactic side effects. In the 1990s, subcutaneous immunotherapy was evaluated for the treatment of peanut allergy, but side effects were so frequent and severe that this program was abandoned (Oppenheimer et al., 1992; Nelson et al., 1997)^[50-51]. It is relevant to note that treatment was carried out with unmodified aqueous peanut extract. FAST aims to develop a safe alternative by replacing aqueous food extracts with hypoallergenic recombinant major allergens, the active ingredients of SIT. On top of that, to further increase safety, the hypoallergens will be adsorbed to aluminium-hydroxide. Both severe fish and fruit allergy are dominated by a single major allergen, parvalbumin for fish and LTP for fruit. This makes development of a novel biotechnological product feasible. In the first part of the project, several approaches were evaluated for achieving hypoallergenicity.

For parvalbumin, an allergeoid (glutaraldehyde modification) and a mutant lacking the molecule's Ca^{2+} -binding capacity were investigated. The starting point was parvalbumin from carp, Cyp c 1. Both modified molecules proved to be highly hypoallergenic, but for further development the mutant was selected (Swoboda et al., 2007)^[52]. The molecule was produced under Good Manufacturing Practice (GMP) conditions, successfully underwent toxicity testing in laboratory animals, and is now being evaluated in a first-in-human safety trial (Phase I/IIa). When the outcome is positive, it will be followed shortly by an efficacy trial (Phase IIb).

For LTP, the major allergen from peach, Pru p3, was chosen because this is considered the most relevant allergenic LTP. In the first part of the project, an allergeoid (glutaraldehyde modification), a reduced and alkylated version and a mutant lacking the eight cysteines typically seen in LTPs (both destroying LTP's four disulfide bridges), a mutant with mutated surface-exposed IgE epitopes, and a wild-type LTP from a poorly allergenic fruit (strawberry) were used. The two versions lacking disulfide bridges proved to be extremely hypoallergenic but poorly immunogenic. The surface mutant and the strawberry LTP were hypoallergenic for some but not for other patients. Based on the overall analysis, none of the molecules were considered good

candidates for further development. Three new molecules are now under development. Preliminary results from these analyses are promising. The most appropriate molecule will soon be selected and then produced under GMP conditions. After toxicity testing, hypoallergenicity will then be tested in a skin-prick test trial.

In conclusion, a subcutaneous treatment for fish allergy is now in clinical testing. The treatment of fruit allergy will follow at a later stage.

Safety assessment of GM foods includes evaluating the potential risk of allergenicity. A good understanding of food allergy is a prerequisite for this type of assessment. The pivotal role of specific IgE antibodies in food allergy determines the focus of the assessment. Knowing which proteins in food bind IgE is vital information. A regularly updated and peer-reviewed database with sequence data of established or putative allergens is the primary tool used to evaluate whether a candidate transgene harbors the risk of being an allergen (www.allergenonline.org). Being from a known allergenic source or having significant homology to an established or putative allergen in the database warrants serum screening of the transgene's protein product using serum of subjects being sensitized to the allergenic source or to the homologous allergen. In depth knowledge of the proteins binding IgE and of the properties of IgE antibodies against them has increased enormously with the advent of molecular allergology. The importance of molecular allergology for assessment of GM foods cannot be underestimated. Being able to establish the clinical relevance of IgE antibodies that can vary from no relevance (e.g., IgE against plant glycans) to a risk factor for severe systemic reactions (e.g., IgE antibodies against the major peanut allergen Ara h 2) will further help robust risk assessment. Establishing whether IgE is likely to bind to a transgenic protein is becoming more and more feasible. On the other hand, science cannot yet predict whether a protein has an increased chance of inducing IgE, i.e., whether a protein has the potential to sensitize. The answer to the question "what makes an allergen an allergen?" is still unknown. Additional research is needed to arrive at an answer that warrants including the risk of being a sensitizer in the protocols to assess the allergenic risk of GM foods.

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CLASSIFICATION OF ADVERSE REACTIONS TO FOOD

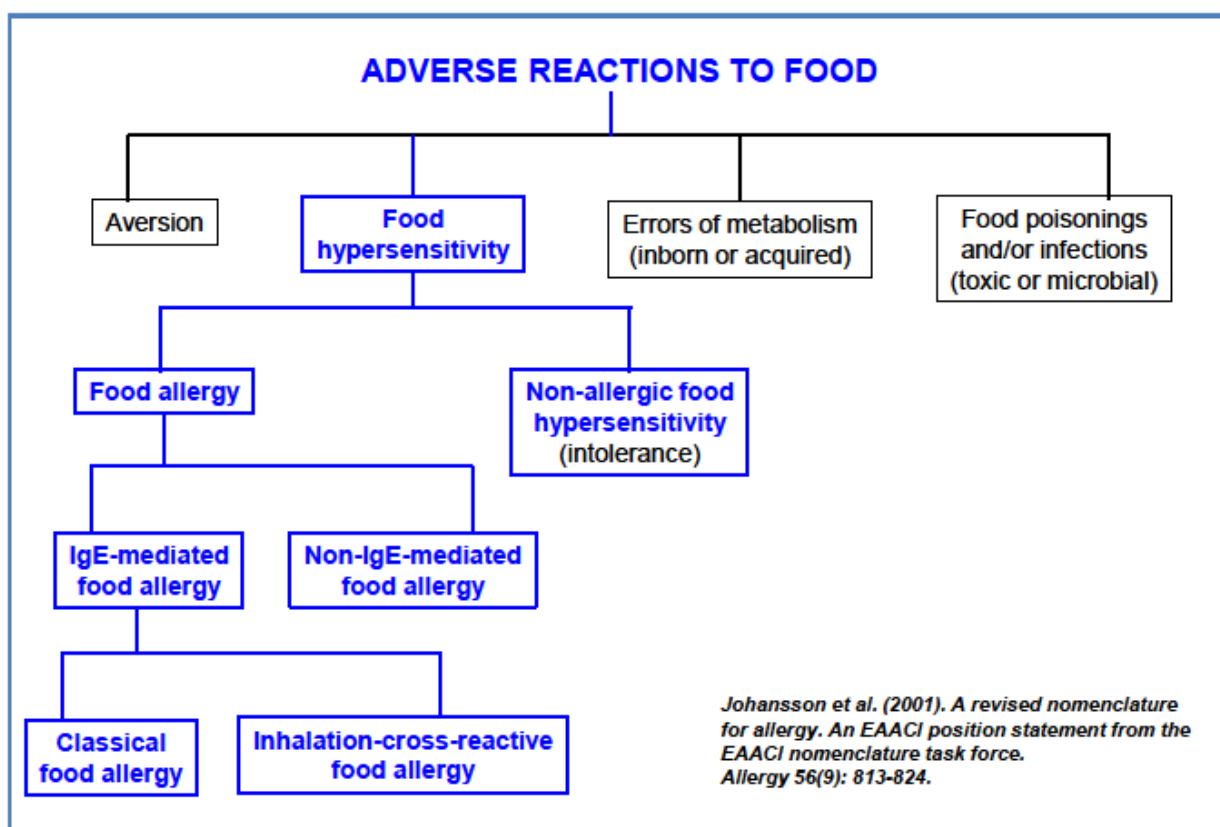


Figure 1. Food allergy is a subgroup of adverse reactions to foods.