

Diagnosis and management of food allergy in children

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Abstract

Food allergy (FA) in children is common, affecting about 6% of children in the UK, and is thought to be increasing in prevalence. Presentation varies widely with age, causative food, type of FA (IgE-mediated or non-IgE mediated) and severity. Assessment of suspected FA includes a detailed clinical history and dietary history and appropriate confirmatory allergy testing. The traditional management of complete dietary exclusion of the causative and related foods is evolving to one of limiting exclusion and early reintroduction. Novel treatments under investigation are mechanisms to prevent FA and oral desensitisation in selected cases in an attempt to cure FA. This article aims to give advice to the generalist about how to assess and initiate appropriate investigation a child presenting with possible food allergy.

Keywords Diagnosis; food allergens; food allergy; oral tolerance; treatment

Introduction

Food allergy (FA) in children is common; so all clinicians treating children will regularly encounter children and families living with FA. The focus of management of FA in recent years has shifted from total allergen avoidance to limiting avoidance, earlier reintroduction and attempts to induce oral tolerance and cure the allergy.

Definition and pathogenesis

'What is food allergy'?

The term *food allergy* refers to 'an adverse health effect arising from a specific immune response that occurs reproducibly on

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exposure to a given food (almost always a food protein)'. The definition for FA encompasses immune responses that are IgE mediated, non-IgE mediated or a combination of both.

Food intolerance is a non-immune reaction that includes metabolic (e.g. lactase or fructose deficiency), toxic (e.g. microbial contamination or Scombroid fish poisoning), pharmacologic (e.g. caffeine), psychological (e.g. panic attacks) and undefined mechanisms. A common misinterpretation that still exists is to refer to non-IgE mediated FA as intolerance, as in cow's milk protein intolerance. The correct term is non-IgE mediated milk allergy.

What are the mechanisms of food allergy?

FA allergy is classified on the basis of the immune mechanisms into IgE-mediated, non-IgE mediated (e.g. cell mediated) or a combination.

IgE-mediated reactions are characterised by early onset symptoms typically within 5–30 minutes of ingestion of the trigger food (and almost always within 2 hours). These reactions classically involve the skin (urticaria, angioedema, pruritus), gastrointestinal tract (nausea, abdominal pain, vomiting, diarrhoea) and respiratory system (runny nose, throat swelling, cough, wheeze and dyspnoea).

In certain at risk individuals, food specific IgE antibodies are produced by plasma cells following prior exposure to the antigen. This is known as 'sensitisation'. These antibodies bind to the surface of mast cells, and when re-exposed to the food, antigenic proteins bind to and cross-link these cell-bound IgE-antibodies and trigger the release of symptom-inducing mediators such as histamine. Individuals can have allergic sensitisation to food allergens without having clinical symptoms on contact with that food. Therefore, sensitisation *per se* (i.e. *having a positive allergy test*) is not sufficient to diagnose IgE-mediated FA. A diagnosis requires typical symptoms on exposure to that food and evidence of sensitisation.

A small proportion of children with hay fever develop 'secondary' IgE-mediated FA called Pollen Food Syndrome (formerly Oral Allergy Syndrome). These pollen allergic individuals develop antibodies to closely related or cross-reacting allergens in fruits and vegetables. Symptoms are limited to areas of direct contact (mouth and throat) and only to unprocessed foods as these allergens are labile and are destroyed by stomach acid and heat.

Non-IgE mediated FA is less clearly defined probably because cases are more difficult to identify as the time delay between food contact and symptoms is prolonged (sometimes up to 48–72 hours) and there is no identifying allergy test. Non-IgE mediated FA usually affects infants and young children with predominantly abdominal symptoms including colic, abdominal cramps, vomiting, diarrhoea, constipation, blood in the stools and failure to thrive. Moderate to severe eczema may be a comorbidity. The only diagnostic test for non-IgE mediated FA is dietary avoidance of the suspected food allergen with demonstration of complete or partial resolution of symptoms followed by reintroduction to elicit symptoms again. Dietary avoidance should be for at least 4 weeks and be under dietetic supervision.

Prevalence and natural history

How commonly does food allergy occur?

FA is said to be common and thought to be increasing in prevalence. It is generally accepted that it affected about 6–8% of children in the UK.

Cow's milk, egg, peanuts and tree nuts are the most common allergens in children, with an estimated prevalence for each of 2–3%. Shellfish, fruits and vegetables are the most commonly occurring allergens in adults. Although any food can trigger an allergic response, and more than 170 have been reported to cause IgE mediated reactions, only a few foods cause the majority of allergic reactions, with most attributed to peanut, tree nuts, milk, egg, fish, shellfish, wheat, soya, sesame and kiwi fruit.

Can a child grow out of food allergy?

The natural history of FA is variable and influenced by food and patient factors. FA to milk, eggs, wheat and soya typically resolves in childhood, whilst FA to peanuts, tree nuts, fish and shellfish tends to persist into adulthood. Prognosis also varies by disorder as, for example, non-IgE mediated milk allergy has a better outcome than IgE mediated. Persistence is furthermore likely with higher early levels of sIgE, presence of other or multiple food allergies and of co-existing allergic conditions like asthma or rhinitis. Decreases in sIgE over time may signal resolution.

The proportion of children who outgrow FA to specific foods varies between analyses, although as a guide around 50–60% of children with milk or egg allergy should demonstrate tolerance by school age. Recent evidence suggests that the rate of resolution for foods commonly outgrown has slowed, and that it can continue into teenage years or even early adulthood.

Assessment of children with suspected food allergy

The diagnosis of a FA is important as it guides appropriate and safe dietary elimination, or where negative, enables safe dietary expansion. Assessment is based on history and allergy tests.

How to take a food allergy focused history

A detailed clinical history and careful dietary history are fundamental to the diagnosis of FA. They can establish the likelihood of the diagnosis, suggest which immunological mechanism is involved and identify the potential culprit food triggers. The history should capture the possible causal food or foods, form (raw, cooked or baked) and quantity ingested as well as the timing of the reaction, symptoms interrogated by systems, and ancillary factors or activities accompanying the reaction (e.g. intercurrent illness, exercise, medications).

Presenting symptoms and signs vary widely, as described above, and are influenced by a number of factors. Young children, for example, cannot describe subjective symptoms like pruritus, chest tightness, anxiety or dizziness. In addition, in this age group symptoms may be obvious but difficult to interpret, for example vomiting after feeds or choking with feeds. Some foods trigger reactions at first known contact (e.g. peanuts), whilst other may have been ingested for some time before symptoms occur (e.g. milk). Furthermore, baking milk or egg reduces allergenicity and many can tolerate this form but not less well-processed forms. By contrast, heat stable proteins found in fish or nuts cause symptoms in all forms.

The severity of presentation also covers a wide spectrum in both IgE mediated FA, ranging from, localised peri-oral urticaria or angioedema to life-threatening or even fatal cardio-respiratory arrest of generalised anaphylaxis; and non-IgE mediated FA, ranging from localised eczematous rash to hypovolaemic shock

from profuse vomiting and watery diarrhoea of food protein-induced enterocolitis syndrome (FPIES). FPIES is an increasingly recognised specific severe form of non-IgE mediated FA. It manifests with profuse emesis and diarrhoea in young infants commonly caused by milk or soya allergy, although any food can cause FPIES.

The history must also identify other atopic conditions such as eczema, asthma, rhinitis and hay fever. These can impact on patient general well-being, as, for example, poorly controlled asthma is a risk factor for anaphylaxis.

Most patients present for an assessment of suspected FA in an outpatient setting quite some time after their suspected reaction. Clinical examination will therefore not reveal these, but is nevertheless important to assess the patient for co-existent allergic conditions e.g. asthma, allergic rhinitis or atopic dermatitis.

How to investigate a child with suspected food allergy

The medical history alone or in combination with the physical examination is not diagnostic of FA. The history is used to estimate the risk of allergy, the causative food or foods and the type of food-induced allergic reaction. This then provides a guide to appropriately select and interpret minimally invasive investigations and arrive at a probability of allergy.

Recommended tests are skin prick tests (SPT), measurement of serum specific IgE (sIgE), elimination diets and oral food challenges. The routine use of total serum IgE measurements, intradermal tests, patch tests and basophil activation tests is not advised. A number of unproved tests including serum allergen specific IgG₄ measurement, hair analysis, iridology, applied kinesiology and electrodermal testing (or the Vega test) are to be specifically discouraged.

IgE-mediated food allergy: determining specific IgE levels in the skin (SPT) or serum (sIgE) are the initial tests used to help in the diagnosis of IgE-mediated FA. SPTs are preferred as results are immediately available.

Non-IgE mediated food allergy: as mentioned (under *Pathogenesis*) there are no validated tests to assist in the diagnosis of non IgE-mediated FA. Diagnosis of these types of food allergies relies on observed reduction in symptoms with dietary elimination and recurrence with reintroduction. In practice, where there is noticeable clinical improvement with dietary elimination, the diagnosis is clear and reintroduction of the offending food is rarely performed. By contrast, where the diagnosis is uncertain, particularly in elimination diets assessing the possibility of delayed onset FA in eczema, reintroduction after a period of elimination is an essential part of the diagnostic assessment.

Food challenges: an oral food challenge (OFC), effectively a supervised exposure to a known allergen, is the gold standard test to assess the presence of IgE-mediated food allergy; with the double blind placebo controlled food challenge as the true gold standard. Oral challenges are most frequently used to make a definitive diagnosis of FA where the history and allergy test conflict, or to assess the development of tolerance. Open challenges are usually used in clinical practice. Blinded challenges,

either single or double, are reserved in practice to assess situations where symptoms are subjective (e.g. abdominal pain), delayed, or where psychological factors may play a role (e.g. anxiety in older children).

An emerging indication for oral challenges is 'anticipatory' testing. Recent evidence suggests that early egg allergy or moderate/severe eczema are risk factors for the subsequent development of peanut allergy, and that where such individuals eat peanut regularly in early life peanut allergy can be prevented. Infants presenting with egg allergy or eczema who are sensitised to peanuts (SPT weal size 1–4 mm) are challenged to peanuts to determine tolerance to allow ingestion.

An OFC service is therefore necessary to complete FA assessments. Requirements for supervised challenges include a day-care facility with trained nursing staff to perform the challenges, medical support to manage any allergic reactions, dietetic support to provide the challenge foods and, most importantly, challenge protocols for each allergen. Our clinic has developed a book on food challenges (available at childrensallergy@uhl-tr.nhs.uk).

Management

The traditional principles of treatment of FA is allergen avoidance or dietary elimination (including traces), advice on substitutes where necessary (e.g. milk allergy in bottle-fed infants), preparation to promptly manage allergic reactions and timely review. Central to these principles is a comprehensive patient and family education programme on how to manage allergic reactions, and dietary advice not only on what the patient cannot eat but what they can eat.

Dietary elimination

Allergen avoidance is the safest way to manage food allergy. Important considerations here include:

1. **Dietetic support:** All FA patients should receive appropriate support from a dietitian with training in allergy. A single consultation may suffice with a simple exclusion. Continued support with follow-up consultations and possibly more regular telephone or email correspondence may be necessary with more complex FA (e.g. multiple food allergies). Advice should cover avoidance tailored to family food choices and lifestyle, when the offending food can be reintroduced into the child's diet and an assessment of nutritional adequacy with weight and height monitoring.
2. **Label reading:** Patients should be educated on how to read ingredient labels to avoid their allergens. European legislation from December 2014, known as Food Information for Consumers Regulation requires manufacturers to declare the presence of 14 allergens clearly in the ingredient list (milk, soya, egg, peanut, tree nuts, sesame, fish, shellfish, cereals containing gluten [wheat, barley, oats and rye], celery, mustard, lupin and sulphites). These laws are to avoid inadvertent contact with so-called 'hidden' forms of allergens, such as ovalbumin or ovomucoid as sources of egg or casein from milk. Catering services that sell unpackaged or loose foods are also required to provide this information in oral or written form.
3. **Precautionary advisory labels:** Advisory labels ('may contain', 'manufactured in factory', 'produced on shared

equipment') are voluntary in most countries including the EU. They are particularly relevant in nut allergy as trace exposure can potentially cause severe reactions. Whilst it may be safer for patients to avoid such labelled products, as they are used so widely avoidance can impose significant limitations on dietary choices. In addition, nut traces have been detected only in snack foods (e.g. biscuits, cakes, sweets, chocolate, ice cream), and not in non-snack foods. A more flexible approach for families may be to risk assess exposure to labelled foods, allowing ingestion only when child is well, where emergency medication is available and avoiding isolated settings.

4. **Cross reactivity:** As related foods share proteins, the potential for cross-reactivity must be considered in dietary avoidance (e.g. cow's milk and goat's milk is 95%, peanut/tree nuts 40%, fish species 50%). However, only those foods to which a patient is allergic should be avoided.
5. **Higher-risk situations:** Advice must also address the management of high-risk situations such as children's birthday parties, school meals, eating out in restaurants, foreign travel and increasing independence of teenagers, but without instilling undue anxiety.

Early dietary reintroduction

Infants with milk or egg allergy can grow out of their FA. Tolerance occurs at an earlier age to processed forms of these foods as baking renders them less allergenic.

Each food is a mixture of allergenic proteins that differ in their stability to heat and digestion. In milk the caseins and serum albumins have more heat stability than the whey proteins. With eggs, ovalbumin, the most abundant protein in egg white, is sensitive to heat denaturation, whilst ovomucoid is heat stable. Protein interactions with other ingredients in processed foods are also important as it generally results in decreased availability of the protein for contact with the immune system (known as the matrix effect). When assessing a milk or egg containing food for potential residual allergenicity, factors to consider are the amount of allergen as ingredient, intensity of processing (i.e. temperature and duration of heating) and the presence of wheat.

Infants can therefore be offered baked forms of milk or egg as early as at 12 months old to start reintroducing these foods into their diets. Once even a tiny amount (e.g. crumb of a baked milk biscuit) is successfully reintroduced, exposure can be gradually increased under dietetic supervision as tolerated. Milk and egg ladders have been developed to support families with this process (Figure 1).

Reintroduction can be performed at home or in hospital. Where infants initially had mild to moderate reactions (skin or gastrointestinal symptoms only) with milk or egg contact, re-exposure can be carried out safely at home, starting with small amounts of the allergen. By contrast, supervised hospital reintroduction (effectively challenges) are recommended when testing tolerance in children who have had severe symptoms (respiratory or cardiovascular) with trace contact, have moderate or severe comorbidities (eczema or asthma), are on regular asthma medication, have other known food allergies or where there is high parental anxiety.

Early reintroduction conveys many benefits. Aside from the obvious improved nutrition and quality of life of being able to

widen dietary exposure by including traces, even small amounts of allergen exposure can accelerate immunological tolerance allowing earlier introduction of raw milk or cooked egg.

Emergency vigilance for IgE-mediated FA

Avoidance of food allergens is difficult to maintain. Half of children with IgE-mediated FA have been reported to experience accidental ingestion to their allergen within 5 years and 75% within 10 years of diagnosis; and more recently half of peanut allergic children within 2 years. Consequently, the essential components of the management of IgE-mediated FA are:

1. **Patient education:** Patients and families must be taught to recognise and treat allergic reactions. Those prescribed an adrenaline auto-injector (AAI) should be trained how to use it. It is useful to provide the family with a training device and instructions to encourage practice regularly at home to mitigate against incorrect use in emergencies.
2. **Action plans:** All patients must be provided with an individualised action plan that outlines the symptoms and signs of mild-moderate and severe allergic reactions and their treatment actions (see www.bsaci.org). Mild to moderate reactions involving the skin or gut can be treated with oral antihistamines. Severe reactions affecting the respiratory or cardiovascular systems should be treated with intramuscular adrenaline. An alternative approach for patients prescribed an AAI experiencing an allergic reactions is to think 3'D's: Is it a **definite** reaction? Is it a **dangerous** reaction? **Do** it if in doubt. A single dose of intramuscular adrenaline has never been shown to cause harm.
3. **Prescription of emergency medication:** Intramuscular adrenaline is the first-line treatment in all cases of anaphylaxis in and out of hospital. The decision to prescribe an AAI

in children with FA depends on the presence of risk factors for life-threatening anaphylaxis. These include allergy to foods where anaphylaxis can more usually occur even with trace exposure (e.g. peanut and tree nuts, seeds, fish and shellfish), history of previous anaphylaxis to other foods (e.g. milk, egg), concomitant severe or poorly controlled asthma and living more than 20 minutes from emergency medical support.

Follow-up

The indications for and frequency of review (face-to-face or virtual – telephone or email) of children with FA differs with patient age and FA group (i.e. resolving or persistent). Two examples are shown.

Child with milk allergy: at the initial clinical contact the parent receives dietary advice on dairy avoidance and dairy-free weaning, and the dietician or paediatrician prescribes suitable replacement milk. Early virtual contact with the dietitian is used to communicate progress on how well the infant is tolerating the new milk. If there are no other clinical concerns only dietetic follow-up is needed and the child will be seen at 4–6 monthly intervals until tolerating the allergen. Visits will allow assessment of nutritional adequacy of the child's diet and further advice on dairy free weaning and safe reintroduction.

Child with nut allergy: at the initial clinic visit a child with nut allergy will have the diagnosis confirmed with allergy tests and the family will receive appropriate dietary avoidance advice and training on the management of anaphylaxis. Where there are no other clinical concerns, a pre-school child would be reviewed 12 months later and then once more before starting school. At the

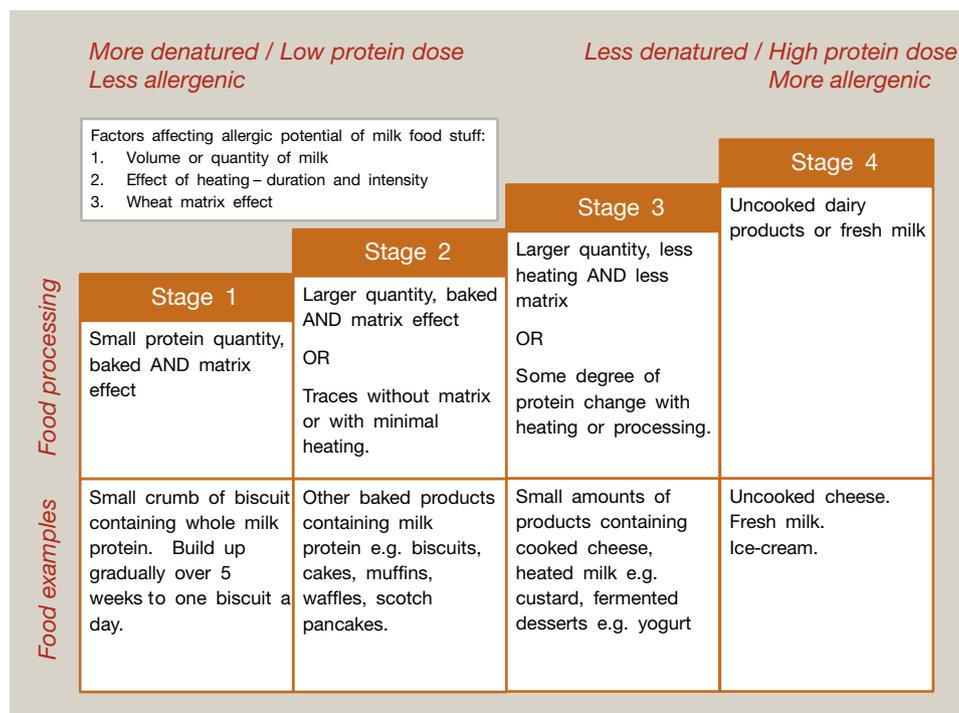


Figure 1 Typical ladder for the reintroduction of cow's milk.

first review visit the clinical team reviews dietary avoidance, revise the use of the AAI and reassess the patient's allergy tests. Our service tests for eight nuts (almond, Brazil nut, cashew nut, hazelnut, peanut, pecan nut, pistachio nut and walnut) as there is an approximate 40% risk of allergy to more than one nut in patients presenting for assessment of nut allergy.

A patient allergic to cashew nut and pistachio nut for example who tests positive to one or more of the other nuts with skin prick test wheal sizes suggesting sensitivity rather than allergy would be offered an OFC to establish tolerance. If tolerance is confirmed, this should allow the individual to reintroduce other nuts into his or her diet. The later clinic visit might facilitate this aspect of management.

Once these assessments are complete, further follow-up at 5-yearly intervals would suffice. There is a small chance that patients with peanut allergy will grow out of this allergy. Tree nut allergy is less likely to resolve.

Future treatments

Strict avoidance of allergens is not curative and leaves the patient at risk of accidental exposure. The current principles of treatment of FA no longer suffice, as they do not provide long-term solutions particularly as FA is an increasing public health challenge with its increase in prevalence and more persistent nature. Several new preventative and therapeutic approaches are being investigated. These are either allergen-specific (e.g. oral immunotherapy) or non-specific (e.g. probiotics).

The early introduction of baked milk or baked egg where it is tolerated is such an approach. This represents a form of immunotherapy or desensitisation as exposure to these foods is shown to accelerate the development of tolerance. It is not strictly true desensitisation as these children can tolerate the allergen in a baked form when reintroduction is started.

In children with persisting milk or egg allergy (and also symptomatic with baked forms) and in children with peanut allergy, oral immunotherapy (OI) is a promising form of active intervention.

OI involves exposing allergic children to increasing doses of the food allergen starting with very small doses and increasing either daily or weekly (depending on protocol and food) to induce tolerance. It has been shown to be a safe and effective treatment option with success rate over 75%. It is not yet recommended for routine clinical use or outside specialist allergy units but certainly is the novel treatment that is closest to clinical application.

Conclusion

The management of FA is evolving with active treatment now central to the care of children and their families. This treatment requires up to date knowledge and expertise of a multi-disciplinary team to provide not only these new treatments but also those of the future; a future where the focus will be on FA prevention.

Financial disclosure

None of the authors have any financial relationships relevant to this article to disclose. ◆

FURTHER READING

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Practice points

- A clinical and dietary history is the cornerstone of the diagnosis of FA and will guide investigations.
- A positive allergy test (SPT or sIgE) signifies sensitisation but alone does not equate to allergy.
- There is no role for SPT or sIgE in the diagnosis of non IgE-mediated FA.
- The management of FA has evolved from avoidance as sole treatment option to reintroduction where the natural history is one of resolution (e.g. milk, egg), and oral tolerance induction in those which persist
- All children with FA should have dietetic review for advice of food avoidance, nutrition and timely appropriate reintroduction.