

## REVIEW

## Food allergy in children

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Food allergy is being increasingly recognised with the highest prevalence being in preschool children. Pathogenesis varies so diagnosis rests on careful history and clinical examination, appropriate use of skin prick and serum-specific IgE testing, food challenge, and supervised elimination diets. A double blind placebo controlled food challenge is the gold standard diagnostic test. Avoidance of the allergenic food is the key towards successful management. IgE mediated food allergy may present as a potentially fatal anaphylactic reaction, and management consists of the appropriate use of adrenaline (epinephrine) and supportive measures. Sensitisation remains a key target for intervention. Disease modifying agents are currently under trial for managing difficult allergies. Management requires a multidisciplinary approach and follow up.

The word allergy can be traced back to the Greek word *allon argon* coined in the 19th century, which means to react differently.

Clemens P Pirquet Von Cesenatico (1874-1929), one of the founders of modern day immunology introduced the term allergy in 1906 to describe both protective immunity and hypersensitivity reactions.<sup>1</sup>

The future King Richard III knew of his adverse reaction to strawberries and arranged for it to be served to him at a royal banquet attended by an arch enemy. He developed an urticarial rash immediately on consuming the fruit and this served as the perfect excuse to accuse the enemy of conspiracy and order his execution.<sup>2</sup>

## EPIDEMIOLOGY

The evidence base with which a general paediatrician can manage food allergy has improved considerably in the past decade. For example, sequential birth cohort studies on the Isle of Wight have confirmed the prevailing impression that sensitisation to peanut doubled in the early 1990s.<sup>4</sup> Food allergy in young children is usually caused by milk (2.5%), egg (1.3%), peanut (0.8%), tree nuts (0.2%), fish (0.1%), and shellfish (0.1%) with the overall prevalence being 6%.<sup>5-6</sup> Food allergy resolves in most affected children although its nutritional and social consequences may be considerable, requiring regular review and support. Resolution of milk and egg allergies is the norm but peanut allergy usually persists (see below).

There has been a significant increase in hospital admissions for systematic allergic diseases with anaphylaxis and food allergies accounting for most. Admissions for food allergy rose from 6 to 41 per million between 1990-1 and 2000-1.<sup>7</sup>

The prevalence of nut allergy also seems to be on the rise and is reflected in the increasing number of children attending allergy clinics with this complaint.<sup>8</sup>

Children with atopic disease are more likely to have food allergies in comparison with the general population; about 30% of children with moderate to severe atopic dermatitis and 10% of children with asthma have been shown to have food allergies.<sup>9-10</sup>

Risk of death from fatal allergic reactions to food has been estimated to be about 1 in 800 000 per year with asthmatic children at a higher risk. In a UK study between 1992 and 2002, eight children died (incidence of 0.006 deaths per 100 000 children 0-15 years per year) secondary to such a reaction.

The same study reports six near fatal reactions between 2000 and 2002 and 49 severe ones, yielding incidences of 0.02 and 0.19 per 100 000 children 0-15 years per year respectively.<sup>11</sup> Cases requiring intubation were deemed near fatal.

A reaction was defined as severe based on one or more of the following criteria: cardiorespiratory arrest; need for inotropic support; fluid bolus of more than 20 ml/kg; more than one dose of adrenaline (epinephrine) by any route or more than one dose of a nebulised bronchodilator.

However, Clarke and Ewan believe these figures to be an underestimate as not all deaths may be registered as allergy or related terms. They propose that anaphylactic reactions are often mislabelled as asthma deaths because of lack of antecedent history or information.<sup>12</sup>

There is evidence in the UK of a doubling of admissions for anaphylaxis between 1991 and 1995. In 385 children, 60 reactions were attributed to food and aetiology was not recorded in 240.<sup>13-14</sup>

An American study identified 32 fatal cases of food allergies between 1994 and 1999. The age range was 2 to 33 years with three subjects younger than 10 years. Sixteen (50%) were females. In contrast with the UK studies where only two of the eight deaths were secondary to nuts, peanut accounted for 20 (63%) and other nuts, 10 (31%) of deaths. The remaining two

**Abbreviations:** IgE, immunoglobulin-E; RAST, radioallergosorbent test; CAP-FEIA, CAP fluorescent enzyme immunoassay; NPV, negative predictive value; PPV, positive predictive value; OAS, oral allergy syndrome

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deaths occurred from milk and fish respectively. Of the 32 deaths, all but one subject was known to have food allergy before the fatal event and most (31) had asthma.<sup>15</sup> Peanut and tree nuts accounted for most food related deaths in a series reported from Manchester by Pumphrey and Stanworth in the mid-1990s.<sup>16</sup>

### Resolution of food allergies

Most children lose their sensitivity to most allergenic foods (egg, milk, wheat, soya) within the first five years of life.<sup>17</sup>

Longitudinal studies support this: 85% of children with cows' milk allergy in the first two years of life are tolerant to milk by the age of 3<sup>4</sup> and up to 80% infants with egg allergy by 5 years.<sup>18</sup> Twenty per cent of children younger than 2 years with peanut allergy develop tolerance to them by school age<sup>19</sup> and children with peanut specific IgE levels of 5 kU/l or less may have 50% chance of outgrowing their allergy.<sup>20</sup>

## PATHOPHYSIOLOGY

Differences are so great that one man's meat is another man's poison. Lucretius<sup>2</sup>

The normal immune response to food antigens is the development of systemic hyporesponsiveness or oral tolerance. This is a dynamic process. The failure to establish tolerance has been shown in many animal studies to be critically affected by genetic background, the timing of introduction of the food, and the nature of the food allergen itself. Although difficult to study in humans, generally the same principles seem to hold true.

Warner *et al* propose that allergy may have its origins in early fetal life.<sup>21</sup> The mature gastrointestinal tract forms a natural barrier that prevents food antigens being absorbed unchanged. Complex biophysical and immunopathological properties of the gut prevent antigens from being absorbed and inciting an inflammatory response.<sup>22</sup>

The fetal and neonatal gut, with mature and active immune cells, has been the principal postulated route of sensitisation, following swallowing of allergens in the amniotic fluid. The fetus also aspirates amniotic fluid into its respiratory tract and is directly exposed through highly permeable skin. Exposure is also postulated to be via direct transfer of allergen across the placenta. This is IgG mediated and occurs in the third trimester of pregnancy.

Sensitisation may also occur in early infancy through breast feeding with the antigen gaining access through the mother's milk.<sup>21</sup> However, developmental immaturity of this barrier in infancy and suboptimal IgA production in the first few years of life may be a reason for increased prevalence of food allergies in children of this age group.<sup>23</sup>

The form of the food and timing of its introduction are also important factors in the development of symptoms, for example, boiled peanuts are less allergenic than the roasted form.<sup>20</sup> Coeliac disease presents after introduction of gluten in the weaning diet.

Attention has focused recently on non-oral routes of sensitisation to peanut in infants. Acquisition of oral tolerance may have been bypassed by encounter of allergen through the skin, especially inflamed, eczematous skin, which may promote allergic sensitisation. This has been proposed in a retrospective epidemiological study<sup>24</sup> and supported by animal studies.<sup>25</sup>

### Th1 and Th2 responses

Despite the clinical focus on IgE as the final mediator of allergic reactions (see below), the T cell remains the orchestrator of the immune response in food allergy, just as it is in other diseases. Cytokines produced by the CD4 subgroup of T lymphocytes (helper T cells) mediate a wide

## Box 1 Definitions

The World Allergy Organisation in 2003 has proposed a new nomenclature for allergy.<sup>3</sup>

*Hypersensitivity* should be used to describe objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons.

In contrast, *intolerance* describes an abnormal physiological response to an agent, which can be certain foods or additives. These are non-immune mediated.

*Atopy* is a characteristic that makes one susceptible to develop various allergies. It is defined as a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins. As a consequence, these persons can develop typical symptoms of asthma, rhino conjunctivitis, or eczema.

An *allergen* is an antigen causing allergic disease.

*Allergy* is a hypersensitivity reaction initiated by specific immunological mechanisms. When other mechanisms can be proved, the term non-allergic hypersensitivity should be used.

*Food allergy* is thus, a term applied to a group of disorders characterised by an abnormal or exaggerated immunological response to specific food proteins that may be IgE or non-IgE mediated.

range of pro-inflammatory and anti-inflammatory responses. Most CD4 T cells belong to Th1 and Th2 subgroups producing Th1 and Th2 cytokines respectively.

Interferon gamma is the archetypal Th1 cytokine and is involved in pro-inflammatory responses, killing intracellular parasites and mediating other inflammatory responses. Interferons 4, 5, 10, and 13 are the principal Th2 cytokines and mediate IgE and eosinophilic responses in helminthic disorders (generally in endemic areas of the developing world, where allergic disorders are less prevalent) and in atopic diseases (generally in the developed world, where helminthic infection is now less common than in previous generations). These patterns seem to hold true in food allergy.<sup>26</sup>

There is also a distinct entity of CD4 cells (5%–10%) that are known as T regulatory (Tr) cells (previously classified under suppressor T cells), which, along with their cytokines such as TGFβ and IL10, seem critical to the control of inflammatory responses.

Normally, there is a dynamic balance between Th1 and Th2 responses with Th2 counteracting the excessive pro-inflammatory and tissue destructive tendencies of Th1. Postnatal persistence of the fetal Th2 dominated microenvironment is considered to be an important feature in the ontogeny of the allergic phenotype.<sup>21</sup> Allergy is regarded as a Th2 weighted imbalance and research into newer therapeutic approaches in managing allergies is being targeted towards redirecting Th2 responses in favour of Th1 responses.<sup>27</sup> Regulatory T cells are capable of suppressing deleterious responses against self or non-self antigens. Recent studies have shown that the emergence of allergic and fatal autoimmune and inflammatory disease may be secondary to the defective development of these regulatory T cells.<sup>28</sup>

A detailed discussion of the role of T lymphocytes in the immunopathology of food allergy is beyond the scope of this text and interested readers are referred to Eigenmann and Frossard's review on the subject.<sup>29</sup>

## TYPES OF ALLERGIC REACTIONS

Allergic reactions can be mild, moderate, or severe. The first comprise of symptoms affecting a specific body area and is

characterised by itchy rash, hives, watering of the eyes, and nasal congestion. The oral allergy syndrome is a typical example.

Moderate reactions spread to other parts of the body and may include difficulty in breathing.

A severe reaction presents as anaphylaxis with accompanying cardiorespiratory compromise.

Allergic reactions to food can be broadly classified as IgE or non-IgE mediated.

### IgE reactions

These occur when IgE antibodies are produced in response to allergen exposure. IgE is normally found in very low concentrations in the serum and only a small proportion of the plasma cells in the body synthesise this immunoglobulin. These bind to Fc receptors on the surface of mast cells and basophils. When IgE molecules are complexed with specific antigens on mast cells in the gastrointestinal tract, there is degranulation of these cells. This leads to the release of vasoactive amines and cytokines and synthesis of a variety of arachidonic acid derived inflammatory mediators.

In a sensitised subject, swelling of the lips and tongue occurs almost immediately after ingestion of food. This is secondary to increased permeability of the capillaries and small vessels with resultant transudation of fluid. Contact urticaria may be seen if the food is brought into contact with skin. The ingested allergen may induce vomiting or diarrhoea, asthma, and rarely, fatal anaphylactic reactions.

A person allergic to a particular food may develop an allergic response to other foods containing similar allergens, which is termed cross reactivity. For example, allergy to birch plant pollen may cause cross reaction to hazelnuts, apple, pear, peach, plum, nectarines, cherry, and carrots. Ragweed allergy may cause cross reaction to melons and banana. More than 50% of people with latex allergy develop allergies to fruit, the so called latex fruit syndrome with cross reactivity to potato, avocado, banana, tomato, kiwi, and chestnut.<sup>30</sup>

### Food dependent, exercise induced anaphylaxis

This is again an IgE mediated reaction after vigorous exercise within several hours of eating an implicated food. If the food is eaten and not followed by exercise or vice versa, no reaction occurs. The pathophysiology entails mast cell activation after metabolic changes brought about by the exercise. The onset is in young adulthood in atopic people and foods implicated include celery, wheat, fruit, peanut, fish, and crustaceans.

### The oral allergy syndrome (OAS)

Itching, irritation, swelling, or urticaria in or around the mouth after ingestion of fresh fruit or vegetables. It is an IgE mediated non-life threatening reaction classically after consumption of fresh food containing heat labile proteins that get destroyed on cooking. It is often associated with reactivity to pollens, which are homologous to the labile food allergens. For example, subjects with birch pollen associated OAS to apple can usually tolerate peeled or cooked apple but cannot eat them raw and unpeeled.

Although the symptoms are mild, they may evolve into severe allergies over the course of time. As the range of such fruits is wide and the allergens are unstable, fresh fruit must be used for diagnostic skin testing either by macerating the fruit and using the pulp or by directly pricking the fruit and then used to prick the patient's skin, the so called prick to prick skin test. This is, naturally, less standardised than commercial skin tests, available for the most common food allergens.

### Non-IgE reactions

In these reactions, allergen specific lymphocytes and IgG antibodies mediate the inflammation.

Non-IgE mediated reactions may result from a direct effect on mast cells via chemical histamine liberators and histamine containing foods (chocolate, tomatoes, and strawberries).

### Heiner syndrome

A non-age mediated adverse pulmonary response to food. It is characterised by an immune reaction to cows' milk protein with precipitating IgG antibodies. These result in lung infiltrates, pulmonary haemosiderosis, recurrent pneumonia, anaemia, and failure to thrive.

### DIAGNOSING FOOD ALLERGY

The key to the diagnosis of food allergy rests on obtaining a good history backed by appropriate tests. Points in the history include<sup>31</sup>:

- Suspected foods
- Time between ingestion and reaction
- Amount of food needed to cause a reaction
- Frequency and reproducibility of reactions
- Signs and symptoms
- Was food raw or cooked
- Could there have been any cross contamination of foods?
- The location of the reaction

### INVESTIGATING FOOD ALLERGY

#### Skin prick testing (SPT)

This is a simple but effective test and carried out by trained staff, even in the primary care setting. Wide ranges of standardised allergen extracts are available and this facilitates testing different extracts at the same time.

SPT has a positive predictive value (PPV) of about 60% but this may not necessarily signify allergy and its diagnostic value is often controversial. However, they are rarely negative in true IgE mediated allergic reactions (excellent negative predictive values (NPVs)).<sup>32</sup>

In a recent study, Hill and colleagues have developed diagnostic cut off levels for SPT to peanut, cows' milk, and egg. They defined 100% diagnostic wheal diameters greater or equal to 8 mm for cows' milk and peanut and 7 mm for egg in children more than 2 years of age and wheal diameters more or equal to 6 mm (cows' milk), 5 mm (egg), and 4 mm (peanut) in the under 2s. In infants under 6 months not previously exposed to the above foods, SPTs were often negative or below the diagnostic cut offs but reached the cut off levels by 2 years.<sup>33</sup>

Although very safe, (rate of systemic reactions of 33 per 100 000 tests, all occurring in patients with asthma),<sup>34</sup> caution must be exercised when testing a patient with a history of anaphylaxis or when using non-standardised, non-commercial extracts.

#### Box 2 Examples of non-IgE mediated allergic response to food

- Skin—angioedema, atopic dermatitis, dermatitis herpetiformis
- GIT—allergic eosinophilic gastroenteritis, proctocolitis, coeliac disease
- Respiratory tract—asthma, Heiner syndrome



### Box 3 Skin prick testing

- A drop of an allergen extract is placed on the skin over the flexor aspect of the forearm
- Eczematous areas of skin are avoided
- Small amount is introduced into the epidermis with a calibrated lancet
- Evaluated in 10 to 20 minutes

A positive reaction produces a wheal secondary to histamine release. The wheal must be more than 3 mm compared with a negative control wheal.

Certain factors can influence the tests and these include site of testing, with a smaller reaction seen if the skin is loose where the test is performed (for example, wrists). Antihistamines must be avoided 48–72 hours before the test and corticosteroids may also affect the reaction. Skin tests may vary slightly over the day and menstrual cycles can influence outcome. SPTs require operator skills and experience but give immediate, visible results that families appreciate. Unexpected results should prompt retesting as these may be attributable to technical difficulties with the test, for example, it can be very difficult to be confident of tests in a very wriggly child.

### In vitro diagnostic tests

Quantitative measurements of food specific IgE antibodies with CAP system FEIA or Unicap (Pharmacia Diagnostics, Uppsala, Sweden) are used as a follow up to positive skin tests. They are predictive of the presence or absence of IgE mediated food allergy.<sup>35</sup> (Note however, that the term RAST is now obsolete).

Table 1 provides diagnostic levels of specific IgE for various foods. Levels exceeding any of these values pose a greater than 95% probable risk of experiencing an allergenic reaction. This is particularly true in cases of allergy to milk, egg, fish, and peanut and their reliability can spare the need for oral challenges. Specific IgE can be used for additional foods (soya and wheat) but the performance characteristics for them is low.<sup>36–38</sup> Such predictive values have not been developed yet for other common allergens such as tree nuts or sesame.

If the food specific IgE is increased above the PPVs, avoiding the food in question must be advised if there is a good history of reactions. Equivocal histories and borderline results may necessitate a formal food challenge. In children with no history of reaction to a food, a specific IgE value that exceeds the PPVs must be interpreted carefully and there may be a challenge in these cases. It must be remembered that the

**Table 1** Predictive value of food allergen specific IgE concentrations<sup>38</sup>

95% Predictive level Allergen	kU <sub>A</sub> /L	PPV
Egg	7	98
Infants ≤ 2 years	2	95
Milk	15	95
Infants < 2 years	5	95
Peanut	14	100
Fish	20	100
Tree nuts	about 15	about 95
Soybean	30	73
Wheat	26	74

values were derived in studies of children with positive histories of reaction to the foods being tested by food challenge. This is an area of active debate at present.

Annual CAP-FEIA testing may be required to monitor allergy status. Decreasing levels may signify possible future resolution and very low levels, the need for an oral challenge to prove resolution. In contrast, rising IgE titres do not automatically signify worsening allergy.

### Elimination diets

These are undertaken after obtaining a thorough and clear history to find out if symptoms have any allergic basis and are useful for diagnosis and management.

Foods suspected on the basis of the history and SPTs are completely excluded from the diet. This is done under medical and dietetic advice and broad elimination diets must be discouraged. Resolution of symptoms on elimination of the offending foods is suggestive of food allergy.

When improvement is noted it may be worthwhile repeating the challenge to justify continued exclusion of the suspected food. The problem with using elimination diets remains that of compliance and cross reactivity of certain foods in causing allergies. Besides, its potential for nutritional deficiencies and social isolation must be borne in mind. These diets must be used under the guidance of an experienced dietician. Allergists and other health professionals must recognise the advantages of elimination diets (improvement of symptoms) as well as disadvantages (increase of the time required to purchase food and prepare meals, impossibility to eat at restaurants, friends' houses, or at school), and choose the most appropriate diets.<sup>39</sup>

### The oral food challenge

Standardised oral challenge (ideally performed double blind and placebo controlled) remains the gold standard in diagnosing food allergy. The selection of foods to be tested depends on the patient history and results of food specific IgE.

The open challenge is easiest to perform and consists of the patient eating a small quantity of the suspected food in its natural form and under careful medical and nursing supervision. A negative test would go a long way in reassuring a patient on the safety of eating the particular food tested but may need to be confirmed by performing a double blind challenge.

Double blinded placebo controlled tests in reality however, are time consuming in clinical paediatric practice. They are reserved for cases in which anxiety (child or parental) is an important feature and also for research studies.<sup>40</sup>

Oral food challenges may be associated with specific risks and those with a clear history of anaphylaxis after an isolated ingestion of the specific food should not be challenged outside a carefully supervised hospital setting.

Applying DNA technology, up to 40 food allergens have been produced in recombinant form, which implies standardised quality and unlimited quantity of the respective proteins. Hence such molecules may be useful in improving diagnosis in future. The first experiments using recombinant food allergens seem very promising.<sup>41</sup>

### Monitoring for resolution of food allergy

Although variations in practice exist in follow up allergy testing, a simple outline of an approach is illustrated in figure 1. In centres where SPT is not routinely available, the algorithm can still be used, relying on the blood tests.<sup>42</sup>

### MANAGEMENT OF FOOD ALLERGY

Once a definite diagnosis of food allergy is made, strict avoidance of the offending food is of paramount importance.

#### Box 4 The double blind placebo controlled challenge

- Food to be tested is avoided for two weeks before challenge.
- Antihistamines are withdrawn
- The patient receives the disguised form on one day followed by dummy challenge on another
- Neither patient or doctor knows whether the food or dummy is being tested (double blind)
- The food is given after a fast or light breakfast to minimise the effect of other foods in its absorption
- The initial dose is selected to be below probable threshold as determined by clinical history (50–250 mg doubled every 15 minutes)
- Once 8–10 g is tolerated, IgE mediated reactivity is generally ruled out (0.6 g/kg for non-IgE mediated hypersensitivities).<sup>31</sup>
- The food is then given in usual quantities to rule out the rare false negative challenge

Patients must be educated on avoiding known allergens and recognition of reactions, some of which may be life threatening. Anaphylaxis education along with educational material and action plans must be agreed upon and circulated.

As is true of other chronic conditions, management requires a multidisciplinary approach. Paediatricians appropriately trained in this regard must coordinate care with nurse specialists and dietitians. Their input is valuable for follow up and prevention of nutritional deficiencies and subsequent retardation of growth.

GPs form an important link between the community and the hospital allergy services. Most children initially present to them and based on a thorough history and clinical examination can be referred appropriately. This can reduce the burden on overstretched and often limited hospital services.

Studies have shown that schools are not sufficiently well informed on the management of acute allergic reactions and they vary in their policies and attitudes.<sup>43</sup> Therefore, school nurses and teachers must be educated regarding the various aspects of allergies and its potential complications.

Food allergies can lead to social isolation and emotional scarring. Children with food allergies are often not allowed to go to parties and other social events, as these settings are perceived by parents or teachers to be a medical risk. Greater awareness and community support is vital and paediatricians, GPs, schools, allergy support groups, and the media all have an important role in disseminating correct information and supporting these families.

## DRUGS

Antihistamines and corticosteroids are useful for symptomatic relief of mild to moderate allergies (for example, oral allergy syndrome). It must be emphasised that they however, do not block systemic reactions for which prompt administration of adrenaline is crucial.

Adrenaline (EpiPen/Anapen Auto-injector 0.3mg or EpiPen Jr/AnapenJr Auto-injector 0.15 mg; Ana-Kit 0.05, 0.1, 0.15, 0.2 or 0.3 mg used for infants available on a named patient basis) remains the most important drug in blocking severe allergic reactions and anaphylaxis.

Adrenaline works by reversing peripheral vasodilatation, reducing laryngeal oedema, dilating airways, increasing myocardial contractility, and suppressing leukotriene and

histamine release. It is generally safe and works best when given early. There is no contraindication to the use of adrenaline to treat severe allergic reactions or anaphylaxis. An intramuscular dose of 10 µg/kg is the recommended dose.<sup>44</sup> The subcutaneous route is no longer recommended in the management of anaphylaxis, because of the variable systemic levels of adrenaline that result from this mode of administration.

Auto-injectors currently represent the most user friendly method of giving the drug but the disadvantage with these is that neither of the two available preparations (0.15 mg for EpiPen Jr/Anapen Jr and 0.3 mg for the EpiPen/Anapen) are suitable for infants and there is a risk of over-dosing.<sup>45</sup> An alternative would be an adrenaline ampoule along with a needle and syringe but during an emergency the question asked is can the right dose be drawn up and given to or by a panicking patient? Similarly, an 80 kg man may be considerably under-dosed by a single injection of 0.3 mg adrenaline. There is therefore a strong case for a wider range of auto-injector doses.

Patients who are at risk of anaphylaxis need to carry adrenaline at all times and need to be educated on its administration. The packs need to be to be labelled so that in a scenario of sudden collapse, someone else can rapidly give the drug. Studies have highlighted the fact that most people who have a fatal reaction did not have adrenaline available at the time of the reaction.<sup>16</sup>

If the patient does not respond to the initial dose of adrenaline, it may be repeated at five minute intervals according to cardiorespiratory function. Continuing deterioration requires volume expansion, intravenous aminophylline, or nebulised bronchodilators. In addition to oxygen, ventilatory support and tracheostomy maybe required in life threatening airway compromise.<sup>46</sup>

After anaphylactic reaction, patients should wear an information tag such as a MedicAlert or Medi-Tag bracelets to alert bystanders in the event of future reactions.

## Who should be prescribed the adrenaline auto-injectors?

There are no clear cut guidelines for the provision of an auto-injector device to a child with food allergy. This has led to criticism of over prescription and under prescription. Every unit must devise protocols based on evidence based recommendations and a suitable approach would be to provide adrenaline if:

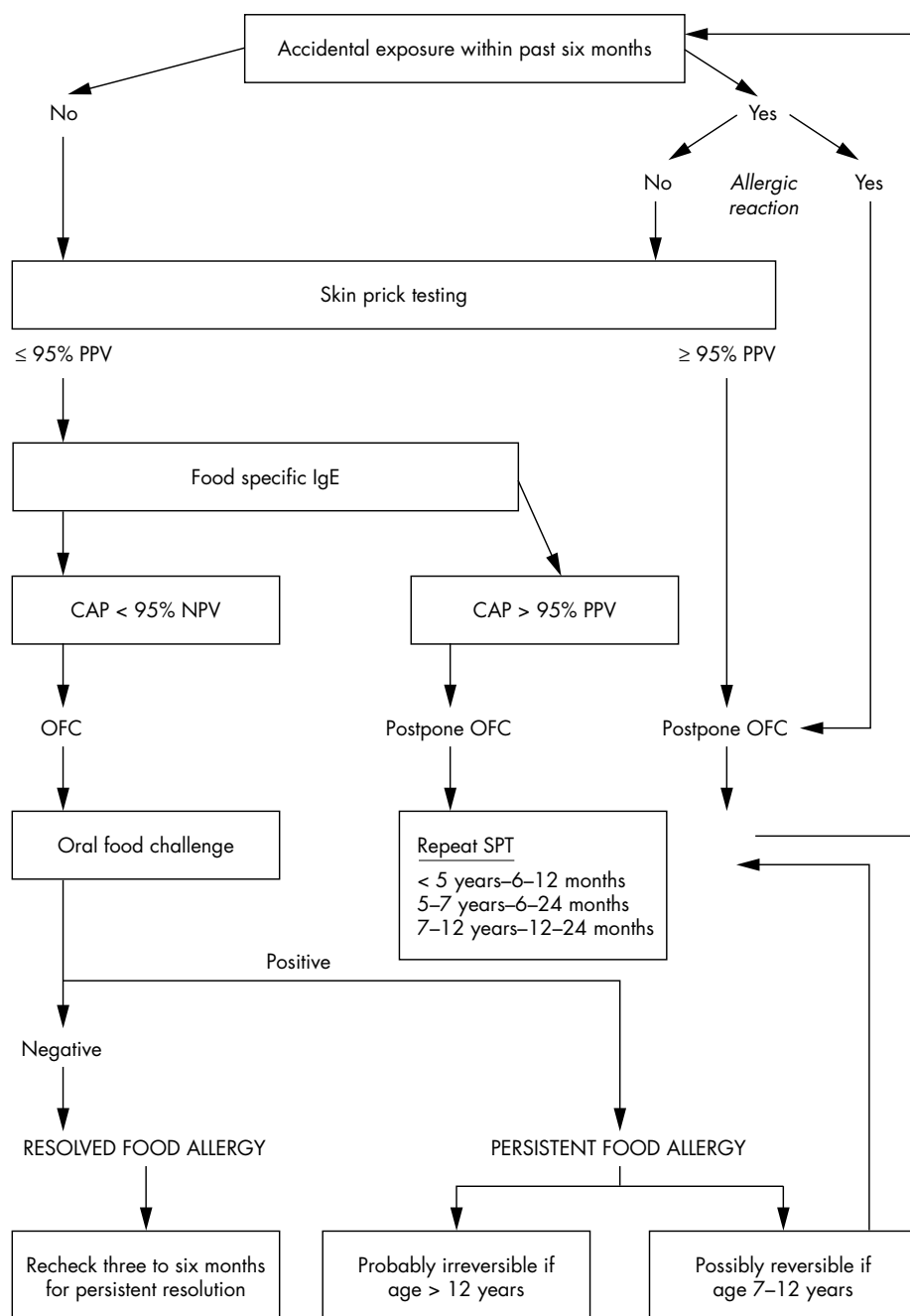
- In the event of a previous life threatening reaction or airway compromise
- An allergic child with severe or poorly controlled asthma
- After full explanation of the pros and cons, the patient or parents request provision (informed choice).<sup>47</sup>

Additional factors needing consideration are peanut or tree nut sensitivity, reactions induced by traces or small amounts of allergen (a larger dose may cause a worse reaction), a strongly positive skin test, and difficult access to emergency care—that is, families living in isolated rural areas.<sup>48</sup> In the USA, auto-injector provision is almost universal for peanut allergy.

The debate for and against prescribing adrenaline auto-injectors will continue until more evidence based guidelines are available based on robust and valid scientific studies. What is important is to realise that it is impossible to predict absolute and acceptable limits of risk.

## VACCINATIONS AND FOOD ALLERGIES

MMR vaccine is cultured in fibroblasts from chick embryos and may contain minute amounts of egg related antigens.



**Figure 1** Algorithm for monitoring resolution of food allergy (adapted from Thong and Hourihane<sup>42</sup>). Outcome of any accidental exposure since the last assessment is determined. If none have occurred SPT is carried out. If mean wheal diameters show a decreasing trend, specific IgE is measured. Positive predictive values below 95% show the need to perform an oral challenge. A negative challenge shows resolution whereas persistence of food allergy is suggested by a positive challenge. If on the other hand, the diameters have not changed or are increasing, the challenge is postponed and SPT repeated at future follow up. A similar plan is followed after accidental exposure not leading to an allergic response. However, should a reaction occur after accidental exposure, oral challenge is postponed and SPT repeated at a later date.

Life threatening anaphylaxis is secondary to an IgE mediated reaction to gelatine or neomycin contained in the vaccine. Studies have shown MMR is not contraindicated in children allergic to egg, including those who have had a previous anaphylactic reaction and this should not delay vaccination.<sup>49-50</sup> Children with known systemic allergic reaction to neomycin or gelatin should not receive the vaccine.<sup>51</sup> It is also recommended that children who have had cardiorespiratory compromise secondary to egg allergy and those with coexisting active, chronic asthma should receive the vaccine in a supervised hospital setting.<sup>52</sup> In our local experience, this is very rare indeed, although we are often referred egg allergic children for immunisation in hospital. If the GP referral letter is adequately detailed or we already have reviewed the child, we advise immunisation in the community, unless parental anxiety is overwhelming.

There is also a frequent controversy regarding egg allergy and influenza vaccine, which is cultured in egg embryo tissue. As a result, vaccine uptake constantly falls short of desired targets and is denied to high risk groups (for example, people with asthma and concomitant food allergies) who would benefit most from them. Various studies have effectively shown its safe administration when specific protocols that include incremental doses of the vaccine, are followed, under experienced and supervised clinical settings.<sup>53-54</sup>

#### When to refer to specialist services?

In an ideal world, a paediatric allergist would see every child with food allergy and parents have a right to expect such care in their region. Sadly this is not currently practical, as paediatric allergy clinics are rare in the UK, although where

### Box 5 Multidisciplinary approach towards managing food allergy

Written plan agreed by parent/child/GP/dietitian/paediatrician with copies provided for school, play group, school nurse or health visitor, SCMO, and hospital records.

- Plan of action for home and school regarding
  - avoidance of allergens
  - recognition of clinical features of a reaction
  - basic life support
  - arranging hospital attendance
- Information and demonstration on the use of pen devices to child, parents, relatives, school and play group staff.
- Liaise with GP on prescription of adrenaline pen device and its timely replacement.
- Kits should be "in date and in weight".
- Follow up to check all the above are in order.
- Recommend obtaining a Medic Alert bracelet.
- Optimise asthma control.
- Further follow up and investigations as appropriate.

they exist they offer integrated care to the highest international standards.<sup>55 56</sup>

Therefore, referral pathways need to be established by dialogue between service providers and the consumers, in this case the organisers of primary care.

Children need to be specifically referred to an allergist if:

- there are concerns about the diagnosis, or about the nutritional consequences of intended elimination diets,
- multiple food allergy is suspected and possibly when challenges are being considered. This second aspect may change as generalists become more familiar with food allergy and the ease and usefulness of food challenges.
- there is doubt about the need for provision of rescue medication such as adrenaline auto-injectors, then an allergist's expert opinion should be sought.
- they have a severe food allergy.

Though unmeasured, it is our opinion that optimising the management of a food allergic child's asthma may be critical in the avoidance of a severe or fatal outcome from an exposure to the relevant allergen, because anaphylactic deaths in children usually follow severe bronchospasm and cardiorespiratory arrest. General paediatricians (who are usually very experienced in the management of asthma) should give asthma care special attention in children with food allergies.

### FUTURE INTERVENTIONS ON FOOD ALLERGY

Food allergy remains an important issue of public concern and several studies have been undertaken to examine the influences of human genetics and the environment in reducing the burden of what is now threatening to be a health epidemic.

Some modalities studied include monoclonal anti-immunoglobulinE, probiotics, traditional Chinese medicine, immunotherapy with modified food proteins, peptide bacterial adjuvants, and immunostimulatory sequences.<sup>57</sup>

Immunologists have long been attempting to change the presumed imbalance between Th1 and Th2 responses with immunotherapy. This aims to change immunological

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responses to allergen exposure from a Th2 dominated profile to a Th1 profile.<sup>58</sup>

High dose exposure to food allergens is undergoing trial along with the use of mycobacterial vaccines to boost Th1 responses.<sup>59 60</sup>

Trials show promising results for foods but current interpretation of these therapeutic options are mostly handicapped by studies limited by sample size, selection bias, and severe side effects.<sup>57</sup>

Several trials suggest that birch pollen immunotherapy also decreases allergy to OAS related foods containing Bet v 1-homologous allergens.<sup>61</sup>

A combination of anti-IgE and allergen specific immunotherapy has been shown to be superior when used in combination in children with allergic rhinitis as shown by symptom scores and use of rescue drugs. There is therefore a strong argument for combined therapy to treat food allergic diseases with improved efficacy, limited side effects, and the possibility of a potential cure.<sup>62</sup>

However, as much as the future holds tantalising promise of curative approaches, avoidance of proven allergens still remains the one clear, evidence based recommendation given to food allergic subjects.

### USEFUL CONTACTS

- The Anaphylaxis Campaign, PO Box 275, Farnborough GU14 6SX; tel: 01252 373793, helpline: 01252 377140, fax: 01252 377140, email: info@anaphylaxis.org.uk
- <http://www.eaaci.net> The home page for the European Academy of Allergy and Clinical immunology.
- <http://www.aaaai.org> The home page of the American Academy of Allergy, Asthma and Immunology.

### MULTIPLE-CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AT END OF REFERENCES

1. The gold standard for diagnosing food allergy is
  - (A) A careful history
  - (B) Skin prick testing
  - (C) Oral food challenge
  - (D) Elimination diet
2. The following are true with regard skin prick tests:



- (A) A positive test is diagnostic of food allergy
  - (B) Antihistamines must be avoided two weeks before testing
  - (C) May be affected by stress
  - (D) Rarely negative in true IgE mediated reactions
3. Oral food challenge:
    - (A) Ideally should be performed as a single blind challenge
    - (B) Has a high false negative rate
    - (C) Should not be performed in children who have had a recent anaphylactic reaction to the food being challenged
    - (D) Recombinant food allergens must be used for testing
  4. The definite indications for prescribing adrenaline auto-injectors are:
    - (A) History of asthma or eczema
    - (B) A positive skin prick test
    - (C) Patient requests one
    - (D) All of the above
  5. Recommended dose of adrenaline for a teenager weighing 80 kg is:
    - (A) 1000 µg
    - (B) 300 µg
    - (C) 500 µg
    - (D) 800 µg

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## ANSWERS

1. (A) F, (B) F, (C) T, (D) F; 2. (A) F, (B) F, (C) T, (D) T; 3. (A) F, (B) F, (C) T, (D) F; 4. (A) F, (B) F, (C) F, (D) F; 5. (A) F, (B) F, (C) F, (D) T.

## WEB TRAWL .....

**T**his month we consider two European web sites that are of international interest. The first provides data on drug induced lung disease, the second collects and provides data on antimicrobial resistance in Europe.

**<http://www.pneumotox.com>** Based in France, at the University Hospital in Dijon, the group running this web site collect together papers dealing with drug induced lung disease. On accessing the home page, the user can select which language they wish to use (a choice of English, French, or Spanish is provided). The home page also provides links to two different search methods. Firstly, the user can search by generic drug name; by the name alone, or with different patterns of lung damage that may occur. Alternatively, they may search by clinical or radiological pattern of lung involvement. Whichever search method is used, the user is provided with a list of published papers dealing with the drug in question and, as appropriate, lung conditions it has been associated with. It is stated on the web site that the list of papers provided is not necessarily exhaustive, but some indication is given of the number of known cases of association between the drug in question and the given condition. Although superficially this seems a simple web site, it in fact provides a wealth of useful information. Information is updated regularly, and a date on which the site was last updated (last month at the time of writing) is stated. Use of the web site is unrestricted and its content will be of interest to doctors and other healthcare professionals in a wide variety of disciplines.

**<http://www.earss.rivm.nl>** This is the web site of the European Antimicrobial Resistance Surveillance System (EARSS). EARSS is an international network of surveillance systems, based in a number of European countries, which collect data on antimicrobial resistance. The home page provides links to pages giving details of how EARSS is organised at a national level, a list of participating countries and individuals, relevant meetings, and standardised protocols for evaluating antimicrobial resistance and collecting data. Much of this is probably only of interest to microbiologists, and indeed access to parts of the web site is restricted to microbiologists and their staff. Of more general interest, and available to all users, is a database pertaining to resistant bacteria. The data can be searched by pathogen, antibiotic, year, or geographical region. Different pages on the web site seem to have been updated at different times, and indeed some of the information on the organisation of EARSS is several years old. The protocols and database however are current, although the information available for 2005 is understandably limited at present. Surprisingly for a European web site, only one language option (English) is available, but it is entirely possible that other language versions are available, but not accessible from the English version. The web site in general will be of specific interest to microbiologists and laboratory staff, but the database will of interest to anyone wishing for information on antimicrobial resistance.

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