

Food Allergy and Anaphylaxis

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Section A

THE PROBLEM OF FOOD ALLERGY

Defining food allergy and anaphylaxis

The umbrella term food hypersensitivity is used to describe all adverse reactions to food and it includes both food allergy and non-allergic food hypersensitivity [1].

Food allergy may be subdivided into IgE or non-IgE-mediated food allergy. Most IgE-mediated food allergic reactions involve the skin and upper respiratory tract, whereas most non-IgE-mediated food allergic reactions (involving IgG or T cells) affect the gastrointestinal tract. Food allergy can occur as an immediate reaction within minutes or up to two hours of consuming a particular food, otherwise as a delayed type reaction after two hours. Symptoms of food allergy may involve one or more organ systems, such as the skin, the gastrointestinal and/or respiratory tract resulting in symptoms such as urticaria, angioedema, worsening of eczema, asthma, rhino-conjunctivitis, vomiting, or diarrhoea.

A non-allergic food hypersensitivity reaction does not involve the immune system and covers pharmacological reactions to vaso-active amines (serotonin, tyramine and histamine), lactose intolerance due to deficiency of gut digestive enzymes and reactions to food toxins which, for example occur in scombroid fish and mushrooms.

Anaphylaxis is an immediate systemic allergic reaction which is potentially lethal and characterised by symptoms affecting the respiratory tract, cardiovascular system, gastrointestinal tract, skin and neurological system. This disorder should be graded according to Sampson's criteria (2003) [2]. Anaphylaxis can affect any age group. Food allergy is the most common cause of anaphylaxis and in the USA, food allergy accounts for 33% of cases of anaphylaxis (resulting in an estimated 200 deaths per year). The next



most frequent causes include reactions to insect stings (14%) and medication (13%). Sometimes the term anaphylaxis is used for mild symptoms but this leads to confusion and an accurate definition of anaphylaxis is therefore essential [3]. However, sometimes mild symptoms, such as tingling in the mouth may be the precursor of an anaphylactic reaction.

The extent of the problem

The whole issue of food allergy is fraught with confusion and public misconception. Approximately 25% of the general population claim to be allergic to one or other foodstuff, but on careful evaluation only 2-3% of adults and 6-8% of children will exhibit true food allergy [4]. The most common food allergens are cow's milk, hen's egg, peanuts, tree nuts, seeds, wheat, soy, fish, and shellfish [5][6].

39 cases of anaphylaxis caused by food in 29 children

- **M/F:** 20/9
- **Age:** 3 months – 9.5 years (mean 2.4 years, median 1.5 years)
- **Causal food:**
 - cow's milk (CM) 12
 - peanut 8
 - egg 6
 - fish/ shellfish: 3
 - wheat: 2
 - potato: 2
 - hazel nut: 1
 - kiwi: 1
 - probably: fish 1, peanut and/or hazel nut 1, "Sharon" fruit 1, additives 1
- **Mean age at anaphylaxis caused by:**
 - CM / potato: 1 year
 - other foods: 3 years

Data from L. De Swert, Belgium 2005

Physicians need to be able to readily recognise the patients who are most at risk for food allergic and anaphylactic reactions. These patients need urgent specialist referral for a full diagnostic work-up and confirmation of their allergy. Once the diagnosis has been confirmed, food allergic patients should undergo thorough instruction and training with regard to diet and emergency management [7][8]. Intervention should always include education on appropriate avoidance diets and an easy to

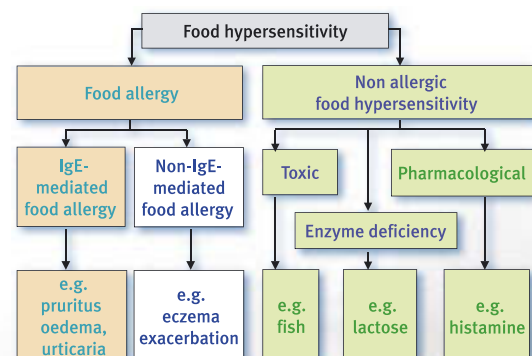
understand action plan for managing food allergic emergencies [9]. The patient or parents should be informed about the expected natural history of the particular allergy. For example, cow's milk allergy is inversely related to age, with two thirds of patients becoming tolerant by three years of age. By contrast, peanut allergy is only outgrown by 20 percent of children and the majority of patients will remain allergic until adulthood.

Those who are not shown to be allergic on testing should be counselled and reassured that they have no evidence of food allergy. This is important in order to prevent a lifetime of unnecessary food avoidance, which could hamper their quality-of-life and perhaps lead to malnutrition.

Those at risk in the community

Most clinical reactions involving food allergy occur in the community where immediate medical assistance is not readily available. It is necessary therefore to prepare each patient, who is at risk or who has a documented food allergy, for an anaphylactic reaction and to become an expert in dealing with their allergic reactions whenever and wherever it might occur. Fortunately, most reactions involving food allergy do not result in severe anaphylactic reactions. However, we need to be able to identify those patients who are especially at risk in order to ensure prompt intervention.

Recent research has highlighted that one third of fatal food allergic reactions occurred while eating at a restaurant while another third occurred at home [10]. In both situations no professional treatment is immediately available and this highlights the need for proper patient education to deal with these emergencies.



Modified from Johansson SGO et al. Allergy 2001; 56: 813-824

Recognising severe food allergy and anaphylaxis

In general, the knowledge and experience of general practitioners in diagnosing, treating and guiding food allergic patients is poor [11]. Even specialists such as paediatricians appear to know only the basics of food allergy and anaphylaxis. Moreover, the psychological and social impact on the patient and their families is considerably underrated. A comprehensive and systematic history of symptoms is therefore essential to identify those individuals with suspected food allergy in order that they may be referred to a specialist physician for accurate diagnosis and treatment. Every physician should be able to recognise those signs of food allergy and anaphylaxis which make appropriate specialist referral mandatory.

Signs of food allergy may involve the skin with features of urticaria, flushing, angioedema, pruritus and/or eczema. Gastrointestinal symptoms may include vomiting, abdominal pain, dysphagia and diarrhoea. Respiratory signs may be in the form of wheezing, dyspnoea, stridor, rhinitis and conjunctivitis. Patients with cardiovascular signs may exhibit tachycardia and arterial hypotension, while neurological signs may manifest with extreme agitation, a “feeling of dread” or even loss of consciousness. Every physician should know that patients who have pre-existing bronchial asthma are a special high risk group for fatal anaphylaxis especially if they are food allergic. Fatal reactions involving food allergy are most commonly associated with a respiratory mode of death rather than cardiogenic shock [10].

Patients who present with suspected food allergic symptoms after having ingested, or had contact with or inhaled food allergens need urgent referral to a specialist who is experienced in food allergy and anaphylaxis. Once correctly diagnosed and a management plan has been set up, they should be followed up by the specialist on a regular basis until stable after which education leading to self-management should take place.

The specialist’s diagnostic work-up

A full medical history should explore particularly: time of onset of symptoms, the kind of foods implicated, associated exacerbating factors at the time of relapse of symptoms, pre-existing medical conditions, history of asthma, atopic eczema and infant feeding problems.

A family history of first degree relatives with atopy is a significant risk factor for developing food allergies.

Also, environmental factors should be explored and a note should be made of those factors which amplify food allergic reactions such as simultaneous intake of alcohol and intake of specific medication (e.g. aspirin, codeine, ACE-inhibitor and beta-blockers). Exercise, stress and hormonal changes during the menstrual cycle may be important and some reactions may be exacerbated by taking a hot shower.

Typical symptoms associated with food induced anaphylaxis

Symptom	n=39 cases	
	n (%)	1st Symptom
skin	39 (100)	34
respiratory: upper airways	12 (31)	11
laryngeal oedema	4 (10)	3
lower airways	14 (36)	6
gastrointestinal	13 (33)	6
cardiovascular	7 (18)	1
neurological	5 (13)	0

Appropriate allergy testing is essential

Suspected food allergy should be confirmed using appropriate diagnostic tests [12][13]. Skin prick testing (SPT) and measurement of serum specific IgE will demonstrate sensitisation to the offending food. In case of delayed hypersensitivity atopy patch testing (APT) might be informative. Specific elimination diets, guided by a dietician experienced in food allergy and implemented over a one to six-week period may help identify trigger foods which were not immediately apparent. The “gold standard” in food allergy diagnosis is still the double-blind placebo-controlled food challenge (DBPCFC). However, the procedure is time-consuming and therefore expensive and it poses a potential risk to the patient. Open challenges may be performed if subjective symptoms or day-to-day variations of allergic symptoms do not play a major role. Oral food challenge tests should always be done under medical supervision. Indications for hospitalising patients for a test such as an oral food challenge include previous life-threatening events or challenges with highly allergenic foods. Oral food challenges including exercise testing should be performed if exercise is considered to play a role as an amplifying factor.

Avoid tests of no proven value

Certain diagnostic practices of unproven value are constantly being promoted to the public via the media. Specific food IgG testing has not been shown to be indicative of allergy as most individuals will naturally produce IgG antibodies to food independent of being allergic. Bioresonance, hair analysis, VEGA testing, Kinesiology, Iridology and blood cytotoxic tests are of no proven diagnostic value in allergy [13][14]. All of these tests have at some point been evaluated in the medical literature and found to lack reproducibility and diagnostic validity. Unconventional practitioners use these tests to incorrectly label people with food allergies and food intolerance. This results in the unnecessary prescription of food exclusion diets, possibly resulting in malnutrition. In addition, it results in food-related anxiety and negatively impacts on quality of life for the whole family.

Section B

FOCUS ON ANAPHYLAXIS

Current guidelines for treating anaphylaxis are based on expert opinion but there is little evidence-base regarding what to use and when to administer treatment such as epinephrine, bronchodilator, antihistamine and corticosteroid medication.

Anaphylaxis is a rapid reaction

The rapid onset of most cases of anaphylaxis has been emphasized previously. The interval between eating the offending food and fatal collapse is usually about 25-35 minutes and the dose required to trigger a reaction can vary from a mere trace of allergen to over 100g [10]. Asthma is a major component of fatal food anaphylaxis, especially when the asthma is poorly controlled. Over 50% of the documented USA anaphylaxis fatalities were due to peanut allergy and 96% had associated asthma symptoms as a major factor in the symptom complex.

Reviewing both fatal and near-fatal food anaphylactic reactions showed that very few patients had epinephrine available at the time of their reaction. Of great concern was the fact that the vast majority had had previous allergic reactions but were still not adequately prepared for anaphylaxis [10][15]

Grading of food-induced anaphylactic reactions					
Grade	Skin	GI Tract	Respiratory tract	Cardiovascular	Neurological
1	Localised pruritus, flushing, urticaria, angioedema	Oral pruritus or tingling mild lip swelling			
2	Generalised pruritus, flushing, urticaria, angioedema	Any of above plus nausea and/or emesis	Nasal congestion and/or sneezing		Change in activity level
3	Any of above	Any of above plus repetitive vomiting	Any of above plus sensation of throat pruritus or tightness	Tachycardia (increased > 15 beats/min)	Change in activity level plus anxiety
4	Any of above	Any of above plus diarrhoea	Any of above plus hoarseness, "barky" cough, difficulty swallowing, dyspnoea, wheezing, cyanosis	Any of above plus dysrhythmia and/or mild hypotension	"Light headedness", feeling of "pending doom"
5	Any of above	Any of above plus loss bowel control	Any of above plus respiratory arrest	Severe bradycardia and/or hypotension or cardiac arrest	Loss of consciousness

All symptoms are not mandatory. The severity score should relate to the organ system most affected.

adapted from H. A. Sampson, Pediatrics 2003, 111:1601-1608

When should epinephrine be prescribed?

This has been a contentious issue because of differing views on aspects such as a fear of inappropriate use, dosage, method of administration and the important aspect of proper training. Although each case should be carefully evaluated, this consensus group feels that epinephrine auto-injectors should be issued to at least the following food allergic individuals:

- any patient with a history of a previous generalised severe reaction
- cases in which the reaction appears to be getting progressively more severe
- those who are confirmed allergic to peanuts, tree nuts and sesame seeds
- patients reacting to minute amounts of allergen, and
- patients with co-existent mastocytosis

Epinephrine should be administered in a weight-related dosage of 0.01mg/kg. It may be repeated within 5 minutes if symptoms worsen or severe symptoms persist [16]. Currently only two strengths of epinephrine (150 micrograms and 300 micrograms) are available in the form of EpiPen and Anapen auto-injectors. Using a dose of 0.01 mg/kg the 300 micrograms auto-injector is just optimal for a 30 kg patient while the 150 micrograms auto-injector is appropriate for a child weighing 15 kg. Problems

arise especially in children of less than 10 kg for whom even the 150 micrograms dose is too high, as well as children who weigh between 20 and 25 kg for whom a decision has to be made as to which dosage is best. Similarly, in heavy adults a dilemma arises because the 300 micrograms dose will not be strong enough and sometimes 2 or 3 auto-injections of the 300 micrograms have to be given simultaneously. A wider range of fixed dosage options or an adjustable device needs to be developed.

A prescription-in-isolation of injectable epinephrine given to patients at risk for an anaphylactic reaction is not adequate treatment. The issue of epinephrine auto-injectors with little or no other emergency management training may have the adverse effect of heightening anxiety and confusion. Therefore, extensive training with clear, written instructions for emergency management has to be given to these patients.

In a community setting epinephrine is best administered via the intramuscular using the antero-lateral thigh. This leads to better absorption than the subcutaneous route [17]. Adequate systemic levels of epinephrine cannot be reached using the inhalation route and this is not recommended. Epinephrine by inhalation should be used only when localised laryngeal oedema is evident. In a hospital setting epinephrine can be used intravenously, but cardiac monitoring is important as inadvertent excess dosages can lead to cardiac arrhythmias. Alternative

routes such as sublingual administration have shown promising results in animal models [18], but further studies are needed in humans as problems with salivary oxidation of epinephrine in the mouth may occur.

All patients with anaphylaxis should be carefully observed for at least 12 to 24 hours in case a biphasic reaction occurs. They should be referred to an allergy specialist for review after each anaphylactic episode.

Proposed management plan

Mild anaphylactic reactions

A mild anaphylactic reaction will manifest with symptoms such as generalised erythema, urticaria, angioedema, abdominal pain and/or vomiting.

Management of this type of reaction involves the following:

- Monitor the patient for worsening of anaphylaxis
- Try to keep the patient calm and give anti-histamines and corticosteroids
- Beta-2-agonists may become necessary for respiratory symptoms
- Call for medical assistance and contact the parent or carer (if you are alone you might need to leave the patient temporarily unattended in order to call for help)
- Locate or obtain injectable epinephrine and keep on standby in case anaphylaxis develops

Moderate-to-severe anaphylactic reaction

Moderate-to-severe reactions which necessitate the administration of epinephrine are those cases associated with noisy breathing, swelling of the tongue, tightness in throat, pallor, difficulty in talking, wheeze and/or persistent cough. At this stage:

- Administer injectable epinephrine into antero-lateral thigh muscle (if not already given)
- Administer beta-agonists if available
- Give oral antihistamines and steroid medication (if not already done)
- Call emergency ambulance explaining that anaphylaxis has occurred and contact the parent or carer (if not already done)

Reactions involving the cardiovascular or cardio-respiratory system or combined with neurological symptoms are regarded as very severe and should prompt even more urgent intervention [19].



Section C

FOOD ALLERGY INTERVENTION

Food allergy is a classic model of a disease where the principle of disease management is synonymous with self-management.

Patients are badly prepared for emergencies

The vast majority of food allergic patients are poorly prepared for an unexpected anaphylactic reaction. Sicherer et al [20] identified that less than 20% of anaphylaxis sufferers have epinephrine at hand. In addition, less than 25% of pediatricians could demonstrate the correct use of an EpiPen. This is compounded by the finding that only 25% of pediatricians have prepared a written action plan for patients in the event of anaphylaxis [20]. Clark et al noted that in North America only 40% of patients who were treated for food allergy in an emergency department had had previous instruction on which foods to avoid. Furthermore, only 16% were prescribed injectable epinephrine. Moreover, only 12% had been previously referred to an allergist for diagnosis and management planning [21].

From the above findings on what appears to be a widespread failure of proper management, it is clear that injudicious epinephrine prescription will never replace a thorough allergy evaluation and accurate diagnosis by a competent specialist. Over-prescribing of epinephrine can also result in an increase in food anxiety and may actually reinforce the psychological fear of an unexpected allergic reaction. Similarly, unnecessary dietary precautions can lead to social exclusion and isolation of individuals and further stunt education and emotional development. It is also clear that all patients with epinephrine as well as their families, teachers and care givers need thorough instruction on how and when to use injectable epinephrine [22]. This has led to calls for a European multilingual step-by-step treatment plan for food allergy and anaphylaxis which can be applied in an agreed manner, according to symptom severity.

Recognising hidden food allergens

There is no cure for food allergy and consequently, there is no effective therapy other than avoidance. In practice, many cases are informed of the diagnosis and simply instructed to avoid the allergen without any further education or support. This common practice is wholly unacceptable and has led to many of the recommendations in this text.

Identification of food allergens in day-to-day foods is extremely difficult for the unwary as common allergens may be labelled with unfamiliar names. Therefore, better food labelling and patient education is mandatory. Every patient with food allergies should see a dietician with specialist training in food allergy for dietary advice and supervision of any elimination diet to ensure that it is nutritionally adequate. The dietician should also help the patient to understand food labelling and be aware of hidden allergens or alternative names for known allergens. For example, milk allergic patients need to know that whey and casein are other names for cow's milk products.



A major breakthrough assisting patients to recognise hidden allergens has been the recent European Union legislation that food labels shall clearly declare whether any one of 12 allergenic substances is present [23]. This abolishes the old «25 percent rule», whereby known allergens had to be incorporated in the label only if the food contained more than 25 percent of that allergen. Now all foodstuffs that contain substances such as cereals (including gluten), crustaceans, hen's eggs, fish, peanut, soybeans, cow's milk, nuts, celery, mustard, sesame seeds and sulphur dioxide must be labelled as such.

Major allergenic foods listed in EU draft directive on labeling of foods

- Cereals containing gluten (i.e. wheat, rye, barley, oats or their hybridized strains) and products thereof
- Crustaceans and products thereof
- Eggs and products thereof
- Fish and products thereof
- Peanuts and products thereof
- Soybeans and products thereof
- Cow's milk and products thereof (including lactose)
- Nuts (i.e. Almond, Hazelnut, Walnut, Cashew, Pecan nut, Brazil nut, Pistachio nut, Macadamia nut and Queensland nut) and products thereof
- Celery and products thereof
- Mustard and products thereof
- Sesame seeds and products thereof
- Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/l expressed as SO₂.

Mills et al, Allergy 2004, 59: 1262-8

There is mounting pressure to ban the labelling of allergen free foods with the disclaimer “may contain traces of nuts” or “processed in a factory that prepares nut containing products” as these statements do not help the patients to decide whether or not a food is safe to eat. Clear-cut labelling is essential. However, we still do not know precisely how much allergen is “too much”. The Lowest Observed Adverse Effect Level (LOAEL) of the various allergens needs to be investigated in highly sensitive individuals [24]. These levels will be critically important for food regulatory agencies in assessing anaphylaxis risk.

Three places of risk for those who are food allergic

Studies have emphasised that food allergic patients experience the greatest risk :

- when out-shopping for food
- when ordering food in a restaurant or from a caterer
- when eating food prepared by friends or relatives at home, or by caretakers at day care centres and schools

A number of countries now have anaphylaxis registers to record reactions. All emergency room staff and primary care physicians should be encouraged to become involved and accurately report all cases of anaphylaxis.

More food allergy awareness

General knowledge about food allergy can be reinforced using written instructions, videos, DVDs, telephone help lines and via internet chat forums with trained allergy facilitators. Action plans need to be individualised but should contain common basic first aid measures. Many experts advocate a “food allergy passport” with an individualised written emergency action plan which will be very helpful for carers, colleagues, teachers and medical personnel who may be faced with emergency situations.

Training and education for the community

A number of European hospitals, clinics and allergy support groups now offer courses to instruct patients with allergies. These courses have been extended to parents, schools, factories and other institutions. There is mounting evidence that if patients are more aware and proactive in their own management, then they are less likely to have accidental adverse allergic events. On average, a minimum of 6 hours needs to be spent in a self-education group environment to get real benefit. There should be regular contact with the group in the first year and this is continued with “support-on-demand” thereafter. Ethnicity and cultural differences should be taken into account when setting up these courses to gain maximum impact and best outcomes. These courses have proved extremely popular with patients and their parents and in some European countries health insurance companies now offer financial support for these programs. Courses in allergy self-management are still not widely available tending only to be accessible in larger cities in the European Union. Unfortunately, training courses specifically focusing on food allergy self-management are much rarer.

Uniform action plan in simple language

Every patient with a history of anaphylaxis and severe food allergy should carry an Action Plan card. This must include essential details of the patient (height, weight, age, concomitant medication and associated illnesses) of their allergy (allergen, severity and medication they carry), as well as contact details for their physician, carer and local hospital.

Use of injectable epinephrine, beta-agonist inhalers, oral antihistamines and corticosteroids must be clearly explained. Concomitant medication that might interfere with treatment must also be identified (such as ACE-inhibitors and beta-blockers which interfere with epinephrine action). The action plan should include graphic visual cartoon's showing exactly how to administer treatment in a step-wise manner.

Effectiveness of education programs

A question which is often asked is “do education and self-management plans make any difference or alter behaviour in the community?” Various clinical studies have been performed to assess the effectiveness of these patient education programs.

Kapor et al showed significant improvement in three parameters after patient education: these included the patient's knowledge of how to avoid a specific food, the family's understanding of how to manage a reaction and finally critical steps in effective EpiPen/ Anapen administration [25].

Follow-up with a contact group and having a permanent designated “contact person” will improve support and help patients and their care givers. Food allergy cook books with local cuisine are very useful and reassuring, but not yet universally available.

Support networks are essential

The Food Allergy Organisation in the Netherlands has introduced a uniform international plastic ID card which identifies the patient's allergies and contains specific information for doctors, care givers and restaurant staff. Self-help food allergy groups such as the Netherlands Stichting Voedselallergie and Nederlands Anafylaxis Netwerk, UK Anaphylaxis Campaign and the French Allergy Vigilance Network provide educational brochures, “safe” restaurant guides, arrange family education days and outings to safe amusement parks. This helps parents regain their confidence and begin to socialise and bond with other parents with similar food allergic children. Ideally these food allergy and anaphylaxis support networks need to be extended across Europe.

Other sources of trustworthy information such as the internet and booklets, will hopefully soon carry a “seal of approval” indicating that the information has been reviewed by experts and found to be accurate and appropriate. Regrettably, many unregulated publications and internet sites may heighten anxiety by “scare mongering” or just offer inaccurate information which then leads to confusion and poor disease control. Reading this conflicting information makes it difficult for the patient to decide what information is correct and what should be ignored.

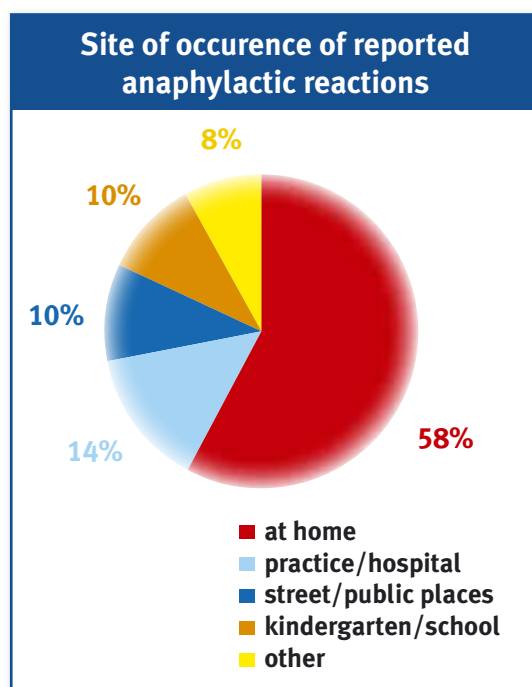
Many aspects need further research

Epidemiological studies will help assess variations in the distribution and frequency of reactions to the principle food allergens in different countries. For example, the preponderance of allergy to peanut in the USA and Western Europe, rice in China, fish in Scandinavia, sesame in the Middle East and poppy seed in Eastern Europe.

Opinion leaders need to encourage countries to set up National Registers of Anaphylaxis to get a clearer idea of the scale of the problem and so plan further appropriate intervention. Near fatal anaphylactic reactions can cause severe psychological consequences to the survivor and their family.

In addition, unnecessary dietary restrictions can result in a nutritionally unbalanced diet and lead to resentment and depression in sufferers and their care givers. Young children may be excluded from kindergarten because staff are unwilling to take responsibility for the child or administering the epinephrine. Studies to assess the social impact of this are a priority in the coming years and government and health care organisations should be encouraged to support these initiatives.

There is also a necessity to study the pharmacology of epinephrine further, to clearly identify the therapeutic window for this drug and to assess the best route for administration. The development of new multi-strength devices is a priority and needs to be explored as a matter of urgency.



Data from B. Niggemann et al, Germany 2005

Innovative developments

Anti-IgE antibody therapy is not a cure but certainly may play a role in reducing severe reactivity associated with exposure to food allergens [26]. Although it may act as a “safety net” in the short term, it is expensive and needs to be administered by injection. Unfortunately, the original tested drug TNX-901 was prematurely withdrawn and the studies have to be repeated with Omalizumab which to-date has not been widely tested in food allergy. Promising new “engineered” recombinant vaccines using modified protein allergens for food allergy are in the process of being developed [27].

Hypo-allergenic foods can be genetically modified to produce pan-allergen (profilin and LTP) free foods but adverse public opinion regarding genetically modified foods is a major obstacle to this. Hypo-allergenic cultivars of certain mass produced crops can be selected and farmed instead. However, whether these will be successful in reducing food allergic sensitisation remains to be seen.

In the interim, there is currently no cure for food allergy or anaphylaxis. It is therefore essential that we educate the patients, their caregivers and physicians in a structured manner, so that they can adequately manage their food allergies and prevent food induced anaphylaxis.

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