ABC OF ALLERGOLOGY

A PRACTICAL APPROACH TO FOOD ALLERGY

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Food allergy is one of the most complex and often controversial areas of allergology clinical practice. This article is a summary of current approaches to food allergy diagnosis and treatment presented at the EAACI/GA2LEN Food Allergy Symposium which took place in Denmark 2006.

What is true food allergy?

True food allergy is an immediate immune-mediated hypersensitivity reaction resulting in mast cell histamine release with tissue inflammation. This occurs following sensitisation and re-exposure to common food proteins in the diet.

IgE-mediated reactions occur within minutes to a couple hours after ingestion of the offending food while **non-IgE-mediated** reactions occur hours to days after ingestion of the food concerned.

Figure 1 illustrates the current nomenclature for adverse food reactions (WAO & EAACI).

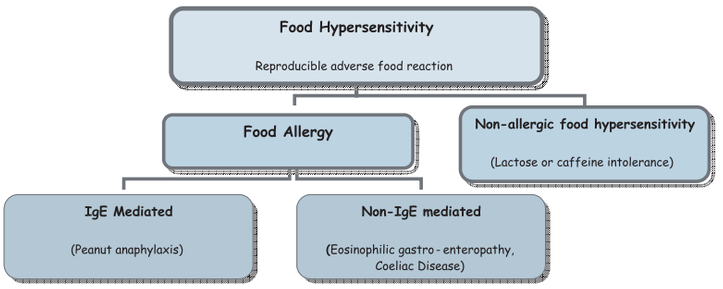

Fig. 1. Current nomenclature for adverse food reactions (WAO & EAACI).

Growing incidence of food allergy

Research reflects that true food allergy affects 6-8% of infants, 3-5% of young children and 2-4% of adults.[1] This incidence has rapidly increased over the last 25 years. Nut allergies which were first documented in the early 1980s are now very common, while the incidence of cow's milk allergy seems to have reached a plateau. As our eating habits change and we become exposed to more exotic foods, so the incidence and range of food allergy increases. For example, we have seen a twenty-fold increase in allergy to Kiwi fruit since this allergy was first recorded in 1981. Food colourant and additive-induced reactions tend to be non-IgE-mediated (via as yet unknown mechanisms), are less common and affect 0.03 and 0.2% of the general population (but 2% of atopic individuals).[2]

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Understanding the food allergic reaction

Primary allergic sensitisation takes place with initial food protein exposure. Production of food-specific IgE antibodies then occurs with long-term T-cell immune memory. On subsequent exposure, these preformed IgE antibodies cross-link food allergens and result in tissue mast-cell degranulation. Mast cells release inflammatory mediators such as histamine, tryptase, chymase, heparin and leukotrienes. This 'early phase' allergic reaction results in increased vasodilation and vascular leakage with erythema, oedema and excess mucus production. As the 'inflammatory cascade' develops, eosinophils are recruited into the site of inflammation where they produce and release newly formed inflammatory mediators such as eosinophil cationic protein (ECP), major basic protein (MBP), as well as leukotrienes and pro-inflammatory cytokines. This promotes persistent tissue inflammation called the 'late phase' allergic reaction which develops 2 to 24 hours after allergen exposure.

High IgE responders (those individuals who produce high levels of food-specific IgE) seem to have more persistent food allergies, while low IgE responders (those with only moderately raised food-specific IgE) tend to have transient food allergies that are often 'outgrown' with age.

Opinion leaders further divide food allergy into Class 1 and Class 2 food allergic responses. Class 1 result primarily from gastrointestinal food sensitisation, occurring predominantly in infants who have robust initial allergic responses, but most of which are outgrown in early childhood (cow's milk, egg, soy, wheat). By contrast, Class 2 food allergic reactions are initiated by respiratory sensitisation caused by pollen inhalation which leads to fruit and nut cross-reactivity. Class 2 reactions are less intense, tend to persist and develop in older children and young adults. A good example of a Class 2 reaction is the oral allergy syndrome (OAS) or pollen-food syndrome in which silver birch pollen sensitisation results in localised oral allergic reactions to common raw vegetables, stone fruit and nuts.

The pattern of allergic sensitisation is very regional with certain food allergens predominantly causing problems in specific geographical locations and populations. For example, peanut is the predominant food allergen in the USA and UK, egg is the principal food allergen in France, seafood in Australia, South Africa and Spain, celery in Switzerland, and poppy seed in Poland while 'birds' nest' soup is the commonest food allergy in Thailand.

As new ingredients are farmed and introduced into everyday foods so patterns of food allergic sensitisation are changing. For example, lupin flour is now mass-produced and supplemented in many baked products particularly in France. Lupin cross-reacts in peanut-allergic individuals, and there has been an increased incidence of reports of lupin flour anaphylax-

is (16% of peanut allergic individuals in France are now lupin-flour-allergic).

Food allergy presents in many different ways

Food allergy may present with varying intensity, from mild oral itching to full blown anaphylaxis with tissue swelling, respiratory obstruction and circulatory collapse, all occurring within minutes of ingesting the offending food. In a typical food allergy the following organ systems are affected to a lesser or greater extent depending on the food type and sensitivity:

- **Oro-pharynx:** Lip and oral itching, tongue and glottic oedema, laryngeal obstruction.
- **Skin:** Acute urticaria, angioedema and atopic dermatitis.
- **Respiratory:** Asthma and rhino-conjunctivitis
- **Gastrointestinal:** Vomiting, gastritis, diarrhoea and acute abdominal pain.
- **Circulatory:** Sudden hypotension and collapse.
- **Anaphylaxis:** Affecting multiple organs with circulatory collapse and even possibly death.

Some individuals are so exquisitely sensitive that they even react to inhaled or skin exposure from food allergen vapours such as fish being boiled, nuts being cooked or raw potatoes being peeled in the home or restaurant. Kiss-induced allergy (KIA) is a common but often overlooked source of allergen exposure. Food allergy is strongly associated with atopy, and other inhalant allergies usually co-exist, while approximately 30% of food-allergic individuals will have multiple food allergies.

Adjuvant factors in food allergy

Certain physical factors may enhance or amplify a food-allergic reaction. For example individuals may have no symptoms if they eat a specific food, but if they engage in certain activities or take certain medication at the same time as eating, they have a reaction. Typical examples include food-dependent exercise-induced urticaria, asthma and anaphylaxis (FDEIA). In FDEIA the person is symptom-free if they eat certain foods such as wheat, celery or shellfish or if they exercise without eating. But if they eat one of these foods and exercise shortly afterwards (within 4 hours) they will experience typical food-allergic symptoms of urticaria, asthma or anaphylaxis. This FDEIA can occasionally occur as a non-specific phenomenon after ingesting any foodstuff that causes gastric dilatation before exercising. Alcoholic drinks speed gastric emptying, cause vasodilatation and aid rapid absorption of food allergens which will make underlying food allergies more severe and of rapid onset. Antacids and proton pump inhibitor medications such as omeprazole and lanzoprazole reduce gastric acidity and thus allow food allergens to pass intact to the gut lymphoid tissue in a more allergenic form. This can result in unexplained and episodic food allergic reactions not seen at other times of normal gastric pH.

A food-allergic reaction can be promoted by concomitant viral illnesses, premenstrually or by pollen-related food hypersensitivity which is more problematic during the peak tree- or grass-pollen season.

Patients with chronic persistent asthma, who have concomitant food allergies, have a far greater risk for developing severe food-related anaphylaxis. Heiners syndrome is a rare condition which includes acute pulmonary haemosiderosis, recurrent pneumonia and eosinophilia which are related to a delayed hypersensitivity to cow's milk proteins.

Who develops food allergies?

Certain people have a familial or genetic predisposition to develop allergies which we term 'atopy'. This 'genetic predisposition' to allergy seems to be carried on multiple candidate genes, and is not limited to a specific chromosome or locus. Breastfeeding appears to be protective for allergy, and the incidence of cow's milk allergy has been in steady decline with increasing breastfeeding practices. In Denmark, cow's milk allergy has declined from 2.2% in 1985 to 1.0% in 1999. This is possibly due to protective secretory IgA antibodies and prebiotic oligosaccharides found in breast milk which promotes the growth of 'protective' gut commensuals (bifido-bacteria such as *Lactobacillus reuteri*). Although we suggest that at-risk mothers should avoid allergenic foods in late pregnancy and during breastfeeding, no convincing evidence for the benefit of this practice has been forthcoming. Studies show that despite rigid avoidance of specific food allergens in the maternal diet, traces of these food allergens will still be found in the breast milk and the pregnant mother's circulation. However, exclusive breastfeeding to at least 4-6 months of age is protective of allergy, as are avoidance of maternal cigarette smoking and the introduction of solid hypo-allergenic foods after 4-6 months of age. During infancy, gastric acidity is not well maintained because of immature acid secretion. This lapse in gastric acidity and pepsin digestion may allow allergens to pass intact to the gut lymphoid tissue and promote food-allergic sensitisation in infancy. Gastrointestinal commensuals including Lactobacilli (bifido-bacteria) seem to enhance gut immunity and studies show a reduced incidence of atopic dermatitis in infants who have early 'probiotic' lactobacilli supplements. There is mounting evidence that 'trace' food allergens exposure in infancy promotes allergic sensitisation while high-dose allergen exposure induces tolerance by switching the T-lymphocyte helper cells from Th2 to Th1 subtypes. Studies are now under way to clarify whether we should in fact be promoting allergen 'bombardment' in infancy and not avoidance! The hygiene (or microbial) hypothesis is based on studies which show that atopic children living on livestock farms and exposed early to animal bacterial endotoxins are far less likely to develop inhalant allergies and food-allergic sensitisation.

General trends in childhood dietary practices indicate that children are eating far more exotic and previously uncommon foods than ever before. This is mirrored by increased reports of allergic sensitisation to exotic foods such as kiwi fruit, Sharon fruit, lupin flour, nuts and shellfish.

Problematic foods

In early infancy, only a few foods are the principal culprits causing food allergic sensitisation. Over 90% of food allergies in infancy are due to cow's milk, hen's egg, wheat flour, soy milk, cod fish and peanut (Class 1 allergens). While in older children and young adults we see allergy to tree nuts (Brazil nut, hazel nut, cashew, walnut and almond), sesame, shellfish (shrimp, mussel), stone fruits (apple, cherry, plum) and exotic vegetables and fruits (kiwi, avocado, Ethiopian eggplant).

Cross-reactivity between pollen sensitisation and food allergens occurs in older children who are pollen sensitised with allergic rhinoconjunctivitis to tree and grass pollen and they later develop associated food allergies. A pan-allergen protein called profilin found in both pollen and certain fruits causes the phenomenon of OAS. Bet v1, one of the profilin pan-allergens found in silver birch pollen that causes hay fever, cross-reacts

with nuts and legumes, while the other Bet v2 cross-reacts with raw stone fruits and vegetables. This OAS which results in localised oral mucosal irritation but usually not life-threatening reactions occurs predominantly in northern Europeans (Scandinavia). Curiously in southern Europe, where silver birch pollen allergy is uncommon, pan-allergen sensitisation with fruits is related to the more heat-stable lipid transfer protein (LTP) fraction. This LTP sensitisation usually leads to more severe oral allergic symptoms and even anaphylaxis to fruits, nuts and vegetables in southern European populations (Spain, Portugal and Italy) and there is usually no associated pollen allergy.

Interestingly, food farming and storage practices can induce the fruits to produce excess 'stress-induced' pan-allergens and render the food more allergenic.

Pan-allergens such as the profilin Bet v1 are heat labile because of their conformational epitopes (highly folded IgE recognition sites). This conformation or 'folding' is damaged by heating and thus the protein is rendered non-allergenic if cooked, processed or canned. The LTP pan-allergen is a linear isotope with IgE recognising an 'unfolded' site on the allergenic protein; hence heating does not significantly alter the allergenicity. LTP is therefore heat and acid stable and cooking does not reduce allergenicity. Paradoxically heat may occasionally increase a foodstuff's allergenicity as occurs when roasting peanuts. The 'raw' peanut is allergenic, but roasting the peanut at very high temperatures rapidly increases this allergenicity by altering the protein conformation. Whereas boiling peanuts at relatively lower temperatures actually reduces allergenicity.

It should be borne in mind that 'allergy-safe' foods can become contaminated with traces of allergen during food processing. Occasionally people will have an allergic reaction to a food that they have safely eaten before, because a known allergen has inadvertently entered the food during processing. For example lupin flour may be added to wheat flour, sesame residue may enter noodles and peanut residue may enter ice cream.

Diagnostic tests in food allergy

Food allergy testing involves screening for food-specific IgE antibodies to common and exotic food proteins. A full and extensive food allergy history is pivotal in guiding the physician to the foods that require specific allergy testing. The double-blind placebo-controlled food challenge (DBPCFC) test remains the most accurate method of confirming a specific food allergy. However, food challenges are time-consuming, need to be conducted in a hospital environment with full resuscitation equipment available and an experienced dietician is essential to 'mask' the placebo and active food ingredient for the patient. As a result, particularly in children, we tend to opt for 'open challenges' using suspected foods, starting with milligram amounts and doubling the test dosage every 20 minutes until a reaction occurs or the patient tolerates a substantial amount of the suspected food.

Outside the hospital environment, more emphasis is placed on the food allergy history and the results of specific allergy testing using skin-prick tests with the fresh native food allergens or specific IgE utilising the ImmunoCAP RAST testing system. The atopy patch test (APT) may be used to determine delayed food hypersensitivities. APT used together with SPT or RAST may give increased positive predictive value (PPV) to the food allergy diagnosis.

Double-blind placebo-controlled food challenge testing (DBPCFC): This accurate food allergy testing process utilises the raw allergen, concealed in a 'cake' or 'broth' so that the actual food's taste and texture cannot be identified by the subject being tested. The physician is also unaware of which is active ingredient or placebo until the code is revealed (double-blinded). This is the most accurate way of determining a true food allergy without any patient or doctor bias complicating the process. The patient is given increasing amounts of the placebo and then on a separate occasion, the active ingredient until a reaction occurs or they tolerate a substantial amount of the food allergen. Obviously the patient is carefully monitored by nursing staff and a doctor in the hospital with full resuscitation equipment including injectable adrenaline and oxygen available. The patient is brought into hospital for the day and monitored; some researchers even suggest the patient should be monitored in hospital for 2 days and then daily thereafter to document any delayed food hypersensitivity reactions. This is a labour-intensive process and only about four food challenges can practically be done per day even in the most well-run allergy unit. As a consequence, more 'open' challenges are performed in hospital when both patient and doctor know which the active ingredient is, and the patient is monitored for objective signs of food allergy.

If there is a reaction to a challenge test food, it is recommended that the child should avoid that food for a further 6-12 months before considering a rechallenge. There is some debate about whether challenge testing actually 'resensitises' the person to the test allergen. It is therefore recommended that once an individual successfully tolerates a food challenge, they should continue to include that particular food in their diet on a regular basis to maintain their tolerance.

Allergen skin-prick testing (SPT): SPT is the most common and cheapest diagnostic procedure used to confirm a food allergy. It is best to use fresh food extracts such as cow's milk, whole hen's egg, wheat paste, soy milk, codfish, and peanut applied to the skin using the prick-prick method. Any foodstuff can be tested in this manner using the native fresh food. The standardised test lancet is dipped into the test food solution and the patient's skin is pricked with this allergen-impregnated lancet. A new lancet is used for each skin test. The skin test site is then observed for 15-20 minutes and any wheal reaction measured. A positive test is a wheal of 3 mm or greater than the negative saline control test. In addition, we always have a positive histamine or codeine control which is used to gauge skin reactivity. This test is simple, safe, cheap and easy to perform and the results are then immediately available.

Variants of SPT include the scratch patch test (the skin is first scratched and the food allergen then applied under an occlusive patch) and skin application food test (in which food is applied to the skin without pricking but examined at 10-minute intevals for a reaction). Neither of these tests is in common use as they offer no benefit over routine SPT with specific allergens. Intradermal testing for food allergies is not generally recommended either.

Specific IgE food allergy tests. Specific food IgE antibody testing has been improved upon since the original radio-absorbent tests (RAST) were introduced in the 1970s. Now the ImmunoCAP specific IgE test can measure individual allergens (over 150 food tests are now available) and test panels for screening nut, cereal, fish and paediatric food allergens are available. This test measures serum specific IgE to recognised food allergens in a particular food (graded 0 to 6 or measured in kU/l of specific IgE). Specific IgE although convenient in food allergy testing is less accurate than using the raw food material in a prick-prick skin test. The ImmunoCAP manufacturers identify relevant food

allergens using the 'western blotting' method and then add these purified recombinant allergens to the test 'CAP' depending on the prevalence of that specific allergy in a particular population group (such as Ara h1 and Ara h2, the principal peanut allergens).

False-positive results of *in vitro* tests for food allergy can confuse the diagnosis. It seems that non-specific anti cross-reactive carbohydrate determinant (CCD) IgE or anti-bromelain IgE antibodies are responsible for these false-positive responses. CCD is a glycan structure (xylose and fucose) found in foods and specific ImmunoCAP tests can measure CCD.

Serum specific IgG testing by contrast is a good measure of food allergen exposure and levels persists for many years but specific IgG and IgG4 antibody level testing offers no allergy diagnostic value.

Atopy Patch Test (APT). APT is a relatively new application of the original contact allergen patch test procedure previously used to diagnose contact dermatitis due to delayed reactions to topical chemicals and contact preservatives. In this test, one drop (50 ?l) of each raw food is applied to the skin for 48 hours in a series of 12 mm Finn chambers. The patch is then removed and the skin re-examined for erythema or blistering after a further 24 hours (72 hours in total). This is a useful test in children for determining a food allergy or delayed hypersensitivity to foods such as cow's milk, hen's egg, wheat and soy in atopic dermatitis and food protein-induced enterocolitis.3 Non-specific skin irritation may initially result from the patch, but only a delayed hypersensitivity reaction should be evident after a further 24 hours. The APT is highly specific for food allergy but lacks sensitivity. Positive APT and SPT in combination increase the likelihood of a food allergy being present in atopic dermatitis.

Reliably predicting food allergy

It is extremely difficult to predict with any degree of accuracy whether an allergen identified by a positive skin test or raised serum specific IgE result is responsible for a food allergic reaction. The patient's allergy history is therefore extremely important in deciding which the offending allergen is, and whether it needs to be excluded from the diet. In this situation, the input from a qualified dietician is invaluable.

Sporik and Sampson in the USA[4,5] and Hill in Australia[6] have produced predictive value cut-off points (with up to 90% confidence intervals) for SPT and specific IgE results above which a food allergy is likely to be present. In individuals with results above these cut-off values, a specific allergy to that food is highly likely to be present and they postulate that allergen challenge testing is therefore unnecessary. Kagan in 2003 found that 49% of asymptomatic atopic children with no previous history of peanut allergy but who tested positive to peanut had allergic reactions on peanut challenge.

The problem with using predictive values is that at least 1 in 10 patients will fall outside the range. For example it is possible to have a positive serum specific IgE level of over 100 kU/l to the peanut allergen but then tolerate peanuts in the diet with no adverse reaction! It is equally possible to have a serum specific IgE level to cow's milk of under 0.35 kU/l and have anaphylaxis on milk exposure. There are therefore limitations to the predictability and accuracy of entrenched cut-off values for skin-prick tests and specific IgE testing and the DBPCFC still remains the allergy diagnostic 'gold standard' for the foreseeable future.

Occasionally non-IgE delayed food hypersensitivity may present as allergic eosinophilic oesophagitis with problematic gastro-esophageal reflux (GER) resistant to medication, and this responds to milk, egg or wheat elimination diets depending on the culprit food. Diagnostic tests identifying delayed hypersensitivity to common infant foods are not currently available, but an oesophageal biopsy may show typical eosinophilc inflammation. Delayed cow's milk hypersensitivity reactions occur in early infancy and usually resolve spontaneously by the end of the second year of life. Other manifestations of delayed food hypersensitivity include food protein-induced enterocolitis syndrome (FPIES) manifesting with severe vomiting, colicky abdominal pain and diarrhoea with dehydration which may be confused with coeliac disease.[3]

Managing food allergy

In food allergy and anaphylaxis the only effective treatment is specific allergen avoidance. Depending on sensitivity, some people will react to microgram traces of allergens in their diet or even the cooking vapours, while others will tolerate small amounts and only react to milligram amounts of ingested allergen. Hypo-allergenic extensively hydrolysed casein and whey cow's milk formulas still contain minimal cow's milk protein, and exquisitely sensitive infants may need to go onto amino acid formulas such as Neocate. Cross-reaction hypersensitivities between food families (legumes and stone fruits) and unrelated foods with similar panallergens (apple and carrot) should always be considered.

Medication

One has to adopt a pragmatic approach and try to preserve quality of life. The treatment of food allergy and anaphylaxis involves an individualised emergency action plan which should include provision of emergency epinephrine by auto-injector (Epipen) especially in those food- and nut-allergic individuals who have concomitant asthma. Milder allergic reactions involving the skin and mucosa may be adequately treated using oral antihistamines but an individualised treatment plans should always consider epinephrine, antihistamines and include oral steroids to contain late reactions. All allergic events should be discussed with a physician or allergist and each allergic reaction requiring treatment should be followed up with emergency room assessment by an experienced physician.

Prevention

Oral sodium cromoglicate prophylaxis for food allergy has been shown to be ineffective and is therefore no longer recommended; nor is the use of low-dose oral steroids recommended as prophylaxis. Long-term prophylaxis with oral antihistamine medication is discouraged as these antihistamines may actually mask the early stages of an allergic reaction. This can lead the food allergy sufferer to misinterpret their usual early-warning symptoms and not take adequate precautions to treat an allergic reaction in time.

In pollen-food allergic (PFA) syndromes such as silver birch pollen OAS, birch- pollen desensitisation immunotherapy may be considered as it can result in diminished reactions to the cross-reacting foods including apple, cherry and hazelnut.

The future of food allergy

Effective food allergy treatment remains strict avoidance of the offending allergenic food. Food allergy vaccines are in the process of development, but there is concern that once desensitised to one allergen such as peanut Ara h1, this may be followed by only a temporary period of food allergen tolerance before further sensitisations occur. The individual will then be at risk of developing further allergies to other food allergens, and so this treatment may be ineffective in the long

term. Genetically modified (GM) foods devoid of the offending allergen have been explored, and again the fear is that individuals will subsequently go on to develop sensitisation to other allergens.

Heat-killed *Listeria* bacteria used in early dog trials seem to increase the dose of peanut allergen tolerated before a reaction occurs, and this may be an effective therapeutic option in the future.

Anti-IgE monoclonal antibodies seem to protect peanut allergic individuals by binding peanut specific IgE, but this treatment is expensive, has to be given by fortnightly injections and the treatment has to be continued indefinitely. Peptide vaccines and mutant vaccines are also being explored, but at this point in time the only effective treatment is specific food allergen avoidance.

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